Fatigue and Prostate Cancer

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Declaration

I hereby declare that this thesis is of my own composition. I conducted all aspects of the studies described, including protocol writing, ethics submissions, recruitment, data collection and analysis, except where acknowledged. This work has not been submitted previously for a higher degree. It was carried out in the Edinburgh Cancer Centre, the University of Edinburgh Cancer Research Centre and the Queen Margaret Hospital in Dunfermline between October 2003 and September 2006.

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Preface

Fatigue is increasingly recognised as one of the most common, debilitating and distressing symptoms experienced by cancer patients. As an oncologist I became acutely aware of this, especially as it was often associated with the treatments I administered. Some patients complained that their fatigue severely impeded their ability to carry out self care, fulfil their responsibilities or interact with their family and friends. This often led to feelings of frustration, inadequacy and isolation. In an attempt to find something that would help these patients, I started searching the literature. It quickly became clear that fatigue was poorly understood and research was in its early stages. In comparison twenty five years ago, nausea, vomiting and pain were the most troublesome symptoms that affected cancer patients. Thankfully however, due to improved understanding of the underlying mechanisms and subsequent development of new treatments, these symptoms are much better controlled. In the hope that similar advances will be made with fatigue, I was inspired to embark on this research project.

Acknowledgements

I am very grateful to the many people who have helped this thesis come to fruition. Unfortunately there is not enough space to name everyone but particular thanks go to my supervisors Professor Michael Sharpe and Professor John Smyth. They have provided both the opportunity to learn about the different aspects of research and enabled me to pursue a clinically important subject that I have been interested in for a long time (rather than slot into a ready made project designed by someone else). Dr Duncan McLaren's encouragement and the way he shared his prostate cancer knowledge with me was also invaluable. I am grateful to Clinical Nurse Specialists Rita O'Dea, Sheila Liggat, and Lesley Frew for their insight into the issues affecting men with prostate cancer, their help recruiting patients and for maintaining excellent clinical databases which made my work a lot easier (along with their colleagues Diane Rankin, Isabel Bennett, Bernadette McCleary and Angela Scally). Thanks also to Morven Shipway who helped me collect the data and to the staff on the Radiotherapy Treatment Floor and the Surgical Day Bed Area for being so accommodating when we needed to see patients. Michelle McGrady's help was invaluable for recruiting men from Nurse Urology Clinic. Many thanks to Rhona Aird, for teaching me how to perform laboratory ELISA assays and thanks also go to Dr Donny McMillan, University of Glasgow for his advice about proinflammatory inflammatory cytokines.

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Finally, a huge thank you to all the patients who contributed to the research, without whom none of this would have been possible.

Abstract

Background

Fatigue is a common and debilitating problem for cancer patients. It is associated with cancer or its treatment. Evidence suggests fatigue may be prolonged after treatment for some cancers and could be associated with a host systemic inflammatory response. Prostate cancer is the commonest male cancer however little is known about fatigue and its associations in this population.

Aims

To explore the incidence of fatigue and its associations during and after treatment for prostate cancer.

Methods

Four studies were conducted: Study A, was a pilot study which examined fatigue over 3 months after different treatments for localised prostate cancer (radiotherapy, brachytherapy and androgen deprivation, n=45). Study B focussed on fatigue over 12 months after brachytherapy (n=51). Two cross sectional postal surveys explored fatigue in recurrence free prostate cancer survivors (Study C, n=443) and hormone controlled prostate cancer (Study D, n=198). Throughout, fatigue was assessed using the Brief Fatigue Inventory and a case definition of clinically significant fatigue (CSF) was also constructed and applied in Studies A and B.

Results

Study A found CSF increased after treatment but returned to baseline 3 months after radiotherapy, whereas it appeared to be prolonged after brachytherapy. CSF was not associated with C reactive protein or interleukin-6. Study B found CSF increased between baseline and 1 month after brachytherapy (6 vs. 29%, p=0.001) and was higher than the non-cancer comparison group (29 vs. 4% p=0.001). CSF returned towards baseline levels by 6 months. There were no baseline predictors of developing CSF. Study C found 29% of recurrence free prostate cancer survivors had fatigue after radiotherapy or radical prostatectomy (33 vs. 22% p=0.024) but it was not independently associated with treatment received after controlling for other factors. 43% of men with hormone controlled prostate cancer had fatigue in Study D.

Conclusions

Fatigue is an important symptom in men treated for prostate cancer but resolves within months of brachytherapy. Almost one third of recurrence free survivors have fatigue but it does not appear to be related to the type of treatment received. Fatigue is most prevalent in men with hormone controlled prostate cancer.

Abbreviations

BFI	Brief Fatigue Inventory
CSF	Clinically significant fatigue
CRP	C reactive protein
DS	Dawn Storey
EORTC	European Organisation for the Treatment Cancer
Gy	Gray
IPSS	International Prostate Symptom Score
HADS	Hospital Anxiety and Depression Score
IL-6	Interleukin 6
IL-1ra	Interleukin 1 receptor antagonist
MDD	Major Depressive Disorder
MS	Morven Shipway
PSA	Prostate Specific Antigen
QL	Quality of life
SCID	Structured Clinical Interview for Depression
SD	Standard deviation
SIMD	Scottish Index of Multiple Deprivation

CHAPTER

1

INTRODUCTION

FATIGUE AND CANCER

Chapter 1

List of sections

1.1 WHAT IS FATIGUE?

Fatigue is a subjective experience which can be normal or abnormal. For healthy people, fatigue can be a protective, even pleasant response to physical or psychological stress. It disappears after a good nights' rest and appears to regulate a healthy balance between rest and activity. When fatigue is abnormal, the individual finds it a problem and it becomes a symptom. Many medical conditions are associated with fatigue (Belza *et al.* 1993;Ream & Richardson 1997;Chaudhuri & Behan 2004;Theander & Unosson 2004;Appels 2004) and cancer patients describe a longer lasting, more intense, unpleasant, distressing experience that limits life activities and tends to be present throughout the day (Holley 2000a;Servaes *et al.* 2002a). In this thesis I am going to address this important topic.

1.1.1 The definition of fatigue for research

There is currently no universally agreed definition of fatigue. It has many synonyms including tiredness, lethargy, weakness, exhaustion or lack of energy. For research purposes, in order to define when fatigue is abnormal there have been attempts to make distinctions between the concepts of fatigue and normal tiredness. Criteria used include severity and duration (overwhelming and sustained) and its lack of response to actions that typically provide relief from tiredness (not relieved by rest). Others simply view normal fatigue as acute, and pathological fatigue as chronic (Piper 1989;Carpenito 1992;Woo 1995;Ream & Richardson 1996;Tiesinga *et al.* 1996;Krishnasamy 2000;Trendall 2000). The lack of definition is not a new problem; almost a century ago Muscio was of the strong opinion that "the term fatigue be absolutely banished from scientific discussion" (Muscio 1921)

Perhaps one of the factors contributing to this confusion is that different researchers have approached fatigue according to their own research specialty. Fatigue has been of interest in the fields of ergonomics, physiology, psychology and medicine. Physiologists refer to functional organ failure or poor physical performance, viewing physical insufficiencies as indicators of neuromuscular or metabolic disorders (Gibson & Edwards 1985;Lewis & Haller 1991). Psychologists tend to refer to suboptimal mental performance including poor concentration and decreased

motivation (Lee *et al.* 1991). In medicine, there is also and added layer of complexity because of a tendency for disease specialists to appropriate fatigue as a disease specific entity. In the oncology literature the term 'Cancer Related Fatigue' is commonly used. The National Comprehensive Cancer Network uses the following definition:

> *Cancer related fatigue is a persistent, subjective sense of tiredness related to cancer and cancer treatment that interferes with usual functioning (NCCN 2006)*

This definition has the characteristics of emphasising the subjectivity of the sensation, the chronicity and interference with usual functioning. It also involves attributing the cause of fatigue to cancer or its treatment. In practice this can be very difficult and perhaps premature. It does not include features that some imply may be characteristic, such as the fatigue being disproportionate to exertion or not relieved by rest.

1.2 MEASUREMENT OF FATIGUE

1.2.1 Objective measurement of fatigue

Like all other symptoms by definition, fatigue is subjective. However when patients are asked to describe it, they often find it difficult and instead describe the consequences of fatigue, such as the way it impairs their ability to function (Magnusson *et al.* 1999). There have been attempts to objectively measure what patients describe as fatigue (or its consequences) by using methods such as physiological muscle testing, actigraphy, or physical exercise performance (Dimeo *et al.* 1997;Monga *et al.* 1997;Stone *et al.* 1999;Servaes *et al.* 2002b;Brown *et al.* 2005). However, the relationship between these and patients' subjective reports of fatigue are notoriously poor. The physiological or relatively objective tests that are currently available do not help. A symptom cannot be measured by an observer and can only be assessed by self report.

1.2.2 Subjective measurement of fatigue

1.2.2.1 Continuous scale measures

There are a multitude of self report fatigue measurement instruments available and no commonly accepted 'gold standard'. To cover them all is beyond the scope of this thesis but they are listed in Chapter 4 and helpful reviews have been published (Wu & McSweeney 2001;Dittner *et al.* 2004). Broadly speaking, measures are classed as uni or multidimensional but in general they all calculate a continuous numerical fatigue score. From a clinical perspective it is not clear at what point along these continuous scale measures that fatigue becomes abnormal or worthy of further assessment or intervention i.e. the individual becomes a 'case' of clinically significant fatigue. Typically a patient need only say they are experiencing fatigue to be considered as having cancer related fatigue, therefore current prevalence estimates may be high and misleading. Additionally the use of different scales makes it difficult to compare studies using different scales.

1.2.2.2 Case definition approach to fatigue

In order to remedy this, diagnostic criteria for cancer related fatigue were proposed (Cella *et al.* 1998). This has been a helpful step forward and will be covered in more detail in Chapter 4. At the time of starting my research it had only been used in two studies, one of which did not apply all the criteria (Cella *et al.* 2001;Sadler *et al.* 2002). One of the key points is that by definition cancer related fatigue has to be attributed to cancer or its treatment. Cause is inherently difficult to attribute and is perhaps premature. It is also far from clear whether the experience of fatigue in cancer patients is different to that with other medical conditions (Paterson *et al.* 2003). A more useful case definition would be for clinically significant fatigue which could be applied to all conditions with fatigue, not just cancer.

1.3 FATIGUE IN CANCER PATIENTS

Fatigue is the most frequently reported symptom in cancer patients. Prevalence estimates vary from 15-99% depending on the population studied, measurement instrument used and the criteria for recording fatigue as present (Stone *et al.* 2000b;Stone *et al.* 2000c;Cella *et al.* 2002;Servaes *et al.* 2002a). Many patients

regard their fatigue as inevitable and untreatable and so it tends to be underreported by patients and underestimated by clinicians (Vogelzang *et al.* 1997;Stone *et al.* 2000c).

Fatigue can be associated with cancer or its treatment. It may be the first manifestation of an underlying malignancy or be induced or worsened by subsequent treatment with surgery, radiotherapy, chemotherapy or biological agents. There is the clinical perception that fatigue severity varies according to the primary cancer diagnosis, stage of disease and type of treatment. There is little research to support this (Stone *et al.* 2000b;Glaus 2001) and the relationship between fatigue and treatment related factors has seldom been investigated (Servaes *et al.* 2002a).

1.3.1 Consequences of fatigue

Fatigue has a negative impact on quality of life, affects compliance with cancer treatments and can impair patients' self care abilities (Rhodes *et al.* 1988;Vogelzang *et al.* 1997;Irvine *et al.* 1998;Curt *et al.* 2000). Many patients report that fatigue is more distressing than pain and nausea and particularly interferes with role performance and ability to meet their own needs and those of their families (Knobf 1986;Cella *et al.* 2001;Servaes *et al.* 2002a). A telephone survey of patients who had received chemotherapy, reported fatigue had detrimental physical, psychosocial and financial consequences. Of those who were fatigued, 91% reported that it had prevented 'a normal life' and 75% had to change their work conditions due to fatigue (Curt *et al.* 2000).

1.3.2 Fatigue during cancer treatment

Until recently there has been relatively little systematic study of fatigue in cancer patients. Much of this research has focused on fatigue associated with chemotherapy and combined chemo-radiation treatment (Servaes *et al.* 2002a). What has received less attention is fatigue in patients who have received radiotherapy alone.

1.3.2.1 Fatigue during chemotherapy or combined chemo-radiotherapy

Many of the fatigue studies to date have been cross sectional. Of the few prospective studies of fatigue during chemotherapy, most have examined breast cancer patients. Some studies found fatigue significantly increased during chemotherapy (Irvine *et al.* 1994;Andrykowski *et al.* 1998;Jacobsen *et al.* 1999;Wang *et al.* 2001;de Jong *et al.* 2004;Donovan *et al.* 2004) but not others did not confirm this (Hann *et al.* 1999;de Jong *et al.* 2002;Jacobsen *et al.* 2004a). In many studies, some patients have also received concurrent radiotherapy making it difficult to attribute fatigue to specific treatment modalities. There is the suggestion that the pattern of fatigue may vary with different chemotherapy regimens but there is limited literature addressing this (Richardson *et al.* 1998;de Jong *et al.* 2002).

1.3.2.2 Fatigue during radiotherapy

There are fewer studies specifically examining fatigue during radiotherapy alone. There is evidence to suggest that fatigue increases during radiotherapy but this does not seem to be the case for all patients (Wratten *et al.* 2004;Hickok *et al.* 2005) and there are differing findings about its trajectory. Contrary to expectations some studies found fatigue did not increase linearly with cumulative doses. Instead it reached a maximum part way through the course and plateaued. (Greenberg *et al.* 1992;Irvine *et al.* 1998). Results also seem to vary according to the measurement instrument used. A study of 41 early breast cancer patients who received 50Gy over 5-6 weeks found fatigue measured by a visual analogue scale increased until week 4 and remained elevated, whereas when measured on the Fatigue Assessment Questionnaire showed a decline in week one and never significantly increased (Geinitz *et al.* 2001). A larger study of patients with mixed cancer diagnoses found a gradual increase in fatigue over the course of radiotherapy. They also found a reduction of fatigue on radiotherapy free days. (Smets *et al.* 1998a). Researchers have found the degree of fatigue in radiotherapy patients differs by cancer diagnosis though whether this is due to differences in biology, gender, tumour or irradiation site is not clear (Smets *et al.* 1998a;Jereczek-Fossa *et al.* 2002). Some suggest that fatigue correlates with the size of radiotherapy field or dose though this has been contradicted by others (Smets *et al.* 1998a;Smets *et al.* 1998b).

1.3.3 Fatigue after cancer treatment

Due to the potentially life threatening nature of being diagnosed with cancer, many patients seem willing to accept the trade off between undesirable acute side effects of treatment such as hair loss, fatigue, nausea and vomiting, so long as they are temporary and the potential result is either cure of their cancer or enables them to live much longer with it. In this situation, quality of life after cancer treatment is of major importance and the question arises whether persistent fatigue may have an adverse effect.

Few studies have addressed fatigue after cancer treatment though there is the suggestion that it may be an important issue for cancer survivors (Cella *et al.* 2001;Arndt *et al.* 2005). Bearing in mind that not all 'survivors' are recurrence free, cancer may contribute to their fatigue rather than be the long term effect of treatment alone. However, studies that have focussed specifically on recurrence free survivors show fatigue is prevalent in patients with a history of Hodgkins lymphoma, breast and testicular cancer (Andrykowski *et al.* 1998;Bower *et al.* 2000;Servaes *et al.* 2002c;Fossa *et al.* 2003;Ruffer *et al.* 2003;Hjermstad *et al.* 2005). Most studies are cross sectional and so do not have pre-treatment fatigue data to refer to. However one prospective study assessed breast cancer patients before treatment then at one, two and three years afterwards and found fatigue remained around the same level of 20% (Nieboer *et al.* 2005). Some studies have compared to a non-cancer population and generally higher levels of fatigue are found in recurrence free survivors (Andrykowski *et al.* 1998;Servaes *et al.* 2002c;Fossa *et al.* 2003;Ruffer *et al.* 2003;Hjermstad *et al.* 2006).

1.3.3.1 Fatigue after radiotherapy

Although there is the clinical impression that fatigue increases during radiotherapy, there is conflicting evidence as to how long it lasts. Some small prospective studies with short follow up showed that fatigue recovered to pre-treatment levels within several weeks (Greenberg *et al.* 1992;Geinitz *et al.* 2001) but not for others (Monga *et al.* 1999;Wratten *et al.* 2004). A cross sectional study of prostate cancer patients

showed that 'severe fatigue' was present in 18.7% of patients approximately two years post radiotherapy (Vordermark *et al.* 2002). Another compared fatigue scores between healthy controls and a group of 154 patients with heterogeneous cancers treated with radiotherapy nine months previously and found there was no difference in fatigue (Smets *et al.* 1998b). It is unclear whether a proportion of recurrence free survivors in specific cancer groups may experience prolonged fatigue and there is a need for longer prospective studies to address this.

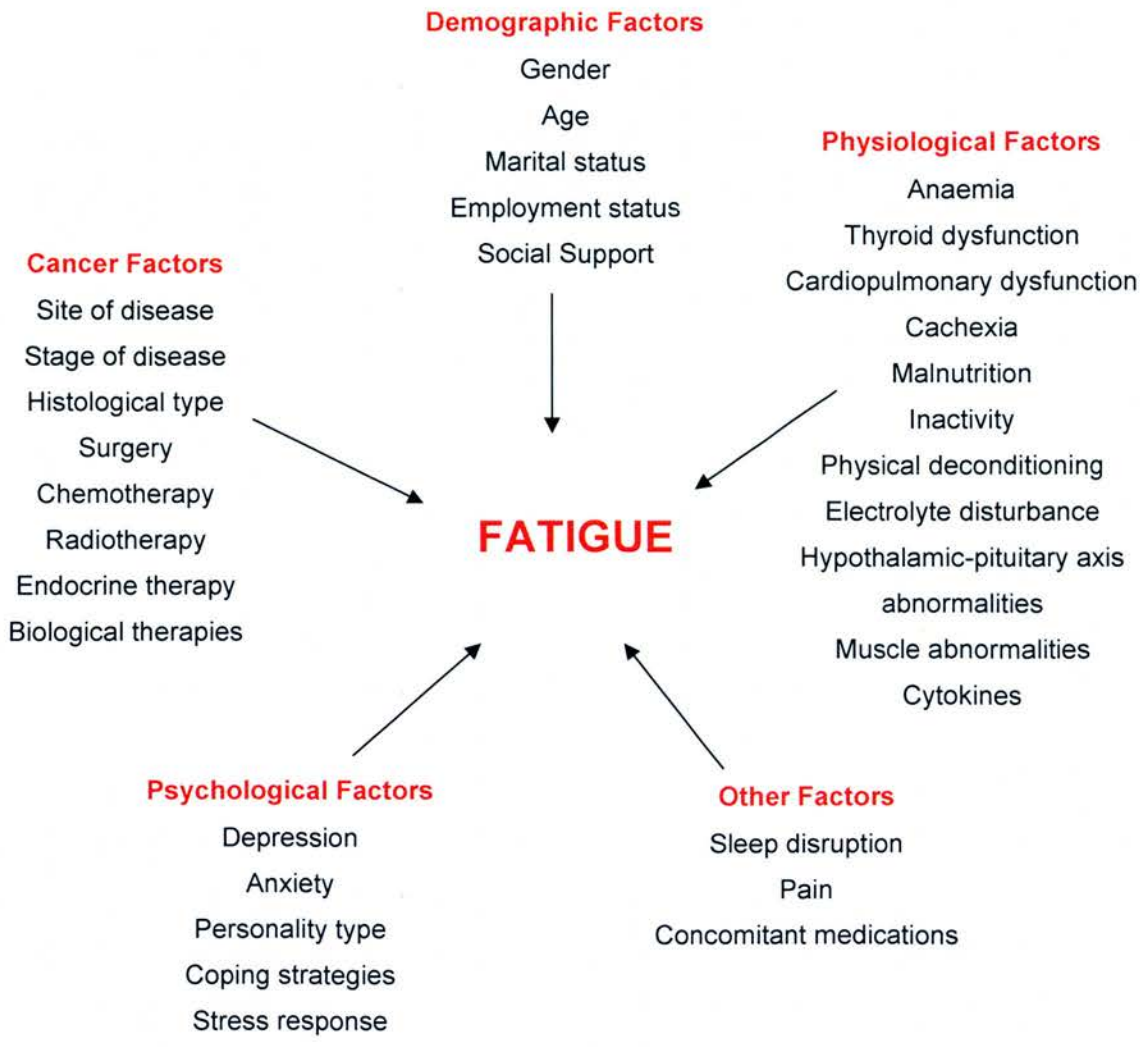
1.4 ASSOCIATIONS AND MECHANISMS OF FATIGUE IN CANCER PATIENTS

A number of demographic, psychological and physiological factors have been reported to contribute to fatigue and are shown in figure 1.

1.4.1 Fatigue and cancer related factors

Fatigue can be caused by the presence of cancer. This can occur in several ways: it can depend on the site of the primary tumour (in the lungs causing mechanical obstruction and hypoxia); the site and size of metastatic tumours impairing organ function (such as liver metastases); substances released by the tumour cells (such as polypeptides from small cell lung cancer) and the body's physiological response to those substances or the tumour (such as the host systemic inflammatory response). There is the clinical assumption that fatigue increases with greater tumour burden and most commonly it is associated with metastatic disease. In fact there have been no studies that systematically examine fatigue in patients with different stages of a single cancer diagnosis. It is not clear whether small localised tumours themselves cause fatigue or whether psychological and treatment factors are more important. It is recognised that surgery, radiotherapy, chemotherapy, endocrine and biological therapies are often associated with fatigue but there are few studies comparing fatigue in the same tumour type with different treatments (Woo *et al.* 1998). There is speculation that tumour growth factors and symptoms associated with cancer and its treatment may have a shared biologic mechanism (Cleeland *et al.* 2003).

Figure 1. Factors contributing to fatigue



1.4.2 Fatigue and demographic factors

There are conflicting findings as to whether marital status, social support, race and working status are associated with fatigue during treatment (Servaes *et al.* 2002a). Many people assume that as age increases then so does fatigue. In fact some studies show no relationship but Woo et al found a significant negative correlation in breast cancer patients. They suggested that this may be because more aggressive chemotherapy regimens were given to women under 60 years old or that younger women were more likely to have jobs and responsibilities of caring for their families, giving them fewer opportunities to save energy (Woo *et al.* 1998). Fatigue is thought

to be most common in women but whether this is due to gender or confounded by the site and type of tumour is unclear. The associations of fatigue in men have not received much attention and are deserving of future study.

1.4.3 Fatigue and psychological factors

Some studies have focussed on the possible psychological mechanisms of fatigue and show a correlation between anxiety, somatisation, catastrophizing coping style and especially depression (Hann *et al.* 1998;Stone *et al.* 2001;Jacobsen *et al.* 2004b). Fatigue is one of the symptoms of the syndrome of Major Depressive Disorder so perhaps this is not surprising. Because of this relationship, there is an assumption that depression and fatigue may follow a similar course but it is not clear whether fatigue causes depression or vice versa. It is worthy of note however, that in three studies, although correlations between fatigue and depression were moderate, depression scores either decreased or did not change while fatigue scores rose over the course of radiotherapy and hormonal therapy (Visser & Smets 1998;Monga *et al.* 1999;Stone *et al.* 2000a).

1.4.4 Fatigue and other factors

Concomitant symptoms and side effects like pain, infection, dehydration, malnutrition, diarrhoea, sleep disturbance and concurrent medications (i.e. opiods) have also been found to be associated with fatigue (Jereczek-Fossa *et al.* 2002;Servaes *et al.* 2002a;Jacobsen & Thors 2003)

1.4.5 Fatigue and physiological factors

Fatigue during breast cancer treatment has been shown to be associated with less day time activity (Berger & Farr 1999). This can form a vicious cycle leading to physical deconditioning which in turn can worsen fatigue and consequently the patient becomes even less active. In patients with advanced cancer, cachexia can also contribute to this.

1.4.5.1 Possible biological mechanisms of fatigue

Biological mechanisms of fatigue in cancer patients are poorly understood. Fatigue is a self reported sensation which may have objectively measurable correlates yet to be identified. Anaemia is commonly associated with fatigue and several studies investigating the use of recombinant human erythropoietin in anaemic chemotherapy patients have reported a decrease in fatigue or increase in quality of life (Cella 1997;Patrick *et al.* 2003b). However the relationship between haemoglobin and fatigue is not strong and has been shown to be confounded by disease stage and tumour response (Wisloff *et al.* 2005). Few studies have examined the biological correlates of fatigue beyond haemoglobin but low cortisol, hypothalamic-pituitary dysfunction, disordered ATP (adenosine triphosphate) metabolism and raised systemic inflammatory response may also play a part (Morrow *et al.* 2002).

1.4.5.1.1 Systemic inflammatory response

Evidence of a systemic inflammatory response is easily detected by the presence of raised levels of C - reactive protein (CRP). CRP production is mediated by proinflammatory cytokines. Cytokines are intercellular signalling polypeptides produced by a variety of activated cells. The most important of these are macrophages and monocytes which release substances including Interleukin-6 (IL-6), IL-1β and Tumour Necrosis Factor (TNF). Hepatic synthesis of CRP in cancer patients is predominantly under the control of IL-6, its soluble receptor and IL-1 receptor antagonist (Gabay & Kushner 1999).

1.4.5.1.1.1 Radiotherapy and systemic inflammatory response

Fatigue in radiotherapy patients may be related to cytokine activation and consequent induction of a systemic inflammatory response (Greenberg *et al.* 1993;Kurzrock 2001). In-vitro and in-vivo studies have shown ionizing radiation can induce production of acute phase response cytokines such as IL-1, IL-6 and TNFα (Beetz *et al.* 1997). These cytokines are known to have sleep inducing and malaise inducing properties (Kurzrock 2001) leading to speculation that cytokine production may be a cause of fatigue in radiotherapy patients. One study reported an increase in fatigue and IL-1 levels in prostate radiotherapy patients (Greenberg *et al.* 1993) but another

failed to find any relationship between fatigue and IL-1, IL-6 and TNFα (or haemoglobin) in women having radiotherapy for early breast cancer (Geinitz *et al.* 2001). The most comprehensive study of inflammatory factors and radiotherapy to date showed baseline fatigue prior to breast irradiation was associated with variety of cytokine and coagulation factors including IL-6 and CRP. However, once body mass index was accounted for, this was no longer the case. Nor was there any relationship between IL-6, CRP and fatigue during radiotherapy (Wratten *et al.* 2004).

Breast cancer survivors with persistent fatigue years after treatment have been found to have elevated levels of proinflammatory cytokines and T-lymphocytes compared to non fatigued survivors suggesting a chronic inflammatory process. In addition they show behavioural changes consistent with proinflammatory cytokine activity including depressed mood, decreased social interest and cognitive difficulties (Bower *et al.* 2002;Bower *et al.* 2003).

1.5 WHY IT IS IMPORTANT TO STUDY FATIGUE IN CANCER PATIENTS

With the development of new therapeutic approaches, cancer treatments are becoming increasingly complex and may result in prolonged, more intense therapy with little or no survival benefit. Consequently patients' quality of life must increasingly be taken into account. Symptom distress is an important component of patients' overall evaluation of their well being. Fatigue is now understood to be the most common symptom associated with cancer and its management and has a major adverse effect on quality of life (Irvine *et al.* 1994;Cella 1997;Yellen *et al.* 1997;Vogelzang *et al.* 1997;Cella *et al.* 1998). Patients tend to cope better with symptoms and side effects of treatment if they are advised about them in advance. It is therefore important to study fatigue and know more about its trajectory so clinicians can warn patients about it.

1.6 WHAT RESEARCH IS NEEDED

There have been few studies in cancer patients that examine fatigue using a fatigue specific measurement instrument. Of those that have, fatigue has often been reported

as mean fatigue scores rather than the proportion of subjects who have fatigue of a clinically relevant severity. There is a need for studies using a case definition of clinically significant fatigue.

Most studies have been cross sectional. Despite a high prevalence of fatigue in cancer patients, there is a lack of research on its causes and trajectory over time. Shortly before the start of this research project, the National Institutes for Health (NIH) in the U.S.A recommended that prospective incidence studies should be conducted to provide clinicians with information regarding the likelihood of occurrence, severity and duration of symptoms after a diagnosis of cancer (Patrick *et al.* 2003a). Many studies to date have several shortcomings: (a) heterogeneous cancer populations with different stages of disease and various treatments (b) they have not used a fatigue specific measurement instrument (c) few have investigated possible biological correlates of fatigue and (d) there is a lack of information as to whether fatigue levels are different to that of the non-cancer population.

After reviewing the literature it became clear that there was a need for studies of homogeneous cancer groups using a fatigue specific measurement instrument to identify fatigue of a clinically significant severity as well as integrating further exploration of biological correlates of fatigue and the inclusion of a non-cancer comparison group.

1.6.1 Why study Prostate Cancer?

Much of the work examining single cancer groups has focused on breast cancer or Hodgkins Lymphoma. Fatigue is thought to increase during treatment and there is evidence to suggest that it may still be a problem for patients, years after curative treatment. Prostate cancer is the commonest male cancer and survival is often in terms of many years. However little is known about fatigue and its associations in this population.

When considering the feasibility of which patient group to study, it was important to have access to a large sample, be able to recruit homogeneous treatment cohorts and

reduce any confounding factors which may influence fatigue. The prostate cancer population appeared to have these attributes: early prostate cancer treatment was unlikely to change during the period of my research (unlike breast cancer treatment at the time); fatigue assessment was less likely to be complicated by dyspnoea (unlike lung cancer); the prostate irradiation field was distant from the chest thus minimising the possibility of fatigue secondary to complications arising from radiation exposure of the cardiopulmonary system (unlike breast and lung cancer). In addition, prostate cancer patients were relatively under researched and therefore less likely to be in a study already (which could have had implications for recruitment). I therefore decided to focus my research on men with prostate cancer.

CHAPTER

2

INTRODUCTION

PROSTATE CANCER AND FATIGUE

Chapter 2

List of sections

2.1 PROSTATE CANCER

2.1.1 Incidence and presentation of prostate cancer

Prostate cancer is commonest male cancer in the United Kingdom accounting for one in five of new cancers in men. Only lung cancer kills more men per year (Toms JR(ed) 2004). The prevalence is highest in men aged over 70 but with the advent of PSA (prostate specific antigen) testing from the age of 50 onwards, greater numbers of men are being diagnosed and treated with curative intent at a younger age.

Commonly prostate cancer can be asymptomatic and diagnosed as a result of a raised PSA or be an incidental pathological finding after a TURP (transurethral resection of prostate). If symptoms are present, they are not specific to cancer but can include lower urinary tract symptoms (such as frequency, poor flow or nocturia), erectile dysfunction or haematospermia. Advanced local disease may present with ureteric obstruction, renal impairment or lower limb oedema. Distant metastatic disease most often presents with bone pain, malaise and fatigue. The liver can also be involved but it is uncommon to present with hepatic dysfunction alone.

Most frequently men are referred to a Urologist on the basis of a raised PSA and/or a suspicious digital rectal examination. The diagnosis is then confirmed by transrectal ultrasound guided biopsies performed under a local anaesthetic. Then, depending on the patient's age, fitness and clinical findings, some men will undergo radiological imaging to fully stage their disease.

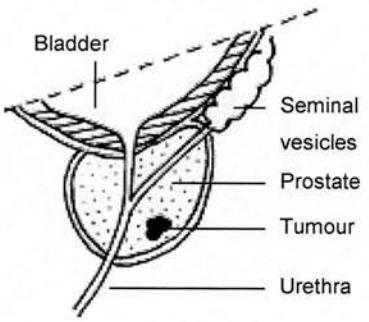
2.1.2 Disease Staging

The TNM (tumour, nodes, metastasis) staging of prostate cancer is shown in figure 2.

2.1.3 Pathological Tumour Grading

Prostate cancer is often a multifocal disease and different histological patterns may be seen within the prostate. The Gleason tumour grade is based on the two most common patterns of gland architecture and are added together to give the score ranging between 2 and 10 i.e. 3+4 = 7. A well differentiated tumour will have a score

Figure 2. TNM definitions of prostate cancer staging (American Joint Committee on Cancer. 2002)



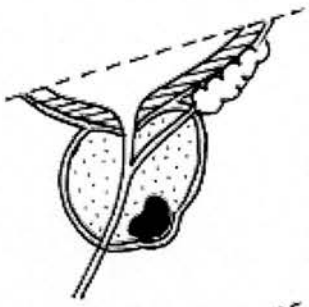
Primary tumour (T)

TX: Primary tumour cannot be assessed

T0: No evidence of primary tumour

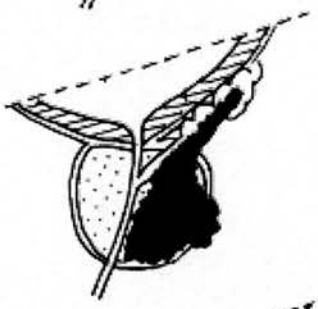
T1: Microscopic tumour confined to prostate and undetectable by a digital rectal exam or imaging

- T1a: Tumour incidental histological finding in ≤5% of tissue resected
- T1b: Tumour incidental histological finding in >5% of tissue resected
- T1c: Tumour identified by needle biopsy (e.g., because of elevated PSA)



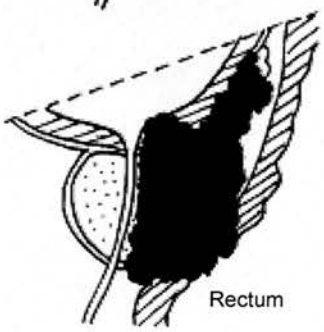
T2: Tumour confined within prostate and can be detected by digital rectal examination or imaging

- T2a: Tumour involves 50% of one lobe or less
- T2b: Tumour involves >50% of one lobe but not both lobes
- T2c: Tumour involves both lobes



T3: Tumour extends through the prostate capsule

- T3a: Extracapsular extension (unilateral or bilateral)
- T3b: Tumour invades seminal vesicle(s)



T4: Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

Regional lymph nodes (N)

NX:Regional lymph nodes were not assessed

N0: No regional lymph node metastasis

N1: Metastasis in regional lymph node(s)

Distant metastasis (M)

MX: Distant metastasis cannot be assessed (not evaluated by any modality)

M0: No distant metastasis

M1: Distant metastasis

- M1a: Nonregional lymph node(s)
- M1b: Bone(s)
- M1c: Other site(s) with or without bone disease

up to 6; poorly differentiated 8 or above. The Gleason score has been found to correlate well with mortality.

2.1.4 Clinical management of prostate cancer

Management depends on a combination of the TNM staging, Gleason score and PSA level. Broadly, the severity of prostate cancer is split into three groups:

(1) Early localised disease (T1-2, N0, M0)
   (a) Good risk: Gleason score $\leq$ 6, PSA $\leq$ 10
   (b) Intermediate risk: if PSA >10 but $\leq$ 20 or PSA < 10 and Gleason 7
   (c) Poor risk: if PSA >10 but $\leq$ 20 and Gleason 7

(2) Locally advanced disease (T3-4, N0-1, M0, Gleason score $\geq$ 8, PSA > 20)

(3) Metastatic (M1, and any combination of T, N, Gleason score and PSA)

2.1.4.1 Early localised disease

Currently there is a lack of randomised clinical trials to indicate which treatment is best in terms of survival or in fact whether early localised prostate cancer needs to be treated at all. The choice of treatment is primarily determined on the basis of the cancer stage, but also with consideration of the patient's age, comorbidities and treatment preferences (taking into account potential side effects such as incontinence and erectile dysfunction). For those who are fit enough for a general anaesthetic, there are a number of different management options: radical prostatectomy; interstitial brachytherapy; external beam radiotherapy; primary androgen deprivation or watchful waiting. The latter three options are available to those who are not fit enough for general anaesthetic (unless there is a contraindication to radiotherapy such as inflammatory bowel disease).

2.1.4.1.1 Radical prostatectomy

This operation is done with curative intent and the prostate is removed via a transverse incision in the lower abdominal wall. The surgery requires a 1.5-3 hour general anaesthetic followed by a minimum four day inpatient stay. Commonly blood transfusions are required and the patient may have to go home with a urinary catheter for some time. Increasingly, some radical prostatectomies are being

performed laparoscopically with a shorter inpatient stay. Common side effects are urinary incontinence, erectile dysfunction (despite 'nerve sparing' surgery) and bowel dysfunction.

2.1.4.1.2 Interstitial prostate brachytherapy

This treatment is given with curative intent and offered providing the prostate volume does not exceed 55cc (measured by ultrasound whilst under a general anaesthetic). Under a general anaesthetic, radioactive Iodine^{125} seeds are implanted throughout the prostate via transperineal needles under ultrasound guidance. The procedure takes approximately one hour and involves an overnight inpatient stay. The seeds deliver a minimum dose of 145Gy (the central part receives 220Gy) over approximately nine months but remain permanently in situ. There is the clinical impression that this treatment has less of a detrimental effect on erectile function and men are back to fitness quicker than with radical prostatectomy. If the prostate measures between 55-70cc, rather than not have brachytherapy, some men undergo three months of androgen deprivation (see below) to shrink the prostate to enable successful implantation.

2.1.4.1.3 Radical external beam radiotherapy

At the Edinburgh Cancer Centre, a radiation dose of 55Gy is given in 20 fractions, Monday to Friday as an outpatient. This treatment is given with curative intent and each fraction takes about ten minutes to deliver. Common acute side effects are urinary frequency, dysuria, incontinence, bowel disturbance and rectal bleeding. In Edinburgh, patients are routinely given three months of neo-adjuvant androgen deprivation therapy (see below) to reduce the prostate volume and enhance the apoptotic effects of radiotherapy. The treatment is delivered using conformal radiotherapy to reduce normal tissue irradiation.

2.1.4.1.4 Androgen deprivation therapy ("hormonal therapy")

Prostate cancer grows in response to the androgen testosterone and can be controlled (but not cured) by androgen deprivation. Previously, this was done by performing a surgical bilateral orchidectomy. Now medical castration is achieved by using LHRH (lutinising hormone releasing hormone) analogue injections (with an initial three weeks of oral biclutamide (Casodex) 50mg once a day to prevent 'flare' of the disease).

Some men with high risk tumours are given adjuvant androgen deprivation therapy (to prevent cancer recurrence) for two years after radiotherapy. However, for those patients for whom this is the sole treatment then the aim is to control the cancer, not cure it. Three monthly LHRH analogue injections are administered alone or in combination with oral anti androgens such as biclutamide (maximal androgen blockade). PSA is monitored and treatment continues until it rises, indicating the cancer has become hormone resistant. The main side effects are impotence, loss of libido, hot flushes and gynaecomastia. The men who have this as their primary treatment tend to be older and have more comorbidities than those who have surgery, radiotherapy or brachytherapy.

2.1.4.1.5 Watchful waiting

One option is to do nothing, known as 'watchful waiting' or 'active surveillance'. This involves regular PSA tests (approximately every six months) and intervening if and when treatment is indicated. Sometimes younger men choose this option to avoid the impact of side effects from treatments, in particular erectile dysfunction. More frequently clinicians advise this for men who are elderly and have other comorbidities

2.1.4.1.6 Other treatments

There are other treatments available for early localised prostate cancer such as cyrotherapy or hyperthermia but these are less well established and not available in Edinburgh.

2.1.4.2 Locally advanced disease

Locally advanced prostate cancer can often be controlled but cure is uncommon. These patients are managed with radical external beam radiotherapy, primary androgen deprivation therapy or less commonly watchful waiting.

2.1.4.3 Metastatic disease

Prostate cancer metastasises to regional lymph nodes, bones and viscera (most commonly liver). Once the cancer has spread beyond the prostate gland, the aim of treatment is palliative. In the UK, primarily this is with androgen deprivation therapy but generally within three to five years the disease becomes hormone resistant. First line treatment is an LHRH analogue alone (average duration of first line hormone response is 18 to 24 months) moving on to second line maximal androgen blockade (average response lasts six months) followed by third line hormonal agents (average six months response). Chemotherapy is increasingly being employed for patients who are fit enough and bisphosphonates can be given to maintain the integrity of the bone. If required, radiotherapy can treat complications from bone metastases such as pain or spinal cord compression. Diffuse bone metastases can also respond to intravenous injections of the radioactive isotope Strontium[89].

2.1.5 Survival for patients with prostate cancer

More than 90% of all prostate cancers are diagnosed in the early localised and locally advanced stages. For those with early disease 10 year survival is similar to that of the normal population but it decreases at 15 years. For locally advanced prostate cancer the prognosis is worse; about 50% alive at 10 years. (American Cancer Society 2006). If the cancer recurs locally it can seed secondary metastases but with good local control, many will die with, rather than from their prostate cancer. Consequently the impact of long term side effects of treatment is of special relevance.

The prognosis for those with metastatic disease is much poorer but still in terms of years (34% five year survival). Hence, maximising quality of life and minimising treatment side effect and symptom burden is also very important for these patients.

2.2 FATIGUE AND PROSTATE CANCER

The physical side effects most frequently associated with prostate cancer are well documented. Generally studies have shown that incontinence and sexual difficulties are reported more frequently by patients who have received radical prostatectomy than by those who received radiotherapy or brachytherapy while bowel dysfunction (e.g. diarrhoea, rectal discomfort) is more frequent in patients who have received radiotherapy or brachytherapy. It is increasingly recognised that the impact of these treatments on quality of life must also be considered and has become more important in determining the best approach to treatment, especially since no study has yet found one of these options to be superior in terms of survival. Studies of American men with prostate cancer show sexual and urinary function were the most important factors determining quality of life. In contrast, a study of Norwegian prostate cancer patients showed that fatigue, physical and emotional function were the only independent predictors of quality of life (Lilleby *et al.* 1999). Fatigue may also be an important consideration in treatment selection for Scottish patients.

2.2.1 Does early prostate cancer cause fatigue?

There is the clinical impression that some cancers intrinsically cause fatigue but that early localised prostate cancer is not one of them. Currently there is no evidence to support this. Stone *et al* found 16% of men with recently diagnosed prostate cancer had 'severe fatigue' (classed as greater than the 95th percentile of healthy volunteers scores on the Fatigue Severity Scale), however their disease stage was unclear (Stone *et al.* 2000b). It is assumed that more advanced disease is associated with worse fatigue but there have been no studies comparing fatigue in patients with different stages of prostate cancer.

2.2.2 Fatigue and prostate cancer treatment – the clinical impression

Prior to embarking on this research project I had come across many patients with prostate cancer who complained of fatigue that adversely affected their lives. When discussing this with other health professionals, most agreed that fatigue was significant problem for men on androgen deprivation therapy (although there is no published data specifically addressing this). No one was sure whether fatigue was an

issue for brachytherapy patients as this was a relatively new and infrequent treatment in Edinburgh. However it became clear there was a disparity of opinion amongst nurses, radiographers and oncologists as to whether fatigue was significant side effect of radiotherapy. Although most oncologists routinely warned patients about feeling tired, they did not perceive it as a major side effect during or after treatment. In contrast, radiographers thought it was a significant problem during radiotherapy and nurses doing follow up clinics believed it was still an issue for some patients several months afterwards.

This disparity of perception could be because, by their own admission the oncologists seldom asked about fatigue after treatment and concentrated their enquiries on other symptoms such as incontinence and erectile dysfunction. It has also been suggested that patients are more likely to mention fatigue to their nurse because they did not want to bother the doctor with symptoms they felt were inevitable, untreatable, not important enough or because the doctor never raised the issue (Stone *et al.* 2003).

Consequently, I began directly asking patients about fatigue. In accordance with the radiographers and nurses I found many men recalled experiencing fatigue during or after their treatment and a smaller proportion described themselves as currently having persistent fatigue that they attributed to their prostate cancer treatment. It became clear this was an issue deserving of more attention. If we were curing men of their prostate cancer yet leaving them with fatigue that interfered with their lives, then perhaps this was a significant long term treatment related toxicity that (a) they should be informed about and (b) we as clinicians should be aware of, understand better and consequently try to prevent or treat.

2.2.3 Fatigue and prostate cancer treatment: the research prior to October 2003

This research project commenced in October 2003, work published after this date is described in the relevant study discussion sections of this thesis.

2.2.3.1 Studies of fatigue and external beam radiotherapy

When this research project was being designed there were no fully published prospective data on fatigue beyond six weeks after radiotherapy. Interestingly, a cross sectional study of 103 men, a median of 2.1 years post radiotherapy (range 0.5-10 years) found that 18.7% had severe fatigue (Brief Fatigue Inventory 'worst fatigue' > 7). However this sample had mixed stages of disease, the majority had also undergone radical prostatectomy and 29% were on androgen deprivation therapy which may have confounded the findings (Vordermark *et al.* 2002).

Cross sectional studies only give a snapshot of fatigue at a given point of time, so prospective studies are more informative about the trajectory of fatigue after treatment. There are several prospective studies of prostate cancer treatment that report fatigue as part global quality of life measures (Janda *et al.* 2000;Egawa *et al.* 2001;Van Vulpen *et al.* 2002;Staff *et al.* 2003) however only those that have assessed fatigue with a fatigue specific instrument will be reported here.

There have been three published prospective studies that specifically examined fatigue during radiotherapy for prostate cancer. The largest published report studied 36 men with localised (T1 and T2) prostate cancer undergoing 68-70Gy in 34 to 38 fractions. They found a 17% incidence of fatigue (Piper Fatigue Scale > 6) during radiotherapy. The mean fatigue score significantly increased during radiotherapy and was decreasing by five weeks post treatment but not to baseline levels. In addition they assessed haematocrit and depression scores, neither of which changed significantly. The five week follow up is short but one of the longest in the prospective studies published prior to October 2003 (Monga *et al.* 1999).

A study of nine men with T1-2 disease who received 68-70Gy in 34 to 38 fractions, demonstrated an increase in neuromuscular fatigue after eight weeks of radiotherapy. The authors commented that this was independent of cardiovascular and psychological factors though not all subjects completed all the tests. In contrast, the self reported fatigue scores (Piper Fatigue Scale) did not change (Monga *et al.* 1997).

The only study to examine cytokines in relation fatigue and prostate cancer prospectively followed 15 patients (T1-3) who received 67.2Gy in 36 fractions (over eight weeks). They found fatigue measured on a visual analogue scale increased to over the first four weeks, plateaued and then rose again over weeks 6 and 7. There was no follow up post treatment but worthy of note was that IL-1 tended to increase as fatigue did (Greenberg *et al.* 1993).

The largest study sample (n=105) was followed up for eight weeks post radiotherapy but has only been reported in an abstract so far (Geinitz *et al.* 2003). Fatigue was measured using the Fatigue Assessment Questionnaire, EORTC fatigue subscale and a visual analogue scale for fatigue. No values were reported but fatigue increased in most measures during radiotherapy but "returned to almost pre-treatment levels" eight weeks post treatment. However it is not clear what stage of disease these men had and 25% had adjuvant radiotherapy after radical prostatectomy with consequent variable radiation doses for the whole sample (55.9-74Gy). Additionally 76 patients had androgen deprivation therapy which may have confounded the results. Haemoglobin did not significantly change during radiotherapy, nor did CRP. However in a personal communication Geinitz informed me they only tested CRP in 60% of the sample.

Most studies of fatigue have been in mixed cancer groups and the results were collectively reported. However one study that reported fatigue according to tumour site showed only the urogenital cancer group had a significant increase in fatigue after radiotherapy (64 prostate, 7 testis, 22 other genitourinary tract cancers) and the main predictor of fatigue was pre-treatment fatigue (Smets *et al.* 1998a). Another study examined 35 men with a range of different stages of non metastatic prostate

cancer before and after radiotherapy (64Gy over six weeks). All had received androgen deprivation therapy beforehand. As the results were reported together with 34 breast cancer patients so it is not possible to deduce any prostate cancer specific information (Stone *et al.* 2001).

None of the prospective studies of fatigue during radiotherapy have accounted for the effect of neoadjuvant androgen deprivation which is routine treatment in Edinburgh. Low testosterone levels can be associated with fatigue and LHRH analogues can still cause castrate levels of testosterone up to eight months after administration (Oefelein 1998). There is a need to see whether this has a significant influence upon the trajectory of fatigue before and after radiotherapy.

2.2.3.2 Studies of fatigue and brachytherapy

There have been no studies that specifically address fatigue in brachytherapy patients. Little is known about the effect of brachytherapy on quality of life but there is the popular perception that patients experience less impairment than with other treatments even though there are few data to support this (Brandeis *et al.* 2000).

2.2.3.3 Studies of fatigue and androgen deprivation therapy

Anecdotally fatigue is said to be a common side effect of androgen deprivation therapy however there is only one study that has prospectively addressed this (Stone *et al.* 2000a). They followed 62 mixed stage prostate cancer patients over three months and found an increase in six out of eight fatigue measures. They compared these results to their radiotherapy study (Stone *et al.* 2001) and said the increase in fatigue was equivalent. However, disease stage may have confounded these results as some of these men had advanced cancer and were receiving androgen deprivation as their primary long term treatment not as neoadjuvant treatment prior to radiotherapy.

2.2.3.4 Studies comparing fatigue years after different prostate cancer treatments

There have been cross sectional studies comparing quality of life in men several years after different treatments for prostate cancer. However there have been no

studies that compared fatigue using a fatigue specific measurement instrument. Those that did reported fatigue as part of a global quality of life scale also included men who had disease recurrence or were receiving androgen deprivation which may have confounded the fatigue findings (Potosky *et al.* 2000;Bacon *et al.* 2001;Davis *et al.* 2001). There is no information specifically addressing the prevalence of long term fatigue in recurrence free men after different treatments for prostate cancer and whether treatment modality predicts fatigue.

2.2.4 Questions that need to be addressed

In summary, the trajectory of fatigue after radiotherapy is unclear and there is no information about fatigue after brachytherapy. These issues are best addressed with prospective studies. There are some radiotherapy data but follow up is short, disease stages are mixed, sample numbers are small and decrease with attrition, none take into account the possible impact of androgen deprivation therapy prior to radiotherapy or compare to fatigue levels to a non-cancer population. Additionally, very few have looked at the biological correlates of fatigue and prostate cancer beyond haemoglobin and routine biochemistry.

In order to address these shortcomings, there needs to be larger and longer prospective studies of prostate cancer patients receiving radiotherapy or brachytherapy. To reduce potentially confounding variables, patient groups need to be homogenous with regard to disease stage and radiotherapy dose and fractionation. It is important to account for androgen deprivation prior to treatment by measuring testosterone in case this confounds fatigue findings. Due to the lack of information about the mechanisms of fatigue development there is a need to build on previous work and examine possible biological correlates of fatigue such as mediators of the systemic inflammatory response. Additionally it is important to put fatigue experienced by prostate cancer patients in context and compare to a male population of a similar age who do not have cancer.

With the advent of PSA screening after the age of 50, increasingly younger men are being diagnosed with early prostate cancer and treated with curative intent. It is in

these men that treatment related toxicity will have the greatest impact. Currently, there is no information specifically addressing the prevalence and severity of long term fatigue in recurrence free men and whether treatment modality predicts fatigue.

Another clinically relevant situation where information is lacking is the prevalence and severity of fatigue in men on long term androgen deprivation for prostate cancer and whether disease stage influences fatigue.

CHAPTER

3

AIMS

3.1 AIMS

The overall aim of this thesis was to explore fatigue during and after treatment for localised prostate cancer.

In order to do this it was planned to:

(1) Devise an interview based case definition of clinically significant fatigue.

(2) Conduct a prospective observational cohort study that would determine the incidence, associations and predictors (psychological and biological, especially proinflammatory cytokines) of clinically significant fatigue in 200 men over the 12 months after receiving either brachytherapy or radiotherapy for early localised prostate cancer.

In response to preliminary work (Study A) these aims changed slightly and other research opportunities arose. This led to fatigue in men with prostate cancer being examined using a combination of approaches including prospective and cross-sectional studies. In addition, men with more advanced prostate cancer were included in this research project.

The aims were then expanded to examine fatigue and its associations in:

3) Recurrence free prostate cancer survivors who had undergone treatment more than one year ago.

4) Men with hormone controlled prostate cancer

A total, of four studies were conducted and the specific aims and hypotheses will be presented in their respective chapters.

CHAPTER

4

GENERAL METHODS:

MEASUREMENT OF FATIGUE

Chapter 4

List of Sections

4.1 CONTINUOUS FATIGUE MEASUREMENT INSTRUMENTS

Fatigue is a subjective experience and is best assessed by self report. There are a multitude of self report fatigue measurement instruments available but no commonly accepted 'gold standard'. In general they all calculate a continuous numerical fatigue score.

4.1.1 Fatigue scales as part of quality of life measures

Some fatigue measures are subscales of larger measures of quality of life or psychological wellbeing such as the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQc30), the Medical Outcomes Short Form-36 (SF-36) and the Profile of Mood States (POMS). Although these are commonly used, they are not viewed as suitable for in depth study of fatigue as they have a few items and a limited number of possible responses (Stone *et al.* 1998). Fatigue specific instruments are more appropriate in this context.

4.1.2 Fatigue specific measurement instruments

There are many fatigue specific measurement instruments. To cover them all is beyond the scope of this thesis but they are listed in table 4.1 and helpful reviews have been published (Wu & McSweeney 2001;Dittner *et al.* 2004). The number of items in a single instrument range from one to 83. Broadly speaking, measures are classed according to whether they measure fatigue intensity (unidimensional) or attempt to measure different fatigue constructs, such as general/mental/physical/ motivational fatigue as well as its severity (multidimensional). There is however, no agreement amongst researchers about the number of fatigue dimensions (generally ranging from two to five) and there is little evidence regarding how the measurement of these different dimensions adds anything to the identification and/or treatment of fatigue. From the patient's point of view, fatigue becomes a problem when it causes them difficulty in doing the things they want to (i.e. it impairs function). Consequently, it was decided that in order to be clinically relevant the instrument for this project must measure fatigue severity and interference with function, be brief, easy to understand and have relevant questions (face validity). After reviewing the

literature and the fatigue measurement instruments available, the Brief Fatigue Inventory was chosen.

Table 4.1. Fatigue specific measurement instruments that have been used in cancer patients (arranged in alphabetical order of the authors)

Fatigue Scale	Reference
Multidimensional Assessment of Fatigue scale	(Belza *et al.* 1993)
Chalder fatigue scale (also known as the Fatigue Questionnaire or the Fatigue Scale)	(Chalder *et al.* 1993)
Fatigue Assessment Questionnaire	(Glaus 2001)
Schedule Of Fatigue And Anertia	(Hadzi-Pavlovic *et al.* 2000)
Fatigue Symptom Inventory	(Hann *et al.* 1998)
Cancer Related Fatigue Distress Scale	(Holley 2000b)
Fatigue Severity Scale	(Krupp *et al.* 1989)
Lee Fatigue scale, also known as Visual Analogue Scale-Fatigue	(Lee *et al.* 1991)
General Fatigue Scale	(Meek *et al.* 1997)
Brief Fatigue Inventory	(Mendoza *et al.* 1999)
Fatigue Assessment Scale	(Michielsen *et al.* 2003)
Cancer Fatigue Scale	(Okuyama *et al.* 2000)
Piper Fatigue Scale	(Piper *et al.* 1989)
Piper Fatigue Scale (revised)	(Piper *et al.* 1998)
Rhoten Fatigue Scale	(Rhoten D 1982)
Schwarz Fatigue Scale 6 (revised)	(Schwartz & Meek 1999)
Schwarz Cancer Fatigue Scale	(Schwartz 1998)
Fatigue Assessment Instrument	(Schwartz *et al.* 1993)
Multidimensional Fatigue Inventory	(Smets *et al.* 1995)
Multidimensional Fatigue Symptom Inventory	(Stein *et al.* 1998)
Multidimensional Fatigue Symptom Inventory Short Form	(Stein *et al.* 2004)
Checklist Individual Strength	(Vercoulen *et al.* 1994)
Wu Cancer Fatigue Scale	(Wu & McSweeney 2004)

4.1.2.1 The Brief Fatigue Inventory

This is a nine item instrument. It consists of three fatigue severity items relating to the present, usual and worst level of fatigue and six items concerning the interference of fatigue with general activity, mood, walking ability, normal work, relations with other people and enjoyment of life (see figure 4.1). These are scored by the patient on an 11 point scale between 0 ("no fatigue"/"does not interfere") and 10 ("as bad as you can imagine"/"completely interferes"). The global fatigue score is the arithmetic mean of all nine items providing a score between 0-10. These items refer to fatigue in the last 24 hours but since I was interested in longer term fatigue this was adjusted to the last week as suggested by the authors (Mendoza *et al.* 1999).

In addition to using a mean global fatigue score of all nine items, cut offs have been proposed for using just one of the nine items; 'worst fatigue' severity. Based on this, the NCCN recommends anyone scoring more than 3 out of 10 on a screening question should receive further clinical evaluation (NCCN 2006). After evaluating this approach with patients in the Edinburgh Cancer Centre it was clear that 'worst fatigue' severity scores gave a misleadingly high prevalence of fatigue. For example, some patients would answer based on recollection of how they felt after a run. Obviously this severity of fatigue did not interfere with normal functioning which was what I was interested in. Consequently it was decided to apply the cut off of greater than 3 to the global fatigue score (referred to as 'Substantial Global Fatigue' in this thesis). This approach has been used by other authors (Shafqat *et al.* 2005).

Justification of choice of Brief Fatigue Inventory (BFI)

The BFI was chosen in preference to other fatigue scales because of its brevity and the items appeared clinically and culturally relevant to the sample population being studied (good face validity). The authors report that the BFI is internally consistent with a Cronbach alpha coefficient of 0.96. It has a high correlation with the longer Functional Assessment of Cancer Therapy-Fatigue (FACT-F) and also the POMS fatigue scale (Cleeland & Wang 1999). In addition the authors claim that the simple wording makes it easy to understand enabling its use with anyone who was educationally disadvantaged.

Figure 4.1 The Brief Fatigue Inventory

	Yes	No
Throughout our lives most of us have times when we feel tired or fatigued. Have you felt unusually tired or fatigued in the last week?	☐	☐

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your fatigue right NOW

0 1 2 3 4 5 6 7 8 9 10

No fatigue — as bad as you can imagine

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your USUAL level of fatigue during the past week

0 1 2 3 4 5 6 7 8 9 10

No fatigue — as bad as you can imagine

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past week

0 1 2 3 4 5 6 7 8 9 10

No fatigue — as bad as you can imagine

Circle the one number that describes how, during the past week, fatigue has interfered with your

A. General Activity

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — completely interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — completely interferes

D. Normal work (includes both work outside the home and daily chores)

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — completely interferes

E. Relations with other people

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — completely interferes

F. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10

Does not interfere — completely interferes

4.2 INTERVIEW DEFINED CASE DEFINITION OF CLINICALLY SIGNIFICANT FATIGUE

The main issue hampering fatigue research is the lack of a commonly accepted measurement tool. The use of different instruments makes it difficult to compare studies and make an accurate estimate of prevalence. In addition, from a clinical perspective it is not clear at what point along these continuous scale measures that fatigue becomes abnormal or worthy of further assessment or intervention i.e. the individual becomes a 'case' of clinically significant fatigue. Typically a cancer patient need only say they are experiencing fatigue to be considered as having cancer related fatigue, therefore current prevalence estimates may be high and misleading. Although fatigue questionnaires enable quantitative assessment of a subjective phenomenon, in clinical practice, they can not be a substitute for talking to patients.

4.2.1 Why we need to define a case of clinically significant fatigue

Although there is an understandable desire amongst researchers and clinicians to move ahead to treatment of fatigue, we have to have an agreed way of assessing fatigue in the first place. Applying a case definition of clinically significant fatigue would provide a homogenous population for research. This would enable a more accurate prevalence estimation of fatigue that is deserving of extra clinical attention. Once this case definition is established, it could become a clinical definition which would have utility for treatment.

4.2.2 Requirements of a case definition

Generally, a 'case' is something that is statistically abnormal and a problem meriting treatment. An analogy would be blood pressure, we all have it, but when it is abnormal and a problem, or likely to cause problems in the future, we treat it. Any case definition is a construction (as is a disease diagnosis) and can be based on validity or utility (Kendell & Jablensky 2003). Validity assumes a natural boundary between conditions (such as a histological distinction between bone and muscle tissue), whereas the point at which the decision is made as to when fatigue is normal/ abnormal is arbitrary and cut-offs are therefore not valid. As validity is not yet possible with fatigue, any case definition needs to be based on utility instead. A

diagnostic construct has utility when it provides non trivial information about prognosis, likely treatment outcomes, and/or testable propositions about biological or social correlates. As fatigue research is in its early stages, only the latter is currently applicable.

A case definition of clinically significant fatigue needs to:

(1) Be easy to apply

(2) Make practical sense to clinicians

(3) Describe a level of fatigue that both clinicians and patients would agree merits attention i.e. is clinically significant

(4) Be reliable

4.2.3 What is offered so far in cancer and other areas

The NCCN definition of cancer related fatigue (see section 1.1.1), though clinically relevant does not help identify individuals who should be considered to represent a 'case' of clinically significant fatigue. Nor do the continuous scale measures described earlier. In the past, the assessment of depression raised similar issues and in addition to measuring depressive symptomatology along a continuum, diagnostic criteria were proposed for a clinical syndrome of Major Depression (American Psychiatry Association 1994). Based on that model, valuable initial work by Cella et al, proposed diagnostic criteria for a clinical syndrome of cancer related fatigue for the International Classification of Diseases 10th Revision (ICD-10) (Cella *et al.* 1998) (see Appendix 1). This is a welcome step forward because they include the DSM IV (Diagnostic and Statistical Manual of Mental Disorders Fourth Edition) definition of clinical significance and they have made an attempt at attributing aetiology by labelling the syndrome as Cancer Related Fatigue.

At the time of embarking on this project there were only two published preliminary studies using this method: a telephone survey of 379 cancer survivors found the prevalence of cancer related fatigue to be 17% but they were only able to apply criteria A and B (Cella *et al.* 2001); and although another study of 51 blood/bone marrow transplant recipients appeared to apply all criteria, it was not reported how

they assessed criterion D, having a comorbid psychiatric disorder (Sadler *et al.* 2002). In my own experience of applying these criteria I found them to be unwieldy and time consuming. The latter has since been confirmed by other authors who reported the structured clinical interview for DSM-IV, Axis 1 (SCID) used for generating psychiatric diagnoses alone took 45 minutes (for criterion D) (Murphy *et al.* 2006) . In addition, when applying these criteria a number of other issues arise which are described below.

4.2.3.1 Using other symptoms to define a symptom; the overlap with depression

Fatigue is a symptom associated with cancer. Defining cancer related fatigue as a syndrome (a collection of symptoms) is not necessarily a step forward. In fact using other symptoms to describe a symptom is of limited use and may be overly complicated, especially when a proportion of symptoms overlap with the syndrome of Depressive Disorder (fatigue, diminished concentration, low motivation, sleep disturbance and emotional reactivity) (American Psychiatry Association 1994). Some argue that fatigue is a subset of depression, not a diagnostic entity within itself (Reuter & Harter 2004). Others have commented that due to overlap of symptoms between syndromes, the criteria may be useful to diagnose a subset of patients who have both fatigue and depression and consequently identify those whose fatigue may respond to antidepressant medication (Jacobsen *et al.* 2003;Wagner & Cella 2004).

4.2.3.2 Who judges whether fatigue is clinically significant?

The patient, main carer or clinician? Fatigue is subjective, so it should be best judged by the patient. Most patients and clinicians would agree when fatigue is severe, but symptoms must be considered in terms of the patient's own expected functional and activity levels (Monks 1989). For example a keen amateur golf player on chemotherapy who, because of fatigue can now only play nine holes of golf rather than 18 may view that as significant impairment of their functioning and quality of life because they can no longer participate in competitions. Whereas the clinician may only judge it significant if the patient did not have the energy to walk on the golf course at all. In addition, many cancer patients are retired and even if they

experience new difficulty in doing daily tasks due to fatigue (which the clinician would view as significant) they feel able to put off doing things until the next day because they have the time. A younger patient who is employed, or looking after children may find the same level of fatigue a very significant problem. If all these scenarios were counted as cases it may give misleading impression of prevalence. On the other hand, not to include them all disregards the patient's perspective, which after all is what we are aiming to measure. A symptom, by definition is subjective and only the patients knows how it feels, and how it affects them

4.2.3.3 Premature attribution of fatigue to cancer

There is a tendency in medicine for disease specialists to appropriate fatigue as a disease specific entity. (Paterson *et al.* 2003;Reuter & Harter 2004). Consequently those in the field of oncology tend to regard the cause of fatigue as being cancer or its treatment. Attributing cause is inherently difficult and perhaps premature. Just because a patient has cancer we can not assume that it is the cause. Confusion arises when taking into account fatigue that has been present before the cancer diagnosis. For example the patient who had fatigue associated with rheumatoid arthritis before they were incidentally diagnosed with a small early stage bladder cancer (which most oncologists would not expect to be biological cause of fatigue). Would she get classed as a case of cancer related fatigue just because she has a cancer diagnosis? If she had metastatic liver disease, would we label that as the cause of her fatigue rather than her rheumatoid arthritis?

In addition, there is so far, little evidence to support the notion that fatigue experienced in cancer is fundamentally different to that experienced in any other chronic illness (though the precipitating factors and associations may be different). Patterson reviewed 35 qualitative studies of fatigue in chronic illness including cancer and noted there are very few qualitative studies comparing the fatigue experience across different disease diagnoses (Paterson *et al.* 2003). One exception compared the fatigue experience of nine cancer patients on chemotherapy to six patients with Chronic Obstructive Pulmonary Disease. They found both groups had a similar fatigue experience. (Ream & Richardson 1997).

Labelling fatigue as 'cancer related fatigue' does not tell us any more about cause or treatment approaches. In the clinical situation one accepts that clinical aetiological judgements are necessary but in the first instance, for research purposes, progress is more likely if associations are first described rather than judged. A clearer, simpler approach would be to use the term, 'clinically significant fatigue', meaning fatigue that interferes with normal functioning, whatever the assumed cause(s).

4.2.4 Proposed case definition of clinically significant fatigue

Measuring the effect of fatigue on activities is more sensitive than simply asking patients to rate their fatigue (Canadian Multiple Sclerosis Research Group 1987). Fatigue becomes a problem to patients when it causes them difficulty doing what they want or need to do. The proposed case definition of clinically significant fatigue is presented in figure 4.3 and a semi- structured interview in figure 4.4. The diagnosis should arise from consensus between the clinician and the patient.

4.2.4.1 Inter-rater and test-retest reliability

Initially, all the interviews were conducted by me (DS). Later, Morven Shipway (MS), an experienced cancer nurse was employed part time between March 2005 and February 2006. She was trained how to conduct the interview and to apply the case definition of clinically significant fatigue. In order to broadly assess inter-rater reliability a convenience sample of 20 cancer inpatients and day case chemotherapy patients were interviewed. Either DS or MS conducted the interview while the other observed. Both circled their answers on the interview sheet and the answers were later compared. There was good inter-rater reliability for the overall rating of CSF (kappa 0.90). For items 1, 2, 3a, 3b, 3c, respectively kappa was 1.0, 0.80, 0.80, .0.90, 0.86. To assess test-retest reliability 10 patients were then interviewed again by the same interviewer three days later either in person or by telephone if the patient was no longer in hospital. There was 90% (9/10) agreement between the first and second interview.

Figure 4.3 Proposed case definition of Clinically Significant Fatigue (CSF)

1) An unpleasant, subjective sense of fatigue/ tiredness/ lack of energy/weariness
2) Present every day or nearly every day (for at least 2 weeks)
3) Causing difficulty in usual functioning (daily tasks or social/occupational activities) attributed to feeling fatigued

All 3 points must be present to be a case

Figure 4.4 Semi-structured interview questions to determine a case of clinically significant fatigue (CSF)

1) In the last month have you felt fatigued/lack of energy/ weariness/tiredness or a need to rest..... **Yes** **No**

If NO stop here

2) How often have you felt like that?
(every day or nearly every day?).....**Yes** **No**

3) a) Does fatigue cause you difficulties in doing things you want or need to do?..... **Yes** **No**
(can you give me an example?)
b) Do you put off doing things because you feel fatigued? ... **Yes** **No**
(can you give me an example?)
c) Do you avoid doing things in case you become fatigued?....**Yes** **No**
(can you give me an example?)

Case of CSF = 1 **and** 2 **and** 3a **or** 3b **or** 3c.....**Yes** **No**

Note
Latterly, question 1 and 2 were amalgamated to " over the past month, has there been at least a 2 week period when you have had significant fatigue, a lack of energy or a need to rest every day or nearly every day" based on (Sadler *et al.* 2002). If the answer was no, the interview stopped there.

CHAPTER

5

GENERAL METHODS:

OTHER MEASURES

Chapter 5

List of Sections

The four studies presented in this thesis had several methods in common. To prevent repetition they are described here and unless otherwise stated apply to all. The different study designs, patient samples and other study specific measures are presented in their respective chapters.

5.1 DEMOGRAPHIC DATA COLLECTED

5.1.1 Scottish Index of Multiple Deprivation (SIMD 2004).

SIMD scores are derived from the patient's postcode and transformed into population-weighted quintiles (1 = least deprived; 5 = most deprived). SIMD scores arise from data derived from the most recent population census including current income, employment, health, education, skills, training, geographic access, telecommunications and housing. http://www.scotland.gov.uk/stats/simd2004/. This data was collected as there is conflicting evidence as to whether fatigue is associated with social deprivation.

5.1.2 Date of birth and age

Obtained from the medical notes

5.2 CLINICAL DATA COLLECTED

5.2.1 Prostate cancer T (tumour) stage

See section 2.1.2. This data was collected from the medical notes or Urology computer databases.

5.2.2 Prostate cancer Gleason score

See section 2.1.3. This data was collected from the medical notes or Urology computer databases.

5.2.3 Charlson Comorbidity Index

The presence of other medical comorbidities may influence fatigue scores. This is a commonly used, well validated measure of comorbidity in oncology patients (Charlson *et al.* 1987). Each comorbid medical condition is allotted a score (1-6) with the total score ranging from 0 to 37. Higher scores indicate more comorbidity. This information was collected from a combination of reviewing the patient's hospital medical notes and interviewing the patient. This measure was used in studies A and B only (see Appendix 2).

5.2.4 Karnofsky Performance Status Scale

This is an 11 point rating scale which ranges from 100 (normal functioning downwards in decrements of 10 to 0 (dead) (Yates *et al.* 1980). It is completed by the observing clinician. This scale is among the most widely used scales for measuring functional ability in cancer patients. This was used in studies A and B (see Appendix 3) only as studies C and D were postal surveys.

5.3 BIOLOGICAL MEASURES (Studies A and B only)

Blood samples were tested by the Haematology and Biochemistry laboratories at the Western General Hospital, Edinburgh using standard techniques (full blood count, urea, electrolytes, albumin, C-reactive protein (CRP), testosterone and prostate specific antigen). Additional serum samples for cytokine analysis were immediately put on ice and centrifuged for 10 minutes at 1000rpm at 4 Celsius. One millilitre aliquots of supernatant were then put into plastic cryotubes and stored at minus 70 Celsius.

5.3.1 Sensitive CRP testing

Those samples that were beyond the lower limit of the standard CRP assay (<3mg/L) at the Western General Hospital, Edinburgh were tested by experienced staff at Glasgow Royal Infirmary Biochemistry Laboratory using a Roche CRP Latex high sensitivity assay on an Hitachi 917 analyser.

5.3.2 Interleukin-6 Enzyme Linked Immunosorbent Assays (IL-6 ELISAs)

Under the supervision of Rhona Aird, Senior Scientific Officer at the University of Edinburgh Cancer Research Centre the IL-6 assays were performed by myself using Quantikine High Sensitivity Human IL-6 ELISA Kits from R&D Systems Europe Ltd, 19 Barton Lane, Abingdon, OX14 3NB. Catalogue Number HS600B.

5.4 SELF REPORT MEASURES

These were in addition to the Brief Fatigue Inventory described in section 4.1.2.1. See Appendices 4, 5 and 6 for copies of the questionnaires.

5.4.1 Hospital Anxiety and Depression Scale (HADS)

Fatigue and depression often coexist and it was important to measure both symptoms. The HADS is a self rated 14 item screening tool with two separate seven item scales for anxiety and depression (Zigmond & Snaith 1983). Each item can be answered on a four point scale (0-3) generating a total between 0 and 21 on each subscale. Higher scores represent more severe symptoms. Patients were asked to report symptoms over the previous week.

To enable comparisons with other published literature, the mean and median continuous scores were calculated. For studies C and D when clinical interview was not possible data were also presented as the proportions with likely clinically significant levels of depression and anxiety according to recommended cut-off scores: 9 or more on the anxiety subscale; 8 or more on the depression subscale (Bjelland *et al.* 2002).

5.4.2 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire core 30 Version 3.0 (EORTC QLQ c30)

This is the most widely used quality of life scale in European cancer patient studies (Aaronson *et al.* 1993). It has 30 items consisting of five functional domains (physical, role, emotional, cognitive and social functioning), three symptom scales

(pain, fatigue, nausea and vomiting) and a number of single items (dyspnoea, loss of appetite, insomnia, constipation, diarrhoea and financial difficulties). Each item relates to the past week and is answered on a four point scale (1-4) ; not at all, a little, quite a bit, very much. The two items relating to overall health and quality of life are rated on a seven point scale (1-7). In accordance with the scoring manual, scores are then transformed to a 0-100 scale; higher scores represent a better level of functioning or a worse level of symptoms depending on the parameter measured (Fayers *et al.* 2001) .

5.4.3 Likert scales for erectile function and how much of a problem it is

Clinicians were interested in the prevalence of erectile dysfunction. These two scales are routinely used at the Edinburgh Cancer Centre and relate to the past month. The response to the question, "Did you get erections" was rated on a four point scale (0 to 3 respectively): "No, erection not possible", "Yes, with severely reduced stiffness", "Yes, with reduced stiffness" and "Yes, with normal stiffness". The second item asked, "How much of a problem was this for you" and again was scored 0 to 3 respectively: "not a problem", "quite a problem", "a bit of a problem" and "a serious problem". Lower scores represented worse function and more severe problem respectively.

5.4.4 International Prostate Symptom Score (IPSS)

Fatigue may have been confounded by urinary symptoms so it was important to measure these. The IPSS is a seven item scale rated on six points (0-5) to assess urinary symptoms (Barry *et al.* 1992). It gives a score 0-35 with a higher score representing worse symptoms. Mean scores were calculated and the proportion with moderate to severe urinary symptoms were presented (IPSS > 7) (Fossa *et al.* 1997).

5.5 CLINICAL INTERVIEW MEASURES (Studies A and B only)

In addition to the semi structured clinical interview for clinically significant fatigue described in section 4.2.4, the following measures were also applied (see Appendices 7 and 8).

5.5.1 Structured Clinical Interview for DSM IV - Major depression section (DSM –IV Axis I Disorders)

This structured psychiatric interview ascertains the presence of the symptoms of Major Depressive Disorder (MDD) (First *et al.* 1996). If five or more symptoms from a list of nine symptoms, at least one of which must be depressed mood or anhedonia, have been present for two or more weeks the diagnosis of MDD is made. In making the diagnosis of MDD, all identified symptoms were counted without making a judgement about whether they should be attributed to cancer or to depression. This 'inclusive approach' is the most widely used and was chosen to maximise the sensitivity and inter-rater reliability of diagnoses (Koenig *et al.* 1997).

5.5.2 Modified physical activity score

Physical activity was graded for each day of the last week (Morris *et al.* 1973). Scores were between 0 (minimal activity) and 4 (very heavy activity). The overall activity score was the arithmetic mean of all seven days.

CHAPTER

6

STUDY A

FATIGUE IN MEN UNDERGOING TREATMENT FOR LOCALISED PROSTATE CANCER:

A PILOT PROSPECTIVE OBSERVATIONAL COHORT STUDY

Chapter 6

List of Sections

6.1 INTRODUCTION

The background to this study has been covered in Chapters 1 and 2. To summarise: prostate cancer is the most common male cancer and survival for patients with early localised disease is often beyond 10 years. There is no definitive data with regards to which treatment gives the best long term survival and so decisions are often made on the basis of likely side effects such as incontinence, erectile dysfunction and bowel disturbance. Patients frequently complain of fatigue during radiotherapy and there is the clinical impression that this persists in a proportion of patients. A small number of radiotherapy studies have been published prior to October 2003 but the trajectory of fatigue remains unclear, follow up is short (maximum six weeks), disease stages are mixed, sample numbers are small and decrease with attrition. None take into account the possible impact of androgen deprivation therapy prior to radiotherapy or put fatigue levels in context by comparing to a male non-cancer population. Commonly fatigue severity has been reported as a continuous fatigue score rather than the prevalence of fatigue that is of a clinically relevant severity. Additionally, very few have looked at the biological correlates of fatigue and prostate cancer beyond haemoglobin and routine biochemistry. There are no published data regarding fatigue and brachytherapy.

There is consequently a need for larger and longer prospective studies that will determine the incidence of clinically significant fatigue (CSF) in patients receiving different treatment regimens. A prospective observational cohort study was therefore planned to examine the incidence, associations and predictors of CSF in approximately 200 men with localised prostate cancer receiving either radiotherapy or brachytherapy. The available numbers would have allowed 80% power to detect a 20% difference between regimens in the incidence of cases of CSF (presumed clinically relevant as there were no data available to guide sample sizes). It was also planned to recruit a non-cancer comparison group of men of a similar age.

Prior to embarking on a large study, it was necessary to evaluate the feasibility of recruitment, the patient questionnaire and clinical interview for CSF. It was also

important to gain information about whether the study design was appropriate and preliminary indications of what results might be obtained.

6.2 AIMS

(a) To assess likely patient recruitment and attrition

(b) With a view to conducting a larger study of brachytherapy and radiotherapy patients

  (i) Assess the incidence of cases of CSF to aid future sample size calculations

  (ii) Assess whether the three months of neo-adjuvant androgen deprivation prior to radiotherapy should be included in the longitudinal assessments

(c) Gain preliminary evidence of associations of cases of CSF and continuous fatigue scores

(d) Gain preliminary evidence of which biological measures, particularly inflammatory markers and cytokines changed most with treatment

(e) Pilot the self report patient questionnaire package

(f) Pilot the clinical interview for identifying cases of CSF

6.3 PROPOSED METHODS

6.3.1 Design

This was a pilot prospective observational cohort study of fatigue in men undergoing treatment for localised prostate cancer compared to a non-cancer comparison group.

6.3.2 Patient Samples

6.3.2.1 Prostate cancer group sample

A consecutive sample of 45 men with localised prostate cancer was recruited at the Edinburgh Cancer Centre. All were planned to receive either brachytherapy or external beam radiotherapy in the near future, or after three months of neo-adjuvant androgen deprivation therapy. For full treatment details see section 2.1.4.1.

There were three treatment groups:

(a) Brachytherapy (15 patients)

Patients had radioactive iodine (I^{125}) seeds inserted into the prostate under general anaesthetic. These remained permanently in situ and a minimum dose of 145Gy was received over several months. Brachytherapy patients did not routinely receive neo-adjuvant androgen deprivation.

(b) External beam radiotherapy (15 patients)

Patients received a dose of 55Gy over 20 fractions (one month, Monday to Friday).

(c) Neo-adjuvant androgen deprivation therapy (15 patients)

Patients received three weeks of biclutamide (Casodex) 50mg daily followed by monthly injections of LHRH analogue Goseralin (Zoladex) 3.6mg (for three months only) prior to receiving radiotherapy.

Justification of prostate cancer patient sample

It is routine practice at the Edinburgh Cancer Centre for patients to receive three months of neo-adjuvant androgen deprivation therapy prior to radiotherapy. Androgen deprivation therapy has been noted to be associated with fatigue (Stone *et*

al. 2000a) but of the few studies that have examined fatigue prospectively during radiotherapy, none have included the neo-adjuvant stage of androgen deprivation. In order to assess the impact of this on fatigue and to inform the recruitment and assessment strategy for future studies, it was decided to include a third group of men who were starting androgen deprivation therapy prior to radiotherapy.

Patients were not eligible if they had high risk tumours (Stage T3 or Gleason score 8 or above) or were planned to continue with adjuvant androgen deprivation after radiotherapy (normally for two years). In preparation for future studies, this was to eliminate the possible confounding factor of prolonged hypogonadism causing fatigue in addition to the radiotherapy. To eliminate any other major confounding factors that are recognised to be associated with fatigue, patients were not eligible if they had another known concurrent cancer diagnosis; anaemia; renal, hepatic or untreated thyroid dysfunction.

Inclusion criteria

(a) Due to receive brachytherapy or radical external beam radiotherapy

(b) Early localised prostate cancer (clinical rectal examination T1 or T2 or early radiological T3)

(c) Able to give informed consent

Exclusion criteria

(a) Planned to continue with androgen deprivation after radiotherapy

(b) Clinically T3 on rectal examination

(c) Gleason 8 and above

(d) Another concurrent cancer diagnosis

(e) Haemoglobin less than 100g/l

(f) Untreated thyroid dysfunction

(g) Serum creatinine more than twice the upper limit of normal

(h) Liver function tests more than twice the upper limit of normal

(i) Unable to communicate adequately because of language problems or cognitive impairment

6.3.2.2 Non cancer comparison group sample

Justification of non cancer comparison group sample

Fatigue can often be a symptom which many attribute to 'getting older'. In addition, some men with prostate cancer experience nocturia which could contribute to disrupted sleep and possible consequent fatigue. In order to assess whether the severity of fatigue experienced by men with localised prostate cancer was different to men of a similar age with urinary symptoms it was decided to recruit a sample of 15 men with benign prostatic hypertrophy. These men were consecutively recruited at the Nurse Urology Clinic at the Western General Hospital, Edinburgh.

Inclusion criteria

(a) Ambulatory patients attending the Nurse Urology Clinic with urinary symptoms attributed to benign prostatic hypertrophy

(b) Within the age range of the prostate cancer patients

Exclusion criteria

(a) A current diagnosis of cancer

(b) Haemoglobin less than 100g/l

(c) Untreated thyroid dysfunction

(d) Serum creatinine more than twice the upper limit of normal

(e) Liver function tests more than twice the upper limit of normal

(f) Unable to communicate adequately because of language problems or cognitive impairment

(g) Concurrent chronic disease in which fatigue is recognised to be a prominent symptom (e.g. multiple sclerosis or severe chronic obstructive airways disease)

6.3.3 Patient recruitment

Patients were recruited between February and May 2004. A record was kept of those who declined entry into the study along with their reason for doing so if this information was volunteered.

Prostate cancer sample recruitment

Potentially eligible patients planned to receive neo-adjuvant androgen deprivation, radiotherapy or brachytherapy were identified at the Urology Clinic, Oncology Clinic and 'Rad Diary' (a computer based appointment system for radiotherapy). They were introduced to the study and given a patient information sheet by their doctor or clinical nurse specialist. If the patient agreed to be contacted, they were telephoned at home by the researcher or seen the next time they were due in hospital. This was to give them the opportunity to ask any questions about the study and if they chose to participate, to obtain informed written consent.

Non cancer comparison sample recruitment

These men were identified in the Nurse Urology Clinic and introduced to the study by their clinic nurse. As they did not routinely return to hospital for several months, they were given a patient information sheet, questionnaire and consent form to take home. With their agreement they were telephoned at home by the researcher to give them the opportunity to ask any questions about the study. If they agreed to participate they were asked to return the signed consent form and questionnaire in the post. Once these were received, the patient was telephoned at a time convenient to them to conduct the clinical interview.

6.3.4 Assessments

6.3.4.1 Baseline data collected

Demographic data

- Date of birth
- Postcode, to assess Scottish Index of Multiple Deprivation (SIMD), see section 5.1.1
- Marital status
- Employment status

Clinical Data

- T stage (prostate cancer patients only), see section 2.1.2.
- Gleason score (prostate cancer patients only), see section 2.1.3.
- Charlson Comorbidity Index, see section 5.2.3

6.3.4.2 Content of each assessment

Self rated questionnaire measures

- The Brief Fatigue Inventory (BFI), see section 4.1.2.1
- Hospital Anxiety and Depression Scale (HADS), see section 5.4.1
- European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire core 30 version 3.0 (EORTC QLQc30), see section 5.4.2
- Likert scales for erectile function and how much of a problem this is, see section 5.4.3
- International Prostate Symptom Score (IPSS), see section 5.4.4
- Sleep quality over the last week. Scores 0-20 with higher scores indicating worse quality sleep (Jenkins *et al.* 1988).

Interview measures

- Semi structured interview for clinically significant fatigue (CSF), see section 4.2.4
- Structured clinical interview for DSM IV (SCID) - Major depression section, see section 5.5.1
- Modified activity score, see section 5.5.2

The interviews were performed by me and tape recorded for quality control.

Clinical and biomedical measures

- Body Mass Index
- Concurrent medications were noted
- Karnofsky Performance Status, see section 5.2.4
- blood samples (full blood count, urea and electrolytes, albumin, testosterone, and markers of systemic inflammatory response: C-reactive protein (CRP) and interleukin-6 (IL-6), IL-1receptor antagonist (IL-1ra) and sgp130 (cell membrane receptor for IL-6). For analysis methods see section 5.3.

Justification of markers of systemic inflammatory response

The main mediators of CRP production are IL-6, IL-1 and their receptors. I was advised by Dr Donny McMillan, University of Glasgow, to measure CRP first and then depending on the results proceed to test the stored samples for the other cytokines and their receptors.

6.3.4.3 Assessment Intervals

The radiotherapy and brachytherapy groups were assessed three times: baseline (pre-treatment), one and three months after initial treatment. This was planned to coincide with anticipated maximum fatigue and routine hospital follow up visits in order to keep the study burden on the patients to a minimum.

The androgen deprivation group was assessed at baseline and at three months. The one month assessment was not performed, as these men did not return to hospital as part of their routine care.

The non cancer comparison group were assessed once only.

6.3.5 Ethical Approval

The study was approved by the Local Research Ethics Committee. Reference number LREC/2003/8/52.

6.3.6 Statistical Analysis

Data was inspected using histograms and scatter plots. Baseline categorical variables were described as percentages; continuous variables as means and standard deviations. The characteristics of the four groups at baseline were compared using Kruskal Wallis tests, one way analysis of variance (ANOVA) or Chi-squared tests as appropriate.

Within each treatment group the proportion of cases of CSF at baseline was compared to one and three months after initial treatment using McNemar's tests; mean global fatigue scores were compared using Wilcoxon Signed Ranks tests. The

proportion of cases of CSF in each treatment group at baseline, one and three months was compared to the non-cancer comparison group using Chi-squared tests; mean treatment group global fatigue scores were compared using Mann Whitney tests.

To explore the change in cases of CSF between treatment groups whilst adjusting for any minor differences in baseline prevalence, the number of new cases of CSF between baseline and one/three months was calculated for each group. These were then compared using Chi-squared tests. A similar approach was used for fatigue scores where the mean difference (change) in fatigue scores between baseline and one/three months was calculated and compared using Student t-tests and one way analysis of variance (ANOVA) as appropriate.

Associations of cases of CSF at one month were explored using Chi-squared tests for categorical variables and Student t-tests for the mean changes in continuous variables between baseline and one month. Pearson product-moment correlation was used for associations between mean changes in fatigue scores and mean changes in other variables between baseline and one/three months. HADS depression question 8 "I feel as if I am slowed down" may be construed as referring to fatigue. Hence associations with depression were performed both including and excluding this item. This approach has been previously reported (Stone *et al.* 2000a).

Analyses were performed using SPSS version 12.0 computer software. Pearson Chi-square test was used for nominal factors, Chi-square test for trend (linear-by-linear association) was used for ordinal factors and Chi-squared with Yates correction (continuity correction) was used for 2x2 tables. No correction for multiple testing was made as these were mainly exploratory and hypotheses generating analyses. A p value of <0.05 was regarded as statistically significant. This pilot study was designed to assess feasibility/methodology, and had limited power (could detect approximately 50% difference in proportions). I was advised by Dr Rob Elton, PhD and Honorary Fellow, University of Edinburgh.

6.4 RESULTS

6.4.1 Recruitment And Attrition

Over three months 49 consecutive men with prostate cancer were eligible for the study and 45 (92%) agreed to participate (15 in each group). Of the four patients who declined, two said they "had too much going on", one patient was concerned it would cause delay with his clinic transport and one patient declined, giving no reason but it was suspected he may have had literacy difficulties that he did not wish to disclose. All 15 non-cancer comparison group subjects invited to participate agreed to do so. The study took eight months to complete and only one of the 45 patients was lost to follow up when he moved abroad i.e. 98% complete data.

6.4.2 Baseline Characteristics

At baseline the four groups (brachytherapy, radiotherapy, androgen deprivation and non-cancer comparison group) were similar for all clinical, self report and biomedical measures. The only statistically significant differences were (a) a smaller proportion of the brachytherapy group had moderate to severe urinary symptoms (13% vs. 47%, 60% and 60% respectively p=0.032. This is not surprising as men with significant urinary symptoms are excluded from receiving brachytherapy as there is a risk they will develop post-operative urinary retention) (b) serum testosterone was lower in the radiotherapy group. Again this was expected as they had already undergone neo-adjuvant androgen deprivation therapy. One man in the androgen deprivation group was diagnosed as having Major Depressive Disorder. Other group characteristics are shown in table 6.2.

Table 6.2 Baseline Clinical Characteristics of patients (p<0.05 in bold)

	Treatment Group				
	Brachy-therapy	Radio-therapy	Androgen Deprivation	Non-cancer	
	n=15	n=15	n=15	n=15	
	% (n)	% (n)	% (n)	% (n)	*p value*
Gleason score					*0.345*
5	**0** 0	**0** 0	**7** 1	**na** na	
6	**73** 11	**53** 8	**47** 7	**na** na	
7	**27** 4	**47** 7	**40** 6	**na** na	
8	**0** 0	**0** 0	**7** 1	**na** na	
Tumour stage					*0.063*
1	**80** 12	**40** 6	**40** 6	**na** na	
2	**20** 3	**47** 7	**60** 9	**na** na	
3	**0** 0	**13** 2	**0** 0	**na** na	
Karnofsky Performance Status					*0.466*
100	**87** 13	**47** 7	**60** 9	**67** 10	
90	**13** 2	**20** 3	**40** 6	**20** 3	
80	**0** 0	**27** 4	**0** 0	**7** 1	
70	**0** 0	**7** 1	**0** 0	**7** 1	
Comorbidity index					*0.252*
0	**80** 12	**47** 7	**60** 9	**40** 6	
1	**7** 1	**33** 5	**33** 5	**47** 7	
2	**13** 2	**13** 2	**7** 1	**7** 1	
3	**0** 0	**7** 1	**0** 0	**7** 1	
Living with spouse	**80** 12	**66** 10	**66** 10	**66** 10	*0.813**
Living Alone	**20** 3	**33** 5	**33** 5	**33** 5	
Mean age in years (SD)	**62.2** (6.3)	**65.5** (4.9)	**65.5** (7)	**67.9** (6.3)	*0.101†*
Mean body mass index (SD)	**27.6** (3.1)	**27.6** (5)	**25.9** (4.1)	**27.8** (3.5)	*0.581†*
Mean activity score (SD)	**1.9** (0.7)	**1.8** (0.4)	**1.8** (0.4)	**2.2** (0.6)	*0.267†*

Not all percentages may add up to 100 as some have been rounded to the nearest whole number. All comparative tests are Chi-squared tests for trend except * Pearson Chi-squared and † ANOVA. SD = standard deviation. na=not applicable

Fatigue results are first presented as cases of CSF then, to enable comparison with published literature, continuous global fatigue scores are also presented.

6.4.3 CASES OF CLINICALLY SIGNIFICANT FATIGUE (CSF)

6.4.3.1 Incidence of cases of CSF after treatment (See figure 6.1)

6.4.3.1.1 Within treatment group comparisons

Brachytherapy

Cases of CSF significantly increased from 0% (0/15) at baseline to 43% (6/14) at one month (p= 0.03). By three months there were still 14% cases (3/14) though this was not statistically different to baseline.

Radiotherapy

Cases of CSF increased from 27% (4/15) at baseline to 46% (7/15) at the end of radiotherapy (one month) and then decreased to 20% (3/15) by three months after radiotherapy had started. None of these changes from baseline achieved statistical significance.

Androgen Deprivation

Cases of CSF decreased from 20% (3/15) at baseline to 13% (2/15) after three months of treatment. This change was not statistically significant.

6.4.3.1.2 Between treatment group comparisons

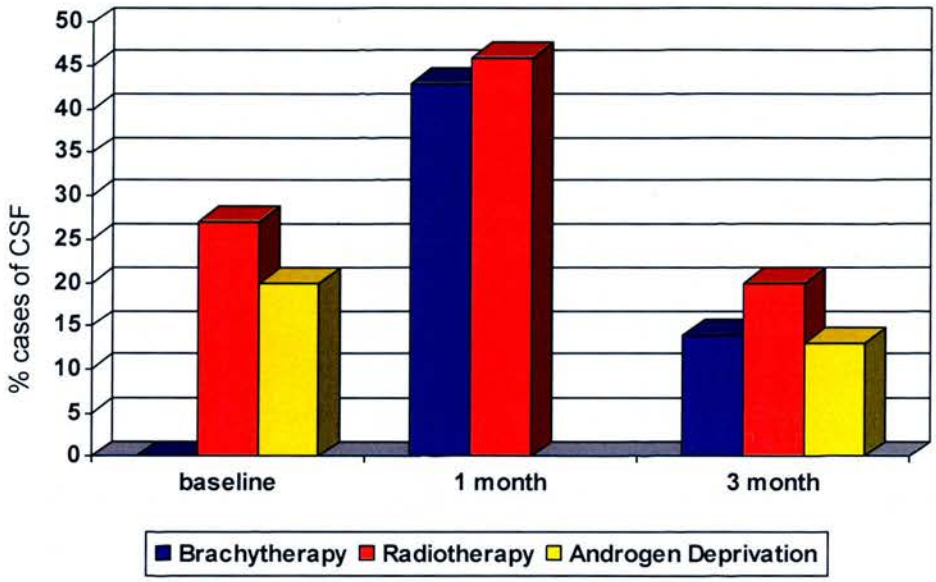
In the non-cancer group, 7% (1/15) were cases of CSF. This was not statistically different to baseline cases of CSF in any of the treatment groups. By one month the proportion of cases of CSF in both the brachytherapy and radiotherapy groups was much larger than the non-cancer group (43% and 46% vs. 7% respectively, both p=0.035) There was a greater incidence of cases between baseline and one month for the brachytherapy group (43%) than the radiotherapy group (19%) but this did not achieve statistical significance (p= 0.18). Between baseline and three months, none of the changes in the proportion of cases between treatment groups were substantially different.

Comment

These comparisons were exploratory and the study was not powered to detect differences between treatment groups as the primary purpose was to assess feasibility. The absence of a statistically significant difference does not mean there is not one.

Figure 6.1. Proportions of cases of clinically significant fatigue (CSF) at baseline, one and three months

6.4.4



Note the androgen deprivation group were assessed at baseline and 3 months only.
Non cancer comparison group cases of CSF = 7%

6.4.4.1 Associations of cases of CSF after treatment

There were no significant differences between the brachytherapy and radiotherapy groups, so for the purposes of assessing associations and baseline predictors of cases of CSF, these two groups have been combined. The prevalence of CSF was highest one month after initial treatment and in view of the small sample size, analysis was concentrated on this time point. As the androgen deprivation therapy group could be considered as being at an earlier treatment stage and did not receive ionising radiation, they have been described separately.

Brachytherapy and radiotherapy group

Between baseline and one month after initial treatment, cases of CSF at one month were associated with a statistically significant decrease in role function, white cell count and basophil count (see table 6.3).

Of the 13 cases of CSF at one month, nine cases were new since baseline. These new cases of CSF were associated with a larger increase in global fatigue scores (1.0 vs. 0.1, p=0.011) and a decrease in activity scores (-0.5 vs. 0.0, p=0.033) compared to non-cases.

Despite statistically significant changes from baseline in haemoglobin (145 to 139g/l, p<0.001) and IL-6 (2.42 to 3.20, p=0.014) there was no association with CSF. There were no statistically significant changes in CRP and it was not associated with CSF either.

Androgen Deprivation Group

Those that were cases of CSF at three months (this group were not assessed at one month) had had a significant decrease in platelets from baseline compared to non cases (-15 vs. 22.6, p=0.034).

Table 6.3 Associations of mean changes in continuous variables from baseline to one month for all cases of CSF (p<0.05 in bold)

	(Brachytherapy and radiotherapy) All cases of CSF at one month				
variable changing between baseline and one month	**Yes (n=13)**		**No (n=16)**		
	Mean change	SD	**Mean change**	SD	*p value*
activity score	**-0.3**	0.7	**0.0**	0.3	*0.130*
sleep score	**0.3**	2.7	**1.4**	1.8	*0.187*
Urinary symptoms (IPSS)	**8.0**	7.3	**9.2**	3.9	*0.584*
Erectile function	**-0.5**	1.1	**-0.5**	0.6	*0.904*
Fatigue (BFI)					
global fatigue	**0.7**	1.5	**0.1**	0.6	*0.119*
HADS					
anxiety	**-1.5**	2.0	**-1.5**	2.5	*0.964*
depression	**-0.4**	2.1	**-0.4**	1.5	*0.938*
depression –Qu8	**-0.3**	1.8	**-0.4**	1.1	*0.905*
EORTC QLQc30					
Health related QL	**-8.3**	20.7	**0.5**	14.1	*0.183*
Physical Function	**-4.1**	13.5	**0.8**	6.4	*0.205*
Role Function	**-19.2**	11.5	**-5.2**	21.7	***0.045***
Emotional Function	**9.0**	20.3	**5.7**	8.5	*0.565*
Cognitive Function	**1.3**	17.3	**2.1**	13.4	*0.889*
Social Function	**-3.8**	18.2	**-2.1**	29.1	*0.851*
Biological Measures					
Haemoglobin	**-6.9**	5.8	**-4.4**	6.5	*0.306*
Red Cell Count	**-0.2**	0.2	**-0.1**	0.2	*0.134*
White cell count	**-1.2**	1.8	**0.2**	1.4	***0.034***
neutrophils	**-0.5**	1.4	**0.6**	1.5	*0.056*
lymphocytes	**-0.6**	0.4	**-0.5**	0.3	*0.507*
monocytes	**-0.1**	0.2	**0.0**	0.1	*0.318*
eosinophils	**0.0**	0.1	**0.1**	0.1	*0.067*
basophils	**-0.009**	0.023	**0.008**	0.014	***0.024***
platelets	**-16.2**	34.2	**-0.6**	25.6	*0.178*
Albumin	**-0.5**	2.3	**-1.0**	4.3	*0.718*
CRP	**-3.9**	11.7	**0.4**	5.2	*0.196*
IL-6	**0.3**	3.1	**1.1**	2.2	*0.432*
Testosterone	**12.0**	15.9	**4.6**	8.8	*0.145*

compared using Student t tests

BFI = Brief Fatigue Inventory, CRP = C reactive protein, EORTC QLQc30 = European Organisation for the treatment of cancer quality of life (QL) questionnaire core 30, IPSS=International Prostate Symptom Score, HADS –Qu8 = Hospital Anxiety and Depression Scores minus question 8, IL-6 = Interleukin 6, SD= standard deviation

6.4.5 THE SYMPTOM OF FATIGUE AS A CONTINOUS VARIABLE

For brachytherapy and androgen deprivation groups, the trajectory of fatigue when measured by the Brief Fatigue Inventory (giving a continuous global fatigue score) was different to when cases of CSF were defined by clinical interview. They were similar for the radiotherapy group.

6.4.5.1 Changes of global fatigue scores from baseline after treatment

6.4.5.1.1 Within treatment group comparisons:

There were no statistically significant changes from baseline in the global fatigue scores at one or three months for any of the treatment groups separately, or the combined brachytherapy and radiotherapy group (figure 6.2 and table 6.4)

Brachytherapy

Mean global fatigue scores increased at one month and continued to increase slightly at three months (whereas cases of CSF decreased between one and three months).

Radiotherapy

Mean global fatigue scores peaked at the end of radiotherapy (one month) and decreased to just below baseline levels by three months. This was similar to the CSF case findings.

Androgen Deprivation

After three months (there was no one month assessment) of androgen deprivation, mean global fatigue scores increased (but cases of CSF had decreased slightly).

Figure 6.2. Mean treatment group fatigue scores at baseline, one and three months after initial treatment

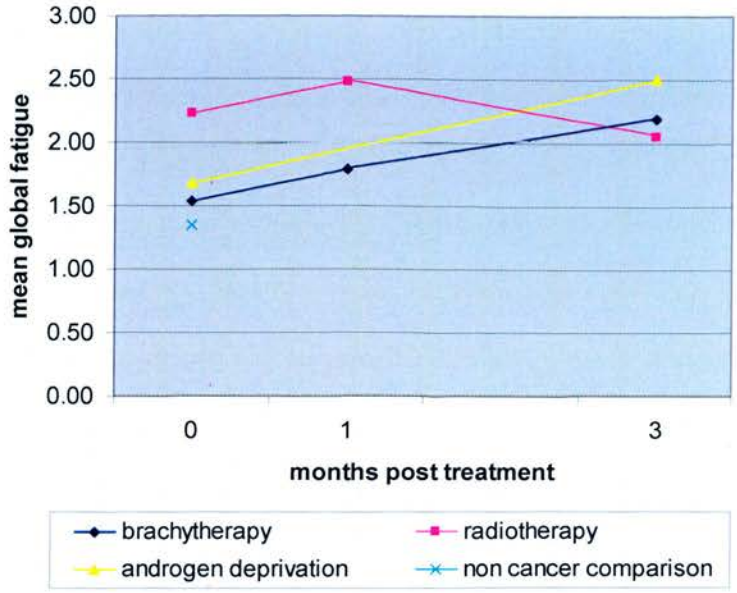


Table 6.4. Mean group fatigue scores at baseline, one and three months

		Mean global fatigue score (standard deviation)					
	n	**Baseline**		**1 month**		**3 months**	
Brachytherapy	**15***	**1.53**	(1.25)	**1.78**	(1.47)	**2.19**	(1.59)
Radiotherapy	**15**	**2.23**	(2.09)	**2.47**	(2.40)	**2.05**	(1.94)
Androgen Deprivation	**15**	**1.67**	(1.08)	**na**	na	**2.50**	(1.74)
Non cancer group	**15**	**1.34**	(1.49)	**na**	na	**na**	na

* except n=14 at 1 and 3 months, na = not applicable

Although there were no statistically significant changes within the mean global fatigue scores over time, further examination of the individual changes revealed that between 47-60% of subjects rated an increase in their fatigue at one month whilst the remainder rated a decrease or the same score (see figures 6.3, 6.4 and 6.5). At the one month assessment I was also aware that some patients would describe themselves as being more fatigued than before treatment and yet their fatigue scores were actually lower than baseline (or vice versa). One way to assess this was to ask the patient to rate their level of fatigue in retrospect (a 'then test'). However, this was an ad hoc process with a small sample of patients and did not reveal any particular pattern.

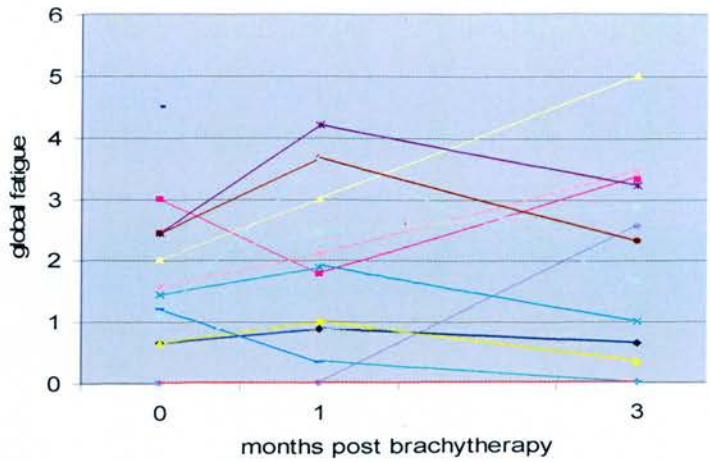
6.4.5.1.2 Between treatment group comparisons

The trajectory of fatigue differed for each treatment group but none of the comparisons of the mean change between baseline and one month achieved statistical significance (brachytherapy vs. radiotherapy, 0.46 vs. 0.24 respectively, p= 0.61). The same was true from baseline to three months although there was a trend for radiotherapy to decrease from baseline while brachytherapy and androgen deprivation groups increased (brachytherapy vs. radiotherapy, 0.56 vs. –0.19 respectively, p= 0.07; brachytherapy vs. androgen deprivation, 0.56 vs. 0.83 respectively, p=0.66; radiotherapy vs. androgen deprivation, –0.19 vs. 0.83, p= 0.08).

Comment

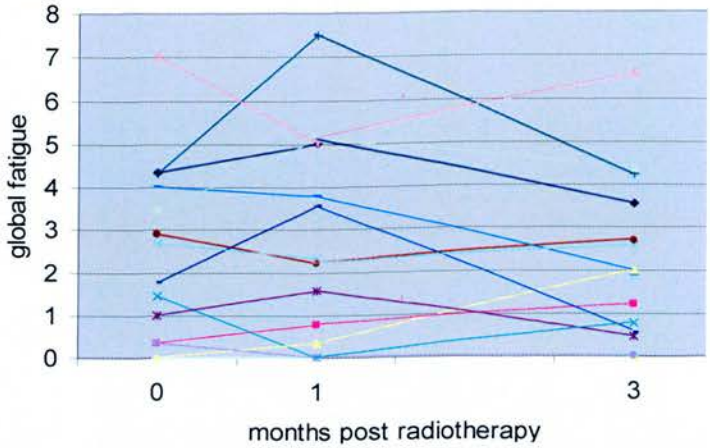
It should be remembered that these comparisons were exploratory and the study was not powered to detect differences between treatment groups.

Figure 6.3. Individual global fatigue scores for the brachytherapy patients



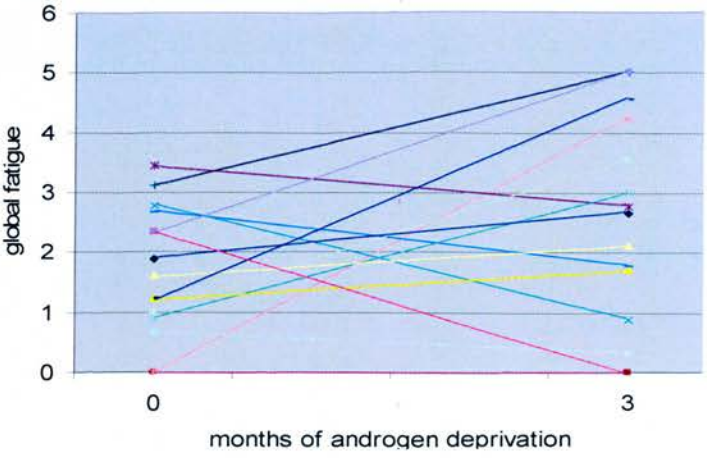
fatigue score direction from baseline	Months post brachytherapy	
	1	3
Up %(n)	60(9)	47(7)
Down%(n)	13(2)	26(4)
Same%(n)	20(3)	20(3)
Lost to follow up	7(1)	7(1)

Figure 6.4. Individual fatigue scores for the radiotherapy patients



fatigue score direction from baseline	Months post radiotherapy	
	1	3
Up %(n)	*47(7)*	*20(3)*
Down %(n)	*40(6)*	*66(10)*
Same %(n)	*13(2)*	*13(2)*

Figure 6.5. Individual fatigue scores for the androgen deprivation patients



fatigue score direction from baseline	months post androgen deprivation
	3
Up %(n)	60(9)
Down%(n)	33(5)
Same%(n)	7(1)

6.4.5.2 Associations of change in global fatigue scores (see table 6.5)

There were no statistically significant variations between the brachytherapy and radiotherapy changes in fatigue scores, so these groups have been combined. The androgen deprivation therapy group did not receive ionising radiation and could be regarded at as being at an earlier stage of treatment, so they are described separately. Some of the associations of global fatigue scores were different to cases of CSF.

6.4.5.2.1 Between baseline and one month

Brachytherapy and radiotherapy

From baseline to one month after initial treatment, changes in fatigue scores inversely correlated with changes in activity levels and role function (same for cases of CSF), physical function, and cognitive function. Changes in depression scores correlated with fatigue scores but not once the confounding fatigue question 8 ('I feel slowed down') was removed. Changes in fatigue scores and testosterone also positively correlated. In common with cases of CSF, despite a statistically significant drop in haemoglobin (145 to 139g/l, $p<0.001$), fatigue scores did not correlate with this, nor was there any relationship to CRP or IL-6.

6.4.5.2.2 Between baseline and three months

Brachytherapy and radiotherapy

From baseline to three months after initial treatment, the only association with an increase in fatigue was a decrease in monocyte count.

Androgen deprivation therapy

From baseline to three months after commencing treatment, changes in fatigue scores correlated with change in depression and anxiety and inversely correlated with role function (cases of CSF were only associated with a decrease in platelets).

Table 6.5 Associations with change in global fatigue scores and other measures between baseline and one and three months after initial treatment (p<0.05 in bold, * indicates p<0.01)

	Pearson correlation (r) with global fatigue score change between baseline and		
	1 month	3 months	
Variable changing between baseline and 1 and 3 months:	**brachytherapy and radiotherapy**	**brachytherapy and radiotherapy**	**androgen deprivation**
Activity score	**-0.485***	0.143	0.235
Sleep score	0.325	0.243	0.124
Urinary symptoms (IPSS)	0.319	0.317	-0.128
HADS			
anxiety	0.351	-0.127	**0.509**
depression	**0.370**	0.084	**0.802***
depression - Qu 8	0.284	0.016	**0.669***
EORTC QLQc30			
health related QL	-0.334	-0.177	-0.317
physical function	**-0.527***	0.116	-0.185
role function	**-0.378**	-0.095	**-0.600**
emotional function	-0.033	0.059	-0.508
cognitive function	**-0.451**	-0.029	-0.260
social function	-0.260	0.206	0.080
Biological Measures			
Haemoglobin	-0.196	0.143	-0.040
White cell count	-0.099	0.044	0.341
Neutrophils	-0.116	-0.003	0.037
Lymphocytes	-0.039	0.177	0.382
Monocytes	0.020	**-0.405**	-0.209
Eosinophils	0.158	0.330	0.305
Basophils	0.033	-0.012	0.124
Platelets	0.239	0.206	0.075
Albumin	0.149	-0.026	-0.075
CRP	0.139	0.087	na
IL-6	-0.115	-0.080	na
Testosterone	**0.525***	-0.084	0.403

CRP - C reactive protein, EORTC QLQc30 = European Organisation for the treatment of cancer quality of life questionnaire core 30, IPSS=International Prostate Symptom Score, HADS –Qu8 = Hospital Anxiety and Depression Scores minus question 8, IL-6 = Interleukin 6, na = not applicable

Cohen's (1988) suggested interpretation of strength of relationship for r:
± 0.10 to ± 0.29 = small, ± 0.30 to ± 0.49 = medium, ± 0.50 to ± 1.0 = large

6.4.6 Changes in biological measures

There was no discernable pattern over time with regards to the relationship between fatigue and CRP or IL-6 (either measured as cases of CSF or continuous fatigue scores). In view of the lack of relationship between fatigue and CRP and IL-6, I was advised that it would not be worthwhile pursuing further expensive cytokine receptor assays for IL-1ra and sgp130.

There were some changes in haemoglobin, white cell count, lymphocytes, eosinophils, platelets and IL-6 between baseline and one/three months indicating that prostate brachytherapy and radiotherapy may have had a systemic effect. The changes over time of these parameters are shown in Appendix 9 for completeness.

6.4.7 Patient self report questionnaire package

Patients reported that the content and length of the questionnaire package was acceptable. As anticipated, some men preferred not to answer questions relating to erectile function. A small proportion commented that they preferred the scales with numerical formats rather than ticking boxes with particular phrases, however an equal proportion expressed the opposite opinion. This was a useful insight into the limitations of the available validated questionnaire measures and patients seemed to appreciate the opportunity to discuss their answers in more detail during the clinical interview.

6.4.8 Clinical interview for identifying cases of CSF

The semi-structured clinical interview for CSF was simple to conduct. The best way to validate a measure is to see whether it agrees with a 'gold standard' measure (criterion validity). However with subjective states this is not possible and so the next best alternative is to assess whether it correlates with other instruments that purport to measure the same thing or would be expected to correlate with it (construct validity). For the clinical interview for CSF, construct validity was assessed by examining whether cases and non cases have significantly different continuous fatigue scores and quality of life measures. The one month time point was chosen as this had the greatest numbers of cases of CSF. For the EORTC QLQc30

functional scales, clinically significant differences have been proposed (moderate = 10 to 20 points, large = more than 20 points) (Osoba *et al.* 1998). Table 6.6 shows cases of CSF had significantly higher fatigue scores (both global fatigue measured by the Brief Fatigue Inventory and the EORTC fatigue subscale) and clinically significantly poorer health related quality of life, physical, role and social function than non cases.

Table 6.6 Cases of CSF compared to non cases at one month after brachytherapy or radiotherapy (compared using Mann Whitney U tests). P <0.05 in bold

	case of CSF at one month (brachytherapy and radiotherapy)				
	Yes n=13		No n=16		
one month variables	mean	SD	mean	SD	p value
Fatigue measures					
global fatigue (BFI)	**3.4**	1.8	**1.1**	1.5	**0.001**
EORTC fatigue subscale	**43**	19	**13**	14	**<0.001**
EORTC QLCc30					
Health related QL	**61**	22	**84**	18	**0.006**
Physical Function	**78**	16	**94**	7	**0.002**
Role Function	**64**	20	**94**	21	**<0.001**
Emotional Function	**85**	14	**92**	11	0.160
Cognitive Function	**85**	20	**91**	12	0.470
Social Function	**76**	23	**92**	22	**0.006**

BFI = Brief Fatigue Inventory, EORTC QLQc30 = European Organisation for the treatment of cancer Quality of Life (QL) Questionnaire core 30. SD = Standard deviation

Examples of what cases of CSF experienced

One man said, "I feel severely drained when doing things. Mentally and physically exhausted. Consequently I avoid doing things that are not absolutely necessary". Another had to get up later than usual in the morning. Since treatment he had to curtail most activities because he felt "a complete lack of energy and no strength". He therefore no longer did any cooking and bought ready meals instead. He did not

even feel able to do his favourite hobby, gardening. One patient described having "very low energy…listless…..I just don't feel able to do anything I used to……I'm frustrated because I don't even have the energy to complete a task at home (like hanging the washing out)….I feel guilty because my wife works and she is still having to do everything". Several expressed that they felt "lifeless" and had to pace themselves when doing anything. This resulted in those who were employed feeling unable to return to work at that point.

6.5 DISCUSSION

6.5.1 Main findings

This study demonstrated that studying prostate cancer patients in the Edinburgh Cancer Centre was feasible. Recruitment was good and only one patient was lost to follow up when he moved abroad. The combination of the questionnaire package, clinical interview and blood test proved acceptable to patients, as did the timing of assessments.

Not everyone experienced fatigue as a side effect of treatment but there was a substantial and statistically significant increase in the number of cases of clinically significant fatigue (CSF) in patients one month after brachytherapy treatment. The number of cases in the radiotherapy group also increased at one month but not as much (and this increase was not statistically significant). To put this in context, at one month after treatment there were 43% and 46% of cases of CSF in the brachytherapy and radiotherapy groups respectively, compared to only 7% in the non-cancer group. By three months cases of CSF had decreased in both groups but there was no substantial change in the androgen deprivation group.

Interestingly changes observed in the continuous measure of fatigue revealed a somewhat different pattern. There were no statistically significant changes from baseline in fatigue scores in any of the groups. Possible reasons for this discrepancy between the self-report continuous measures and clinically rated cases are: (a) the Brief Fatigue Inventory was not sensitive enough to pick up clinically detectable changes in fatigue (b) during the course of treatment the patients adapted to the increased fatigue to the point of regarding the new level as 'normal' (this change in internalised standard is referred to as response shift (Visser *et al.* 2000)) (c) the interviewer (me) was biased and over diagnosed CSF (observer bias). However I postulate that (d) because approximately half the group increased their fatigue rating and the rest did not, the mean scores for the group evened out and did not show any statistical change.

The discrepancy in results between cases of CSF and continuous scale measures in fact raises doubt about the validity of the use of scale based questionnaires in fatigue research as a whole. Therefore further work examining the use of a case definition approach is warranted.

6.5.2 Subsidiary findings

Some of the radiotherapy group were cases of CSF at baseline. This group also had higher mean baseline global fatigue scores than the other treatment groups. A contributory factor may have been that their testosterone levels were low having completed their neo-adjuvant androgen deprivation therapy. After a rise in fatigue scores at the end of radiotherapy (one month), most of the scores returned to baseline levels by three months. Whereas for the brachytherapy group, three months after the implantation there is a suggestion that fatigue scores may still be increasing. In addition, CSF cases had not returned to baseline levels. One hypothesis is that the suggestion of prolonged fatigue after brachytherapy may be due to long term delivery of low dose radiation that may continue for up to nine months. Further follow up of the brachytherapy group is justified to determine that trajectory of fatigue.

In common with another study (Stone *et al.* 2000a) there was a trend for fatigue scores to increase in the group undergoing androgen deprivation therapy. In the present study this was not associated with an increase in cases of CSF so impact on functioning was minimal.

Fatigue is part of the syndrome of depression and it would be expected that the symptoms of fatigue and depression would be associated. This was confirmed for the androgen deprivation group where the increase in fatigue scores from baseline to three months strongly correlated with changes in depression scores. The relationship was weaker for the brachytherapy and radiotherapy group. This disparity may be explained by the clinical impression of differing levels of anxiety of patients who were at different stages of their 'cancer journey'. Radiotherapy and brachytherapy patients tended to be less anxious after their treatment was completed whereas those

on androgen deprivation were about to embark on radiotherapy (which some found a daunting prospect) and in addition they had had to contend with side effects from low testosterone such as erectile dysfunction, weight gain and loss of muscle mass; all of which seemed to impact on their feeling of well being.

There were no strong indications that fatigue in the brachy/radiotherapy group was associated with systemic inflammatory response. There were no statistically significant changes in CRP during or after treatment and no association with cases of CSF or fatigue scores. This is similar to findings only published in abstract form so far (Geinitz *et al.* 2003). IL-6 did statistically significantly increase after one month in the brachytherapy group but this was not associated with changes in fatigue scores or cases. Given the lack of change in CRP and no relationship between fatigue and IL-6, I was advised there was not sufficient scientific rationale to justify further expensive assays for IL-1ra and sgp130.

There were some associations between fatigue and biological parameters but no consistent pattern. In the radiotherapy and brachytherapy group, although there was a statistically significant fall in haemoglobin one month after initial treatment, this did not correlate with fatigue scores. This is probably because the drop from a mean of 145g/L to 139g/L was not clinically significant. Two other studies of prostate radiotherapy patients had similar findings (Windsor *et al.* 2004;Chander *et al.* 2005). It had been expected that the relationship between fatigue and testosterone would be inverse (more fatigue, less testosterone). The opposite was true but it is unlikely that fatigue occurs directly as a result of higher testosterone. It is more likely that this result reflects recovery of testosterone production in the radiotherapy group once neo-adjuvant androgen deprivation therapy has been stopped.

For the brachytherapy and radiotherapy group, cases of CSF at one month were associated with a decrease in white cell and basophil count from baseline. Similarly between baseline and three months, fatigue scores inversely correlated with monocyte counts. This was the opposite of what was anticipated as it was hypothesised that fatigue would be associated with a systemic inflammatory response

to radiotherapy and brachytherapy (and hence raised white cell counts). It is possible that these results arose from multiple testing. However, these changes may represent the cytotoxic effects of ionising radiation affecting the bone marrow in the pelvis or the circulating blood volume through the prostate and surrounding tissues. Lymphocytes are particularly sensitive to radiation but monocytes and macrophages (which primarily produce CRP and cytokines) less so. In another study, fatigue has been found to be predicted by baseline neutrophil and monocyte counts in breast cancer patients receiving radiotherapy (Wratten *et al.* 2004).

Fatigue scores and cases of CSF shared the some but not all associations. This may be because fatigue scores are continuous variables and cases of CSF are categorical. Using the latter whilst being more clinically meaningful, reduces the statistical power of detecting a relationship between a variable and an outcome (Altman & Royston 2006).

6.5.3 Limitations

All findings in this preliminary study have to be viewed in the context of the small sample size. It had power only to detect very large (approximately 50% difference in proportions) differences between brachytherapy and radiotherapy groups. It cannot therefore be assumed that the negative findings mean there were no differences in the incidence of fatigue. It is unlikely however that the absolute size of the difference would be of clinical significance.

This was a hypothesis generating study and multiple statistical tests were performed. Some significant results may have arisen by chance and there was no correction made for this possibility, hence caution must be exercised when interpreting results.

As this was not a randomised study one cannot be sure the patients in each group were similar and must be cautious making comparisons. In clinical practice there is a pre-treatment selection bias that may well be present in this sample. For example brachytherapy patients tend to be younger than radiotherapy patients and have to be fit enough to undergo a general anaesthetic. In order to address this possible bias, the

changes in fatigue scores and cases of CSF were compared rather than the absolute values. However, in order to address this shortcoming in a subsequent study, I looked into the possibility of performing a subsidiary study of fatigue as part of a national multicentre randomised controlled trial. The 'ProtecT' study (Prostate Cancer Testing and Treatment www.epi.bris.ac.uk/protect) is attempting to address questions regarding which treatment gives best outcome for localised prostate cancer. However, a subsidiary fatigue study comparing fatigue with different treatments was not feasible or appropriate because brachytherapy is not included as a treatment option in the 'ProtecT' study and it is not totally randomised as patients can choose a treatment if they do not want to be randomly allocated to one.

IL-6 is produced as part of the host's systemic inflammatory response. It is also produced by prostate cancer cells and acts as an autocrine growth factor (Okamoto *et al.* 1997). It is not possible to determine what was the source of the IL-6 in this study.

6.5.4 Related literature

To my knowledge this is the only study to prospectively examine fatigue in men receiving prostate brachytherapy so these results can not be directly compared to other literature.

As mentioned in section 2.2.3.1, there have been a limited number of prospective studies specifically examining fatigue in prostate cancer during radiotherapy. A study of 36 patients found fatigue increased by the end of radiotherapy (measured using the Piper Fatigue Scale) and then decreased by six weeks afterwards, though not quite to baseline levels (Monga *et al.* 1999). An abstract examining 105 patients receiving prostate radiotherapy (some of whom had had surgery as well) also found fatigue increased with radiotherapy but 8 weeks afterwards had still not reached baseline (Geinitz *et al.* 2003).

Studies published since October 2003

One of the difficulties in comparing previous published work regarding fatigue is the use of different fatigue measures that are not comparable. Since starting this work, two studies that used the same fatigue measure as the present study (the Brief Fatigue Inventory, BFI) have been published.

1) 65 men who received radiotherapy (50Gy in 20 fractions) for prostate cancer were randomised to participate in an exercise intervention or be in a control group (Windsor *et al.* 2004). In common with the findings in the present study, both groups had an increase in BFI fatigue score by the end of radiotherapy (but this was only statistically significant in the control group for whom fatigue remained raised four weeks post radiotherapy). There was no difference in fatigue between the groups at baseline or after radiotherapy (and the equivalent mean global fatigue scores were approximately 1.4 and 2.4 respectively, so comparable to the present study values). Depression was not measured. It should be noted however that although patients had 'localised' prostate cancer, this group was not homogeneous as 19 patients were receiving androgen deprivation therapy and although 51/65 had T1or T2 tumours it is not clear whether the some of the remaining 14 men had T4 disease. In common with other studies, follow up was short and limited to four weeks after completion of radiotherapy.

2) A study of 28 patients with prostate cancer who received radiotherapy (74Gy delivered in 30-37 fractions) showed that mean BFI global fatigue statistically significantly increased to a maximum at the end of radiotherapy (Truong *et al.* 2006). They had similar values to this study (an equivalent mean global fatigue score of 1.27 at baseline, 2.61 at the end of radiotherapy and 1.67 a median of 6.5 weeks post radiotherapy). They had a longer course of androgen deprivation therapy prior radiotherapy than the present study (median duration of 12.2 months) and included patients with more advanced disease (stages T1-T4)

The study with the longest follow up reported 40 out of 62 prostate radiotherapy patients with complete data between 12-24 months post treatment (Monga *et al.*

2005). Results showed fatigue (Piper Fatigue Scale) was still statistically significantly higher than baseline at 4-8 weeks and at 12-24 months post treatment. However it should be noted that the follow up intervals were very variable, only two thirds of the study patients had complete data and it was not clear what proportion received androgen deprivation therapy.

Overall, these studies suggest that there may be a small proportion of patients who have fatigue as a longer term side effect of radiotherapy though this was not the case in the present study.

6.5.5 Conclusions

(1) This study demonstrated that studying prostate cancer patients in the Edinburgh Cancer Centre was feasible.

(2) The assessment methods were acceptable to patients.

(3) Not everyone experienced fatigue as a side effect of treatment.

(4) There was evidence of a substantial increase in fatigue one month after initial radiotherapy/ brachytherapy but only with regards to cases of clinically significant fatigue not fatigue scores. There was an increase in fatigue with androgen deprivation but this did not have much clinical impact.

(5) Prostate radiotherapy and brachytherapy appeared to have a systemic effect but there was no strong evidence to suggest fatigue in this population was associated with a systemic inflammatory response.

(6) Fatigue seemed to be transient in the radiotherapy group and was back to baseline levels by three months. However, there was the suggestion of prolonged fatigue in the brachytherapy group which was worthy of future study.

(7) Given the lack of supportive evidence for prolonged fatigue after radiotherapy (consistent with some of the existing literature) and lack of any published fatigue data in relation to brachytherapy, it was decided the clinically important question to address is what happens to fatigue in the longer term after brachytherapy.

CHAPTER

7

STUDY B

FATIGUE IN MEN WITH LOCALISED PROSTATE CANCER UNDERGOING BRACHYTHERAPY:

A PROSPECTIVE OBSERVATIONAL COHORT STUDY

Chapter 7

List of sections

7.1 INTRODUCTION

Following analysis of the preliminary study (Study A), it was decided to focus attention on men with early localised prostate cancer receiving brachytherapy. This was because (a) there was a suggestion of fatigue still increasing three months after implantation and (b) to date, there has been no published data relating to fatigue after brachytherapy so this would generate new information.

7.2 AIMS

To determine the incidence, associations (biological and psychological) and predictors of cases of clinically significant fatigue (CSF) and continuous fatigue scores in men with localised prostate cancer up to 12 months after receiving brachytherapy

To determine whether the prevalence of CSF in men at baseline, one, three, six, nine or 12 months after brachytherapy is significantly different to a non-cancer comparison group.

7.3 HYPOTHESES

There would be more cases of CSF/higher global fatigue scores (a) at one, three, six and nine months after brachytherapy than at baseline (b) in the brachytherapy group than the non cancer comparison group.

Cases of CSF/higher global fatigue scores at any time point would be associated with (a) greater depression (b) lower physical activity (c) lower serum testosterone (d) lower quality of life (e) more severe urinary symptoms and (f) raised C reactive protein (CRP)

Cases of CSF which persisted twelve months after starting treatment, would be predicted by (a) higher baseline fatigue (b) higher baseline depression (c) lower baseline physical activity than non cases.

7.4 METHODS

7.4.1 Design

A prospective observational cohort study of fatigue in men undergoing brachytherapy compared to a non-cancer comparison group of men with benign prostatic hypertrophy.

7.4.2 Patient Samples

Following on from the preliminary study (Study A), the consecutive samples of brachytherapy and non-cancer comparison group patients were extended from 15 to 50 men in each group.

7.4.2.1 Brachytherapy group sample

Inclusion criteria

(a) Due to receive brachytherapy

(b) Able to give informed consent

Exclusion criteria

(a) Another concurrent cancer diagnosis

(b) Haemoglobin less than 100g/L

(c) Untreated thyroid dysfunction

(d) Serum creatinine more than twice the upper limit of normal

(e) Liver function tests more than twice the upper limit of normal

(f) Unable to communicate adequately because of language problems or cognitive impairment

Brachytherapy group sample recruitment

Between January and October 2005 potentially eligible patients planned to receive brachytherapy were identified at the Oncology Clinic. They were introduced to the study and given a patient information sheet by their doctor or clinical nurse specialist. If the patient agreed to be contacted, they were telephoned at home by a researcher or seen the next time they were due in hospital. This was to give them the opportunity to ask any questions about the study and if they chose to participate, to obtain informed written consent. A record was kept of those who declined entry into the study along with their reason for doing so if this information was volunteered.

7.4.2.2 Non-cancer comparison sample

The inclusion and exclusion criteria remained the same as the pilot (Study A) except that as this study was focused on brachytherapy patients who were generally younger and fitter than radiotherapy patients, the age and fitness criteria of the non cancer comparison group had to be adjusted accordingly.

Inclusion criteria

(a) Ambulatory patients attending Nurse Urology (at the Western General Hospital) with urinary symptoms attributed to benign prostatic hypertrophy

(b) Within the same age range as the brachytherapy patients

(c) Potentially fit enough for a general anaesthetic

Exclusion criteria

(a) A current diagnosis of cancer

(b) Haemoglobin less than 100g/L

(c) Untreated thyroid dysfunction

(d) Serum creatinine more than twice the upper limit of normal

(e) Liver function tests more than twice the upper limit of normal

(f) Unable to communicate adequately because of language problems or cognitive impairment

(g) Concurrent chronic disease in which fatigue is recognised to be a prominent symptom (e.g. multiple sclerosis or severe chronic obstructive airways disease)

Non-cancer comparison sample recruitment

These men were identified in the Nurse Urology Clinic and introduced to the study by their clinic nurse. As they did not routinely return to hospital for several months, they were given a patient information sheet, questionnaire and consent form to take home. With their agreement they were telephoned at home by a researcher to give them the opportunity to ask questions about the study. If they agreed to participate they were asked to return the signed consent form and questionnaire in the post. Once these were received, the patient was telephoned at a time convenient to them to conduct the clinical interview.

7.4.3 Assessments

All methods and measures were identical to Study A except the measure of sleep quality was eliminated because patients generally had difficulty answering this. It had not varied significantly between or within treatment groups over time in study A.

7.4.3.1 Baseline data collected

Demographic data

- Date of birth
- Postcode, to assess Scottish Index of Multiple Deprivation (SIMD), see section 5.1.1
- Marital status
- Employment status

Clinical Data

- T stage (prostate cancer patients only), see section 2.1.2.
- Gleason score (prostate cancer patients only), see section 2.1.3.
- Charlson Comorbidity Index, see section 5.2.3

7.4.3.2 Content of each assessment

Self rated questionnaire measures:

- The Brief Fatigue Inventory (BFI), see section 4.1.2.1
- Hospital Anxiety and Depression Scale (HADS), see section 5.4.1
- European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire core 30 version 3.0 (EORTC QLQc30), see section 5.4.2
- Likert scales for erectile function and how much of a problem this is, see section 5.4.3
- International Prostate Symptom Score (IPSS), see section 5.4.4

Interview measures:

- Semi structured interview for clinically significant fatigue (CSF), see section 4.2.4
- Additional questions
    - Do you feel that fatigue is a problem for you? (Yes/No)
    - What do you think causes your fatigue?
- Structured clinical interview for DSM IV (SCID) - Major depression section, see section 5.5.1
- Modified activity score, see section 5.5.2

Clinical and biomedical measures:

- Body Mass Index
- Concurrent medications were noted
- Karnofsky Performance Status, see section 5.2.4
- blood samples (full blood count, urea and electrolytes, albumin, testosterone, and C-reactive protein (CRP). For analysis methods see section 5.3.

Until March 2005, all assessments where performed by the author (DS). Between March 2005 and February 2006, Morven Shipway, a part time NHS research nurse with previous oncology experience was also trained to conduct the assessments. She received training in how to administer the clinical interview for clinically significant fatigue from DS. The SCID interview training was conducted by staff from the Symptom Management and Research Trials (SMaRT) team based at the University of Edinburgh Cancer Research Centre.

7.4.3.3 Assessment Intervals

The assessments were extended over a follow up period of 12 months (baseline, one, three, six, nine and twelve months) because in Study A there was a suggestion that fatigue was still increasing at three months post brachytherapy.

The non cancer comparison group were assessed once only.

7.4.4 Ethical Approval

The study was approved by the Lothian Research Ethics Committee. Reference number LREC/2003/8/52.

7.4.5 Statistical Analysis

Based on preliminary data from Study A, the expected proportion of men experiencing CSF 12 months post brachytherapy was 0.15. Recruiting a total of 50 brachytherapy patients provided a 95% confidence interval width of +/- 0.10. Comparing to 50 non-cancer men gave 80% power to detect a 25% difference (assumed to be clinically significant) in CSF between the two groups, at a significance level of 0.05.

The data were inspected using histograms and scatter plots. Baseline categorical variables were described as percentages; continuous variables as means and standard deviations. The number of baseline cases of CSF in the brachytherapy and non-cancer groups were compared using Chi-squared tests; Mann Whitney U tests and

Student t-tests were used for continuous variables as appropriate. C- reactive protein (CRP) results were heavily skewed so were log. transformed prior to analysis.

Changes in the number of cases of CSF at one, three, six, nine and twelve months were compared to baseline using McNemars Test; continuous fatigue scores were compared using Wilcoxon Signed Rank Tests.

Associations of new cases of CSF at one month post brachytherapy were examined using Chi-squared test for categorical variables and Mann Whitney U Tests for continuous variables. The mean difference (change) in continuous variables between baseline and one month were calculated. Correlations between changes in continuous fatigue scores and other continuous variables were examined using Spearman Rank Order Correlations. HADS depression question 8 "I feel as if I am slowed down" may be construed as referring to fatigue. Hence associations with depression were performed both including and excluding this item. This approach has been previously reported (Stone *et al.* 2000a).

The proportion of cases of CSF at each time point was compared to the non cancer comparison group using Chi-squared tests; continuous fatigue scores were compared using Mann Whitney U Tests.

Data were analysed using SPSS 13.0 computer software. Pearson Chi- square test was used for nominal factors, Chi-square test for trend (linear-by-linear association) was used for ordinal factors and Chi-squared with Yates correction (continuity correction) was used for 2x2 tables. A p value of <0.05 was regarded as statistically significant, though those <0.01 have also been highlighted. I was advised by Dr Rob Elton, PhD and Honorary Fellow, University of Edinburgh.

7.5 RESULTS

53 men were eligible for the study and the participation rate was 96.2% (51/53). Two declined participation. One man had a severe needle phobia and did not want to have the blood tests, the other had previously participated in a number of research studies because of a relative's medical condition and already felt overburdened.

51 patients entered the study. One patient had his brachytherapy implant and subsequently did not return for follow up (he moved abroad). One patient was found to have bone metastases within three months of his brachytherapy implant and was started on androgen deprivation therapy. This patient was followed up but has been excluded from the prospective analysis because of the possible confounding effects of metastatic cancer and androgen deprivation therapy on fatigue. Data was collected from the 49 remaining patients at all assessment points except the six month interval (35 patients). The first 15 patients form the preliminary study had already passed this time point once ethical approval had been obtained for the study extension.

7.5.1 Characteristics of the sample (See tables 7.1 and 7.2)

The mean age of the brachytherapy group was 62.7 years (SD 5.7). There were no statistically significant differences between the demographic, clinical or self report measures between the brachytherapy and non-cancer comparison group at baseline except the brachytherapy patients had less severe urinary symptoms and lower testosterone levels (11.1 vs. 16.3nmol/L, $p>0.001$).

Comment

This shows men with benign prostatic hypertrophy were a good comparison group. One of the original reasons for choosing these men in study A was to be able to control for urinary symptoms, especially nocturia, which may contribute to disrupted sleep and fatigue. This was less of an issue for brachytherapy patients because in order to be eligible, they needed to have good urinary flow. It is therefore not surprising they had lower IPSS scores than the non-cancer comparison group. There was however no association between fatigue and urinary symptoms or insomnia, so it is unlikely that this difference is relevant.

The lower testosterone levels in the brachytherapy group were due to 14 patients having undergone neo-adjuvant androgen deprivation to reduce their prostate volume. This was a larger proportion than originally expected and arose because of technical differences between referral centres in measuring prostate volumes prior to formal brachytherapy eligibility assessment.

Table 7.1. Baseline comparison of continuous variables between the brachytherapy and non-cancer comparison group (p<0.05 in bold)

	Non-cancer group n=51		Brachytherapy group n=51		p
Baseline variable	**mean**	SD	**mean**	SD	**value**
Age (years)	**65.0**	6.3	**62.7**	5.7	0.062‡
Fatigue (BFI) †					
Global fatigue	**1.4**	1.2	**1.8**	1.6	0.402
HADS scores §					
anxiety	**4.2**	3.7	**4.6**	3.4	0.501
depression	**3.1**	2.2	**3.1**	3.1	0.429
depression - Qu8	**2.1**	1.9	**2.1**	2.6	0.440
EORTC QLQc30 Scores					
Health Related QL*	**82**	13	**80**	17	0.753
Physical Function*	**93**	9	**91**	15	0.625
Role Function*	**94**	13	**91**	17	0.596
Cognitive Function*	**80**	16	**85**	15	0.098
Social Function*	**89**	16	**88**	19	0.875
Pain**	**10**	18	**7**	17	0.335
Insomnia**	**21**	26	**25**	25	0.281
Constipation**	**7**	15	**6**	16	0.469
Diarrhoea**	**7**	15	**7**	15	0.804
Activity score	**2.3**	0.4	**2.1**	0.6	0.180
Urinary symptoms (IPSS) Ω	**10.7**	5.3	**6.7**	5.2	**<0.001**

BFI = Brief Fatigue Inventory, EORTC QLQc30= European Organisation for the Research and Treatment of Cancer Quality of Life core 30, HADS –Qu8= Hospital Anxiety and Depression Score minus question 8 ('I feel slowed down'), IPSS = International prostate symptom score, SD = Standard Deviation

* Higher scores = better function, ** Higher scores = worse symptoms

Non cancer and brachytherapy group respectively:
† Global fatigue > 3 = 10% and 14%;
§ anxiety ≥ 9 = 12% for both groups, Depression ≥ 8 = 4% and 6%, Depression ≥ 8 –Qu8 = 4% for both groups
Ω IPSS >7 65% and 28%

All comparative tests are Mann Whitney U Tests except ‡ Student t-test

Table 7.2 Baseline comparison of categorical variables between the brachytherapy and non-cancer comparison group (p<0.05 in bold)

Baseline variable	Non-cancer group n=51 %	(n)	Brachytherapy group n=51 %	(n)	p value
Case of Clinically Signif. Fatigue					0.647
no	**96**	(49)	**94**	(48)	
yes	**4**	(2)	**6**	(3)	
Employment status					0.232
retired	**63**	(32)	**49**	(25)	
working	**37**	(19)	**51**	(26)	
Marital status					0.991
unmarried	**6**	(3)	**6**	(3)	
married/with partner	**78**	(40)	**80**	(41)	
divorced	**12**	(6)	**10**	(5)	
widowed	**4**	(2)	**4**	(2)	
Deprivation Index (SIMD)					0.437
1	**45**	(23)	**49**	(24)	
2	**28**	(14)	**22**	(11)	
3	**22**	(11)	**10**	(5)	
4	**6**	(3)	**10**	(5)	
5	**0**	(0)	**8**	(4)	
Karnofsky Performance status					0.232
70	**0**	(0)	**2**	(1)	
90	**8**	(4)	**12**	(6)	
100	**92**	(47)	**86**	(44)	
Comorbidities score					0.472
0	**65**	(33)	**77**	(39)	
1	**33**	(17)	**18**	(9)	
2	**2**	(1)	**6**	(3)	
Tumour stage					na
1	**na**	na	**73**	(37)	
2	**na**	na	**27**	(14)	
Erectile function					na
not possible/severely reduced	**37**	(18)	**39**	(20)	
normal/slightly reduced	**63**	(31)	**61**	(31)	
Erectile function a problem					na
not a problem/ a bit of a problem	**80**	(39)	**78**	(40)	
serious/quite a problem	**20**	(10)	**22**	(11)	

SIMD = Scottish Index of Multiple Deprivation, na = not applicable (descriptive only).
All comparative tests are Chi-squared tests

Results are first presented as cases of clinically significant fatigue, then secondly as mean global fatigue scores (to allow comparison with previously published data).

7.5.2 CASES OF CLINICALLY SIGNIFICANT FATIGUE (CSF)

7.5.2.1 Incidence of CSF cases over 12 months after brachytherapy

There was a statistically significant increase in the number of cases of CSF between baseline and one month after brachytherapy (6 vs.29%, p=0.001, incidence of 23%). The prevalence then decreased to 16% at three months, 11% at six months, 12% at nine months and was 14% at twelve months (see figure 7.1 and table 7.3). There were three cases of CSF before brachytherapy and all except one remained cases during the 12 months follow up. Most cases of CSF occurred at one month post brachytherapy but three of the seven who were cases of CSF at 12 months did not have CSF at that point. The individual patient profiles of CSF over time did not show any particular pattern (figure 7.2).

7.5.2.2 CSF in brachytherapy patients vs. non cancer comparison group

The non-cancer comparison group had a CSF prevalence of 4% (2/51). Post brachytherapy CSF was significantly higher than the non-cancer comparison group at one and three months, but not at six, nine or 12 months (see table 7.3).

Figure 7.1 Cases of clinically significant fatigue (CSF) after brachytherapy

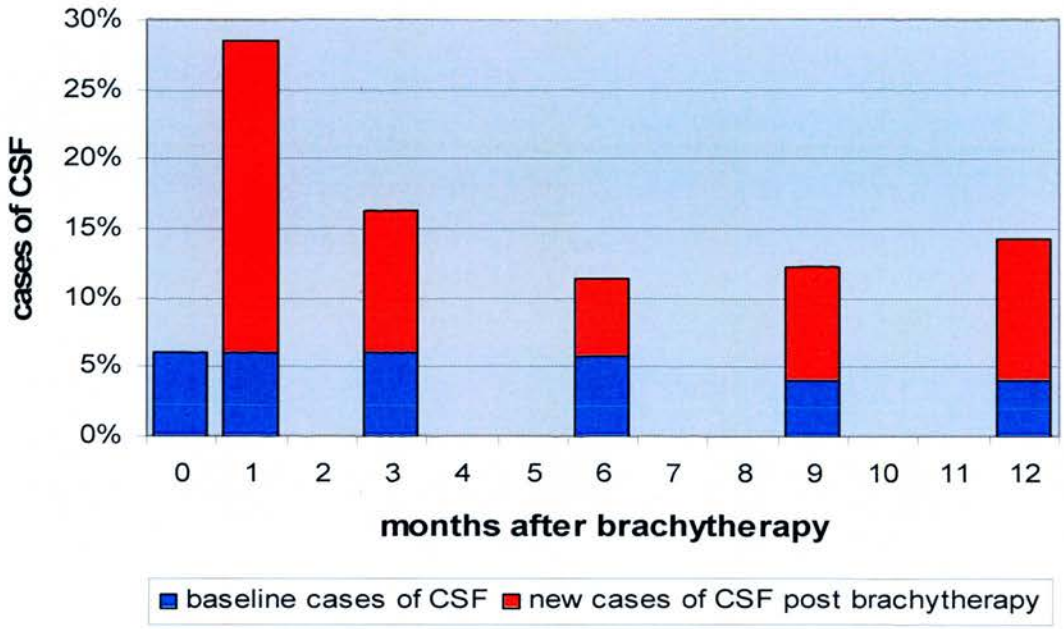


Table 7.3. Cases of Clinically Significant Fatigue (CSF) after brachytherapy

	months post brachytherapy					
	0	**1**	**3**	**6**	**9**	**12**
Total n	49	49	49	35	49	49
Total cases of CSF % (n)	**6** (3)	**29** (14)	**16** (8)	**11** (4)	**12** (6)	**14** (7)
Baseline CSF % (n)	**6** (3)	**6** (3)	**6** (3)	**6** (2)	**4** (2)	**4** (2)
new cases of CSF % (n)	na	**23** (11)	**10** (5)	**6** (2)	**8** (4)	**10** (5)
total compared to baseline CSF. p value*	na	**0.001**	0.063	1.000	0.375	0.219
total brachytherapy CSF vs. non-cancer group (2/51,4%) p value **	0.678	**0.001**	**0.049**	0.219	0.156	0.089

*Compared using McNemar test, ** compared using Chi-squared test

Figure 7.2. Individual patient profiles of clinically significant fatigue (CSF) after brachytherapy

	months post brachytherapy					
Patient	0	1	3	6	9	12
1				na		
2				na		
3				na		
4				na		
5				na		
6				na		
7				na		
8		na	na	na	na	na
9				na		
10				na		
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41						
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44						
45						
46		ex	ex	ex	ex	ex
47						
48						
49						
50						
51						

LEGEND

case of CSF

not a case

na — not assessed

ex — Excluded from analysis because of metastatic disease and on long term androgen deprivation therapy

7.5.2.3 Associations of new cases of CSF at one month

The highest prevalence of cases of CSF was one month after brachytherapy. As hypothesised, those who were cases of CSF before brachytherapy tended to remain so after treatment. It was therefore of interest to examine those who became new cases of CSF after brachytherapy.

New cases of CSF at one month reported statistically significantly poorer health related quality of life, physical functioning, role functioning and higher depression scores compared to non cases. There was also a trend for new cases of CSF to have poorer social functioning and more pain (see table 7.4). There were no differences in the severity of anxiety, urinary symptoms, activity levels or any of the blood parameters.

Comment

Previous published studies have shown a strong association between fatigue and continuous HADS depression scores. This study confirms that finding however it should be noted that mean scores were low and decreased from baseline over time (baseline, 1, 3, 6, 9 and 12 months: 2.98, 2.31, 2.63, 2.37, 2.37, 2.33 respectively). There were hardly any patients who had clinically relevant levels of depression (see table 7.4). Anxiety scores also decreased from baseline (0, 1, 3, 6, 9 and 12 months respectively 4.61, 3.22, 3.1, 3.29, 3.04, 3.20). In contrast to the hypotheses, CSF was not associated with lower physical activity, more severe urinary symptoms, or CRP.

Table 7.4 Associations of new cases of Clinically Significant Fatigue (CSF) and continuous variables at one month post brachytherapy (p<0.05 in bold)

One month post brachytherapy variables	Total n	new case of CSF one month post brachytherapy: Yes n=11 mean	SD	No n=35 mean	SD	P-value
Fatigue (BFI)						
global fatigue	46	**2.6**	1.4	**1.2**	1.6	***0.004***
HADS scores §						
anxiety	46	**3.5**	2.8	**2.7**	3.1	*0.320*
depression	46	**3.2**	1.9	**1.6**	2.3	***0.007***
depression - Qu8	46	**1.8**	1.5	**1.1**	2.0	***0.049***
EORTC QLQc30						
Health related QL*	46	**65**	22	**86**	14	***0.004***
Physical function*	46	**86**	12	**95**	9	***0.009***
Role function*	46	**73**	8	**94**	12	***<0.001***
Emotional Function*	46	**86**	13	**90**	12	*0.234*
Cognitive Function*	46	**88**	11	**90**	12	*0.538*
Social function*	46	**82**	14	**90**	14	*0.067*
Pain**	46	**17**	17	**8**	14	*0.080*
Insomnia**	46	**18**	23	**20**	25	*0.874*
Constipation**	46	**15**	23	**8**	16	*0.253*
Diarrhoea**	46	**12**	17	**11**	18	*0.813*
activity score	46	**1.8**	0.3	**2**	0.6	*0.177*
Urinary symptoms (IPSS)	46	**15.6**	8.4	**11.7**	7.3	*0.146*

BFI = Brief Fatigue Inventory, EORTC QLQc30 = European organisation for the research and treatment of cancer quality of life core 30 scale, HADS –Qu8= Hospital Anxiety and Depression Score minus question 8 ('I feel slowed down'), IPSS = International Prostate Symptom Score, QL quality of life, SD = Standard Deviation,

* Higher scores = better function, ** Higher scores = worse symptoms

For new cases of CSF and non-cases respectively:
§ anxiety ≥ 9 = 9% and 6%, Depression ≥ 8 = 0% and 3% (same for Depression ≥ 8–Qu8)

Compared using the Mann Whitney U Test

Changes from baseline in new cases of CSF at one month

It was of interest to find out what had changed between baseline and one month post brachytherapy for those that had become new cases of CSF. As anticipated they had a statistically significant increase in global fatigue scores. They also had a decrease in health related quality of life, physical function and role functioning and an increase in pain scores. Statistically significant results however do not necessarily translate to clinically significant changes. A change of between 10-20 points on the EORTC scale has been defined as a moderately large clinically significant change (Osoba *et al.* 1998). Changes in quality of life, role function and increase in pain scores all achieved these criteria. However, there were no substantial differences between cases and non cases with regards to changes in urinary symptoms, blood measures, anxiety or depression (see table 7.5).

Table 7.5 Changes between baseline and one month after brachytherapy for new cases and non cases of CSF (p<0.05 in bold)

Variable changing between baseline and one month	Total n	new case of CSF one month after brachytherapy: Yes n=11 mean change	SD	No n=35 mean change	SD	p-value
Fatigue (BFI)						
global fatigue	46	**0.91**	1.15	**-0.29**	1.39	***0.011***
HADS						
anxiety	46	**-0.91**	1.22	**-1.71**	2.26	*0.263*
depression	46	**0.09**	1.30	**-0.97**	2.05	*0.420*
depression -Qu8	46	**-0.27**	1.10	**-0.66**	1.64	*0.282*
EORTC QLQc30						
Health related QOL	46	**-9.85**	21.35	**2.14**	11.67	***0.031***
Physical function	46	**-5.45**	13.27	**0.57**	6.74	***0.025***
Role function	46	**-19.70**	14.56	**0.00**	11.43	***<0.001***
Emotional Function	46	**1.52**	10.42	**5.71**	11.39	*0.254*
Cognitive Function	46	**1.52**	15.73	**2.86**	13.70	*0.746*
Social function	46	**-1.52**	17.41	**-3.33**	17.53	*0.742*
Pain	46	**12.12**	15.08	**1.90**	15.00	***0.035***
Insomnia	46	**-9.09**	26.21	**-4.76**	21.61	*0.522*
Constipation	46	**6.06**	13.48	**2.86**	12.45	*0.470*
Diarrhoea	46	**0.00**	14.91	**5.71**	22.12	*0.428*
Activity score	46	**-0.39**	0.50	**-0.11**	0.47	*0.177*
Urinary symptoms (IPSS)	45	**8.55**	7.49	**5.65**	5.97	*0.272*

BFI = Brief Fatigue Inventory, EORTC = European Organisation for the Research and Treatment of Cancer Quality of Life scale, HADS –Qu8 = Hospital Anxiety and Depression Score minus question 8 score (' I feel slowed down'), IPSS = International Prostate Symptom Score, QOL = Quality of life, SD = Standard Deviation

Compared using Mann Whitney U Test

7.5.2.4 Baseline predictors of new cases of CSF at one month

The only baseline variable that predicted becoming a new case of CSF one month after brachytherapy was having poorer social functioning (83 vs. 93, p=0.007). There was no relationship with baseline global fatigue score, depression or activity (new cases of CSF vs. non cases respectively: global fatigue 1.73 vs. 1.51 p=0.250, HADS depression 3.09 vs. 2.60 p=0.373, HADS depression minus question 8 'I feel slowed down' 2.09 vs. 1.77 p=0.320, activity scores 2.2 vs. 2.1 p= 0.392). Similarly there was no relationship to having neo-adjuvant androgen deprivation therapy (46% vs. 23% p=0.147).

Comment

Analysis focussed on new cases of CSF so it is not surprising that baseline global fatigue scores did not predict new cases of fatigue (because baseline cases' fatigue scores were not included). It appears that the development of CSF is quite unpredictable as virtually no parameters showed any relationship although the sample numbers were small so statistical power was limited

7.5.2.5 Associations and baseline predictors of CSF at 12 months

There were seven cases of CSF at 12 months post brachytherapy, two of these had been cases throughout the whole 12 months of follow up but the others had no particular pattern. In view of the small numbers and inconsistency of CSF over time, it was decided further analysis of predictors of twelve month CSF would be inappropriate.

7.5.3 FATIGUE AS A CONTINUOUS VARIABLE

To allow comparison with published data, fatigue has also been presented as measured by The Brief Fatigue Inventory. In contrast to the cases of CSF, there were no significant changes in the global fatigue scores over time. In fact the scores appeared to decrease slightly (see figure 7.3). There was a trend for the brachytherapy group to have higher global fatigue scores than the non-cancer group but this did not achieve statistical significance (see table 7.6).

Comment

Many patients clearly described feeling more fatigued after brachytherapy, yet this was not reflected in the group global fatigue scores. Closer examination of individual fatigue scores (figure 7.4) indicated that approximately half the group's scores increased (52%) at one month post brachytherapy and the other half decreased (38%) or stayed the same (8%). This may explain why the mean group score did not change much. In addition, despite some patients saying in the clinical interview that they were more fatigued, their self rated scores had actually decreased from baseline.

Table 7.6 Mean global fatigue scores over 12 months after brachytherapy

	Months after brachytherapy					
	0	**1**	**3**	**6**	**9**	**12**
total n	49	49	49	35	49	49
Mean global fatigue	**1.71**	**1.68**	**1.72**	**1.50**	**1.47**	**1.48**
(SD)	(1.61)	(1.66)	(1.65)	(1.53)	(1.49)	(1.49)
p value compared to baseline	-	0.752	0.704	0.290	0.700	0.276
p value*. Brachytherapy vs. nor cancer group, n=51, mean global fatigue 1.45 (SD 1.24)	0.404	0.811	0.717	0.695	0.641	0.604

SD = standard deviation

Compared using Wilcoxons Signed Rank Test except *Mann Whitney U Test

Figure 7.3. Mean global fatigue score over 12 months after brachytherapy.

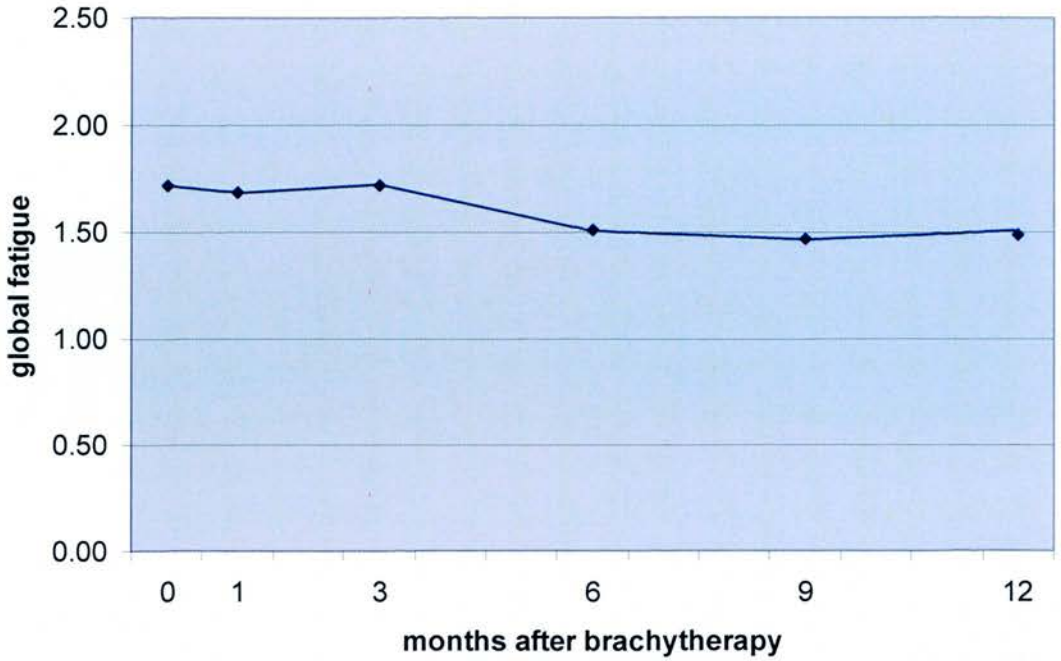
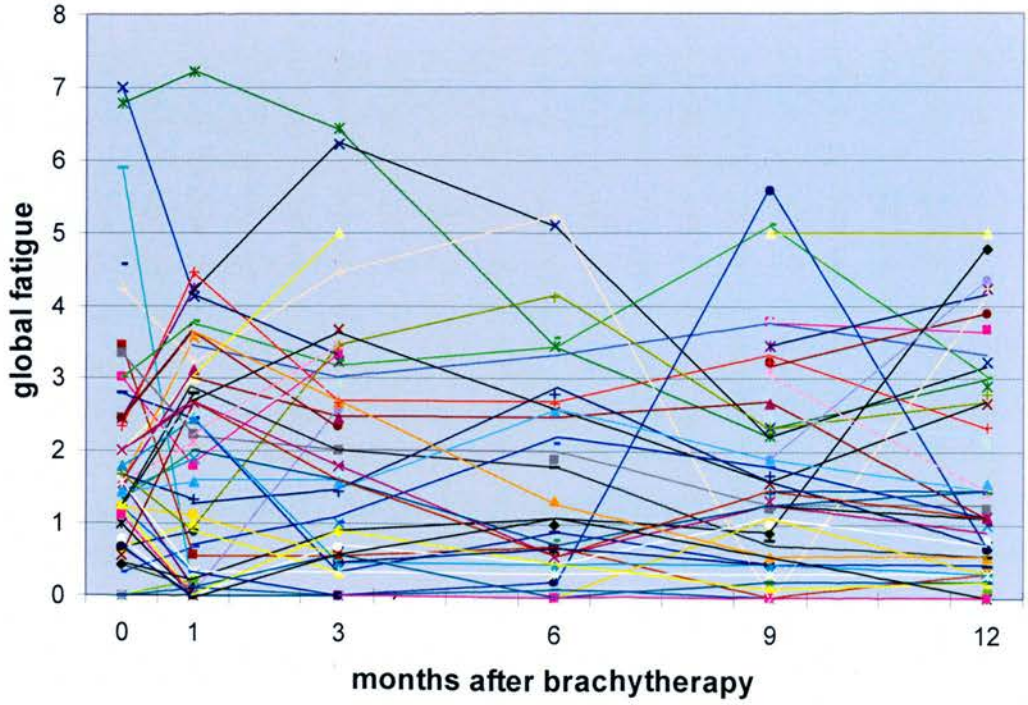


Figure 7.4 Individual patient global fatigue scores after brachytherapy



7.5.3.1 Correlations of mean change in global fatigue between baseline and one month (table 7.7)

Changes in global fatigue between baseline and one month correlated with changes in anxiety, depression, (including when the fatigue item, question 8 was removed), pain, insomnia, red blood cell count, and eosinophils. Changes in global fatigue inversely correlated with quality of life, physical, role, emotional and cognitive function. All other changes were not statistically significant notably, urinary symptoms, activity and CRP.

Despite statistically significant decreases from baseline in the following blood measures there was no correlation with fatigue scores: haemoglobin (150 vs.146g/L at one month, p=0.001) white cell count (6.8 vs. 6.1 $x10^9$ /L at three months) and lymphocyte count (1.8 vs., 1.49, 1.37, 1.55, 1.45, 1.49 $x10^9$ /L at 1, 3, 6, 9 and 12 months respectively, all $p<0.001$).

Table 7.7 Correlation of change in global fatigue from baseline to one month ($p < 0.05$ in bold, * indicates $p<0.01$)

variable changing between baseline and 1 month	Spearman correlation (rho) with change in global fatigue from baseline to 1 month
HADS	
anxiety	**0.461***
depression	**0.531***
depression -Qu8	**0.376***
EORTC QLQc30	
Health related QOL	**-0.436***
Physical function	**-0.330**
Role function	**-0.437***
Emotional Function	**-0.499**
Cognitive Function	**-0.325**
Social function	-0.275
Pain	**0.337**
Insomnia	**0.347**
Constipation	0.104
Diarrhoea	0.199
Activity score	-0.125
Urinary symptoms (IPSS)	**0.303**
Blood measures	
Haemoglobin	0.241
Red blood cells	**0.308**
White cell count	0.112
neutrophils	0.113
lymphocytes	0.124
monocytes	-0.053
eosinophils	**0.325**
basophils	-0.006
platelets	0.112
Albumin	0.207
CRP	-0.209
Testosterone	0.054

EORTC QLQc30= European Organisation for the Research and Treatment of Cancer Quality of Life core 30, HADS –Qu8= Hospital Anxiety and Depression Score minus question 8 ('I feel slowed down'), IPSS = International prostate symptom score

(Cohen 1998) suggested interpretation of strength of relationship for r:
± 0.10 to ± 0.29 = small, ± 0.30 to ± 0.49 = medium, ± 0.50 to ± 1.0 = large

7.5.3.2 Fatigue and neo-adjuvant androgen deprivation

A larger proportion of patients than expected had received neo-adjuvant androgen deprivation prior to brachytherapy (14 patients). In case low testosterone levels in these patients had confounded results, fatigue scores were examined for those who did and did not receive androgen deprivation therapy. There was an initial trend for the androgen deprivation therapy group to have higher fatigue scores up to six months after brachytherapy. By nine months scores were similar to those who had had brachytherapy alone (see table 7.8). I postulated that this may be due to delayed testosterone recovery after androgen deprivation which can take a median of four to nine months (Nejat *et al.* 2000). However, mean serum testosterone levels were the same in both groups by one month post brachytherapy so androgen deprivation therapy is not likely to contribute to longer term fatigue.

Table 7.8 Mean global fatigue scores after brachytherapy for those who did and did not receive neo-adjuvant androgen deprivation

	months post brachytherapy					
	0	**1**	**3**	**6**	**9**	**12**
brachytherapy only group (n)	36	35	35	24	35	35
mean global fatigue	**1.55**	**1.52**	**1.62**	**1.28**	**1.56**	**1.58**
(SD)	(1.34)	(1.44)	(1.47)	(1.43)	(1.65)	(1.63)
androgen deprivation prior to brachytherapy (n)	14	14	14	11	14	14
mean global fatigue	**2.33**	**2.09**	**1.96**	**2.00**	**1.24**	**1.23**
(SD)	(2.20)	(2.12)	(2.07)	(1.67)	(0.99)	(1.10)

7.5.4 RELATIONSHIP BETWEEN FATIGUE SCALES AND CSF DEFINITION

Interview rated cases of CSF significantly increased one month after brachytherapy and gradually decreased over 12 months. However the self-report continuous global fatigue scores did not change much. The global fatigue score on the Brief Fatigue Inventory (BFI) was the primary fatigue scale measure but in case these results were an anomaly of the BFI, EORTC fatigue subscale results were also examined. These showed a slightly different third pattern and although the scores did not change

substantially over time (baseline,1,3,6,9,12 months: 20.6, 19.0, 17.0, 19.7, 17.0, 17.5 respectively) or achieve the lowest proposed clinically significant change (5 points (Osoba *et al.* 1998)), they were statistically significantly lower than baseline three months after brachytherapy (20.6 vs. 17.0, p=0.047).

The CSF interview appeared to measure the same construct as the fatigue scales because cases of CSF had higher global fatigue scores than non cases at each time point (see table 7.9).

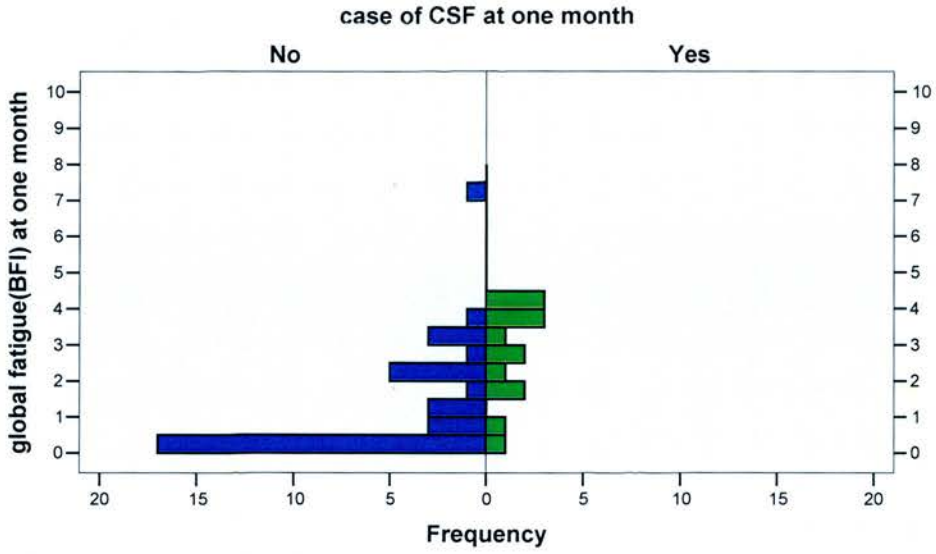
Table 7.9 Differences in global fatigue scores between cases of CSF and non cases at each time point (p<0.05 in bold)

	cases of CSF						
	Yes			No			
months after brachytherapy	n	Mean	SD	n	Mean	SD	p value
0	3	**4.0**	2.6	47	**1.6**	1.5	**0.032**
1	14	**2.8**	1.3	35	**1.2**	1.6	**<0.001**
3	8	**3.5**	1.9	41	**1.4**	1.4	**0.001**
6	4	**3.6**	2.1	31	**1.2**	1.2	**0.016**
9	6	**3.7**	1.4	43	**1.2**	1.2	**<0.001**
12	7	**3.4**	0.7	42	**1.2**	1.3	**<0.001**

As shown in figure 7.4, the lack of change in mean global fatigue scores could be because half the group rated an increase and the other half rated a decrease or no change so there was no overall change in the mean score for the group. Therefore the relationship between fatigue scores and cases of CSF was examined further.

It appears that the scale measures do not appear to be very good at identifying interview defined cases of CSF. In figure 7.9 it would be expected there would be more cases of CSF (in green) than non cases (blue) at the higher end of the fatigue scores (top right hand side of the graph). Although there is a trend towards this, there are still some cases who had low fatigue scores and one outlying non-case who had a high global fatigue score. At first glance the EORTC scale looks marginally better because the scores seem to be more widely distributed, but this is could be

Figures 7.9 Distribution of fatigue scores for cases and non cases



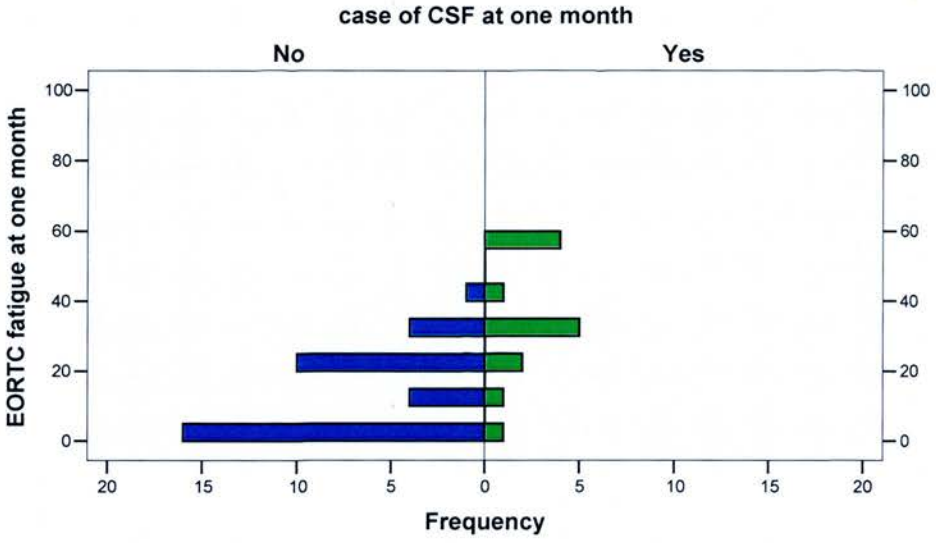


Table 7.10 Proportions of cases of CSF and non cases in relation to previously published 'cut offs' for the Brief Fatigue Inventory (BFI)

	cut off	BFI global fatigue > 3	
		%	n
Cases of CSF	above	**50**	7
n=14	below	**50**	7
non cases	above	**11**	4
n=35	below	**89**	31

misleading. The scores are generated in 11 point increments whereas the global fatigue score is a continuous range making them look more clustered together.

A clinical interview is more rigorous than a questionnaire measure. However it appears that some patients say different things when talking about how they feel compared to answers on a questionnaire. For example, there was a case of CSF who had low fatigue scores (0.11 out of 10 on the global BFI and 11 out of 100 on the EORTC fatigue scale) but in the clinical interview described how since his brachytherapy implant he had to use an electric buggy to get around the golf course and could no longer fulfil his responsibilities of doing the gardening or do-it-yourself (DIY) tasks because of fatigue. Conversely, there was one patient who is not a case of CSF despite a global BFI of 7.22. Possible reasons for this will be covered in the discussion section.

A cut off for moderate to severe fatigue has been suggested as scores greater than 3 on a 1 to 10 fatigue scale (Mock 2005). When this was applied to the global fatigue score 50% of the interview defined cases of CSF in this sample were identified, so this cut off appears to be slightly high (see table 7.10). However as the sample size and number of cases of CSF was small, these results must be interpreted with caution.

7.6 DISCUSSION

7.6.1 Main findings

Between baseline and one month after brachytherapy the incidence of CSF was 23%. In total 29% of patients were affected at one month which was significantly higher than baseline. CSF gradually decreased over 12 months but not quite to baseline levels and the prevalence of CSF was significantly higher than the non-cancer comparison group at one and three months after brachytherapy. CSF was associated with having poorer quality of life and had a significant impact on physical functioning and patients' ability to fulfil their roles. Those who were fatigued before brachytherapy tended to remain so afterwards but there were minimal baseline factors that predicted new cases of CSF. Mean global fatigue scores however showed a different pattern and did not significantly change over time, nor were they significantly higher than non-cancer comparison group.

Fatigue was assessed using two different approaches and the results were inconsistent. There could be several reasons for this: (a) the fatigue scale measures were not sensitive enough to pick up cases of CSF (b) some patients may have misunderstood the fatigue questionnaire (c) the researchers may have been biased and over diagnosed CSF (observer bias) (d) half the group's fatigue scores increased one month after brachytherapy but the other half decreased or stayed the same resulting in the mean fatigue score not changing much (e) patients got used to being fatigued and subconsciously adjusted their internal standards accordingly (known as response shift). One way this was demonstrated was when some patients who were nine/twelve months since treatment and feeling well, volunteered the information that it was only in retrospect that they recognised how fatigued they had been. Sometimes the internal adjustment of standards was a conscious decision and after brachytherapy some patients described themselves as 'listening to my body' or 'taking things more easy because my family say I should' as if they now had permission to do so.

The interview was more rigorous than the questionnaire measures because there was the opportunity to explore things in more detail. The patients generally filled in the

questionnaire before the clinical interview and it was noticeable that sometimes patients said different things on paper to when they were talking to someone. This demonstrates the shortcomings of questionnaires in general but there may have been other contributory factors: (a) the interview concentrated on fatigue that had been present for at least two weeks, whereas the Brief Fatigue Inventory referred to the last week. It could be that fatigue was truly different from one week to another but it has been suggested that people tend to answer questionnaires in relation to how they have felt so far that day, regardless of the timescale mentioned on the questionnaire (recall bias) (Gendreau *et al.* 2003) (b) during the interview, on occasions it became clear that a minority of patients had not wanted to admit the extent of their fatigue on the questionnaire. There were differing reasons for this. Firstly, some men were keen to say how effective they believed the brachytherapy was and that it was 'killing the cancer'. This anxious and slightly forced positive attitude may have contributed to some patients not wanting to acknowledge their fatigue on paper in case that was an indication the treatment had not gone well. Secondly, some seemed embarrassed to admit fatigue because they viewed it as not 'manly'. This sometimes became evident when their spouse was present at the interview. Some men answered that they were not fatigued on the questionnaire and said that initially in the interview but their wife would then disagree and give a very different picture! Thirdly, a small number of men seemed keen not to be seen as complaining in case they seemed ungrateful for the treatment they had received for their cancer. This had not been anticipated. It is possible that because the researchers could have been perceived as part of the brachytherapy team, then this minority of patients initially did not feel they could be entirely honest about how they were feeling.

Overall, the impact of fatigue was not severe. Although some individuals' fatigue scores had increased, they were not classified as a case of CSF because it did not cause them problems. This may partially be explained by two factors. Firstly, because many men were retired they could put off doing things without any major consequences but expressed that had they been in employment, they did not think they could have gone back to work. Secondly, most men had a female partner and between them they held traditional household roles. Consequently their spouse would

continue to do the cooking, cleaning, shopping and take care of them so fatigue did not have a major impact on the patient's life. In other research, fatigue appears to be more distressing for female breast cancer patients. This may be because they tend to be slightly younger and have to continue to care for their families (Woo *et al.* 1998). It may also reflect differences in tumour type and treatment.

7.6.2 Subsidiary findings

Fatigue was associated with depressive symptoms (measured by the HADS) in this population but it is important to recognise that depression scores were on the whole very low and decreased from baseline. Often the depression scores are similarly low in the published literature but some reports appear to over emphasise this relationship. None of the brachytherapy patients developed Major Depressive Disorder (as diagnosed by the DSM IV SCID interview) over the 12 months of follow up.

Fatigue after brachytherapy was not associated with testosterone levels or neo-adjuvant deprivation therapy.

Fatigue was not associated with CRP in this population. However this should be interpreted with caution because of (a) the small sample size (b) possible confounders such as infection (one patient was recovering from a chest infection and had a raised CRP) or concurrent administration of medications that modulate the host inflammatory response such as non-steroidal anti inflammatory medications and steroids (several patients were on aspirin or painkillers such as ibuprofen and two patients had steroid inhalers for their asthma. However, as numbers were small it was not possible to account for this in the analysis). Originally the plan was to examine other cytokines but these tests are very expensive and following results of study A it was decided there was not sufficient scientific rationale to justify these.

Eosinophils significantly increased and also correlated with fatigue one month after brachytherapy. It could be that they release substances that mediate fatigue (or this result may also have arisen from multiple testing). Some research groups have

examined markers of immune response such as T lymphocytes (Bower *et al.* 2003) or genetic polymorphisms that influence interleukin production but so far no definitive biological correlates of fatigue have emerged.

Haemoglobin, white cell count and lymphocyte count significantly decreased after brachytherapy but did not correlate with fatigue. The haemoglobin drop could be explained by bruising after having brachytherapy needles and seeds inserted through the perineum. However a drop in haemoglobin also occurred in the radiotherapy patients in study A (who have not undergone an operation) and similar results were found in a larger study of radiotherapy patients (Windsor *et al.* 2004). It is possible that there could have been a systemic effect of ionising radiation from the prostate brachytherapy seeds affecting the pelvic bone marrow or blood volume circulating through the prostate. Lymphocytes are known to be sensitive to ionising radiation and they remained significantly lower than baseline throughout the follow up period.

Having men with benign prostatic hypertrophy (BPH) as the comparison group may underestimate the difference in fatigue levels compared to the general population. A paper was published after this study had started showed that men with BPH and prostate cancer had similar fatigue levels but both were higher than men in the general Swedish population (Jakobsson *et al.* 2004).

7.6.3 Other limitations

In addition to above, one of the limitations of this study was the small sample size and multiple statistical tests. No adjustment was made for this and so results should be interpreted with caution. There is an increased risk of Type I errors (thinking that a result is significant when in fact it could have occurred by chance). An alternative would be to apply Bonferroni's adjustment but some argue that this is not helpful and merely increases Type II errors (accepting the null hypothesis when there is a real difference) (Perneger 1998). In this study, a p value of 0.05 was taken to be statistically significant. When examining results it may be worth paying more attention to results with a p value < 0.01, meaning only one result out 100 could have arisen by chance (as opposed to one in 20).

The hypotheses were based on Study A. Inclusion of Study A patients in this cohort may have biased results, making the hypotheses more likely to be proved positive.

Response shift is a recognised drawback of longitudinal studies of subjective symptoms (Visser *et al.* 2000). During some patients' assessments I suspected this had occurred if their fatigue score had moved in a different direction to what they described during the interview. One way of addressing possible response shift would have been to do a 'then test'; asking patients to retrospectively rate their fatigue score before brachytherapy (not to recall what they put). This was done informally for a small number of patients once I recognised it might be occurring. It would have been more rigorous to formally assess everyone but this requires very careful interviewing and it was important not to make the patient feel they had put the 'wrong' answer.

The case diagnosis of CSF proposed in this thesis was made regardless of supposed cause. This may have overestimated the prevalence of CSF that is secondary to brachytherapy. There is a natural tendency to assume that fatigue one month after brachytherapy may be related to the procedure. It is less clear how to judge fatigue with no obvious cause that develops for the first time several months after brachytherapy. Some clinicians may judge it not related to brachytherapy but strictly speaking we can not exclude the possibility of it being a late effect. In this study one patient was a case of CSF at the nine month time point only. In the clinical setting I would have attributed his fatigue to having a lower respiratory chest infection/flu like illness (i.e. not related to prostate cancer or brachytherapy). However he had to be classed as a case of CSF regardless. Other authors have proposed that cancer or its treatment must be considered to be the cause of fatigue when defining 'cancer related fatigue' (Cella *et al.* 1998). However this is also unclear and raises other questions. Where should the line be drawn regarding other medical conditions? Just because a patient has cancer does that automatically mean their fatigue is related to it? A parallel situation that has raised similar issues is the assessment of symptoms relating to the syndrome of Major Depressive Disorder in cancer patients (such as weight loss which may be due to either cancer or depression). Here, authors have advocated an inclusive approach rather than to attribute cause (Koenig *et al.* 1997).

In any study we can only identify associations, not cause. In clinical practice however, a judgement about cause tends to take place at some point. Attributing cause is inherently difficult but is only helpful if it identifies a treatment that may alleviate the condition. More work needs to be done to clarify a method of fatigue measurement. It is important to have an agreed measurement tool to enable consistency with regards to research and future investigations of the efficacy of treatment.

7.6.4 Other literature

This is the first longitudinal study to specifically examine fatigue after brachytherapy so there are no others to directly compare to. Obviously, no studies have used the same case definition, so the next best comparison is to look at those that used the same fatigue specific measurement tool in men with prostate cancer (the Brief Fatigue Inventory, BFI). A paper published whilst this study was in progress examined fatigue in men undergoing external beam radiotherapy. Their population had similar BFI global fatigue scores to this study (though they reported the sum global fatigue scores rather than the arithmetic mean) but fatigue scores significantly increased between baseline and the end of radiotherapy (50-52Gy over four weeks). They also found that men adhering to a physical exercise intervention had less of an increase but this was not statistically significantly different (Windsor *et al.* 2004).

7.6.5 Conclusions and implications

Although almost a third of patients experienced clinically significant fatigue, the majority did not. However it is difficult to predict who was likely to be affected to this degree. CSF appears to return back towards baseline levels by six months, however it may persist for a minority and patients should be warned about it. Those who are fatigued before brachytherapy are likely to remain so. Further work is required to ascertain biological correlates of fatigue and identify mechanisms that may help identify treatments. Perhaps most crucially of all, the issue of how best to measure fatigue continues to impede further progress and clearly more work is required in this area.

CHAPTER

8

STUDY C

FATIGUE IN RECURRENCE FREE SURVIVORS TREATED FOR LOCALISED PROSTATE CANCER MORE THAN ONE YEAR AGO:

A CROSS SECTIONAL SURVEY

Abstract presented at ASCO Annual Meeting June 2007, Chicago, USA

Awarded ASCO Merit Award for high quality abstract

Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 9044

Chapter 8

List of Sections

8.1 INTRODUCTION

The background to this study has been covered in Chapter 2. To summarise: the choice of treatment for localised prostate cancer is primarily determined on the basis of disease stage, but also with consideration of the patient's age, medical comorbidities and treatment preferences. There is no conclusive evidence as to which treatment is best in terms of survival so patient decisions are often made on the basis of likely side effects. The physical side effects most frequently associated with prostate cancer are well documented. Generally studies have revealed that incontinence and sexual difficulties are more common in patients who have received radical prostatectomy than by those who had radiotherapy or brachytherapy. Bowel dysfunction however, is more frequent in patients who have received radiotherapy or brachytherapy. It is increasingly recognised that the impact of these treatments on quality of life must also be considered in determining the best approach to management. Fatigue is increasingly recognised as an acute side effect of radiotherapy, and has been found to be a major determinant of quality of life after treatment for other cancer survivors (Bower *et al.* 2000;Fossa *et al.* 2003;Hjermstad *et al.* 2006). Less is known about longer term fatigue after prostate cancer treatment and this too may be an important consideration in treatment selection.

While this study was being designed, only one publication had specifically addressed fatigue in prostate cancer patients after treatment (Vordermark *et al.* 2002). This was a cross sectional survey of 103 men who had received radiotherapy and found 18.7% had 'severe fatigue'. Associations between fatigue and factors such as urinary and bowel symptoms were explored but other issues likely to influence fatigue such as depression and anxiety were not. This study included men who still had cancer or were on androgen suppression which may have confounded the findings. At the time, there was no information about long term fatigue after brachytherapy or radical prostatectomy.

There is a need for a representative study specifically examining clinically relevant fatigue and its associations in recurrence free men after different treatments for prostate cancer.

8.2 AIMS

To determine the prevalence and associations of Substantial Global Fatigue (Brief Fatigue Inventory global fatigue >3) in recurrence free men who previously received treatment for localised prostate cancer more than one year ago.

To determine whether there is any difference in the prevalence of Substantial Global Fatigue between patients who have undergone radical prostatectomy, radiotherapy or brachytherapy for localised prostate cancer.

To compare the prevalence of Substantial Global Fatigue to a historical non-cancer comparison group of men with benign prostatic hypertrophy (from Studies A and B).

8.3 HYPOTHESES

Substantial Global Fatigue in recurrence free men would be associated with poorer quality of life, depression, anxiety, more severe urinary symptoms and adjuvant androgen deprivation therapy.

The prevalence of Substantial Global Fatigue would be higher in recurrence free men who have had radiotherapy than brachytherapy or radical prostatectomy.

Recurrence free men previously treated for prostate cancer would have a higher prevalence of Substantial Global Fatigue than a historical non-cancer comparison group.

8.4 METHODS

8.4.1 Design

This was a descriptive, cross sectional, self report postal survey supplemented with retrospective clinical data.

8.4.2 Patient Sample

The Edinburgh Cancer Centre is a regional, tertiary, cancer centre that is the sole provider for specialist cancer services to a geographically defined area of approximately 1.5 million people in the South East of Scotland UK. The multidisciplinary care of prostate cancer patients occurs in conjunction with the Urologists at the Western General Hospital which is on the same campus. After treatment for their localised prostate cancer, patients are followed up for a year in the outpatient clinic. Thereafter they are routinely put on a postal follow up system which is led by the Clinical Nurse Specialist. Every six months patients are sent a postal questionnaire which they are asked to fill in and return. This coincides with a PSA (prostate specific antigen) test taken by the General Practice Surgery. The Clinical Nurse Specialist then collates the results and acts accordingly.

This setting provided the ideal opportunity for collecting data from all men previously treated for localised prostate cancer at the Edinburgh Cancer Centre/ Western General Hospital and who remained recurrence free. In addition they were used to completing questionnaires. It was assumed that since this was a formal postal follow up system, patients were able to understand English and did not have cognitive impairment.

Inclusion criteria

- The patient had received treatment with curative intent for localised prostate cancer (external beam radiotherapy, brachytherapy or radical prostatectomy) more than one year previously (seeing as persistent fatigue was the focus of this study, rather than acute fatigue after treatment).
- Localised (stage T1- T3) cancer at time of treatment

Exclusion criteria

- Localised (stage T1-T3) cancer on 'watch and wait' policy (these patients still have cancer and have not received treatment).
- Localised (stage T1-T3) cancer on primary androgen deprivation therapy (which is a palliative treatment , not one given with curative intent)
- Stage T4 (too advanced to be cured)
- Suspected relapse of prostate cancer (the specific focus of this study was recurrence free patients)
- Metastatic prostate cancer (for the reasons above)
- Another concurrent cancer diagnosis (as other cancers can be associated with fatigue and this may confound the findings).

Recruitment

Between August and November 2005 eligible patients were identified and the CNS then introduced the survey in a letter which accompanied the patient information sheet, consent form and survey questionnaire. Patients were invited to participate in the survey and post back the questionnaire and consent form in a stamped addressed envelope provided. Potential participants who did not return the questionnaire within one month, were sent another one by post. Cancer treatment and demographic details of non responders were noted.

8.4.3 Non-cancer comparison group

This was a historical comparison group which comprised of the 63 men with benign prostatic hypertrophy recruited for Studies A and B.

8.4.4 Data collected from patient records

- Date of birth
- Postcode, to assess Scottish Index of Multiple Deprivation (SIMD), see section 5.1.1
- Date and type of previous treatment for prostate cancer (radiotherapy, brachytherapy or radical prostatectomy)

- Currently on androgen deprivation therapy or not. The patient was also asked about this in the questionnaire as sometimes the hospital notes were not always up to date.

8.4.5 Self Rated Questionnaire Measures

- **The Brief Fatigue Inventory (BFI)**. As it was not possible to interview patients, a cut off of global fatigue >3 was used to define fatigue of a clinically relevant severity (termed Substantial Global Fatigue), see section 4.1.2.1.

- **Two additional questions** which could be answered ,"Yes" or "No"
  - "Has fatigue been a problem for you in the last week?" This was asked because it was found during the preliminary work that although some patients said they felt fatigued, they did not find it a problem because they were able to adjust their lives accordingly by for example putting things off until the next day because they were retired.
  - "Have you felt fatigued for longer than one month?" This was to ascertain whether fatigue was more than an acute problem. A period of one month was chosen as this corresponded to the work that was done regarding the case definition of CSF (clinically significant fatigue).

- **One open question** "If yes, to either of the above, what do you think contributed to it or caused it [fatigue]?"

- **Hospital Anxiety and Depression Scale (HADS)** see section 5.4.1

- **European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire core 30 version 3.0 (EORTC QLQc30)**, see section 5.4.2. In order to focus on the most relevant issues for this population, only the following subscales and items were selected: physical, role, and social functioning, two symptom scales (pain, fatigue), and single items (insomnia, constipation, diarrhoea, dyspnoea). This reduced the patient

questionnaire burden and avoided replication of question themes (i.e. using both the HADS and the emotional functioning subscale to measure similar things).

- **International Prostate Symptom Score (IPSS)** see section 5.4.4.

- **Likert scales for erectile function** and how much of a problem this is, see section 5.4.3.

- **Likert scales for common prostate cancer treatment side effects**, as fatigue may be associated with symptom burden. These side effects were also of particular interest to the responsible clinicians. Each item related to the past week and is answered on a four point scale; not at all, a little, quite a bit, very much.
    - urinary incontinence and dysuria (these are not covered by the IPSS)
    - faecal incontinence and rectal bleeding

- **Other Comorbidities**

  Patients lived throughout South East Scotland and Dumfries. Although I had access to Western General Hospital and Edinburgh Cancer Centre medical records it was not feasible to obtain peripheral hospital notes or to ask the GP about each patient's past medical history and comorbidities. Instead the patients were asked about the most common comorbidities that may influence fatigue (cardiovascular and respiratory problems, diabetes, stroke, depression, musculoskeletal problems or another cancer diagnosis) and whether they were taking medication for them. There was also an open question allowing them to mention any other medical conditions they thought we should know about. This approach is similar to that employed by other authors (Lilleby *et al.* 1999).

8.4.6 Ethical Approval

The study was approved by the Lothian Local Research Ethics Committee. Reference number 05/S1104/7.

8.4.7 Statistical Analysis

The data were inspected using histograms and box plots and described using means, medians and percentages of categories as appropriate. To assess whether the data was representative of the eligible sample, data from participants and non participants were compared using Student t-tests and Chi squared tests as appropriate.

Fatigue was described as the global fatigue score and the percentage who had Substantial Global Fatigue (global fatigue score >3). Prevalence of Substantial Global Fatigue was compared to the non-cancer group using Chi squared tests

Univariate associations of Substantial Global Fatigue were examined using binary logistic regression for categorical variables and Student t-tests and Mann Whitney tests as appropriate for continuous variables. Independent associations of Substantial Global Fatigue were examined using multivariate analysis with no selection. Variables such as physical, role and social functioning were not included as these could be regarded as outcomes of fatigue rather than predictors. HADS depression question 8 "I feel as if I am slowed down" may be construed as referring to fatigue. Hence associations between Substantial Global Fatigue and depression were performed both including and excluding this item. This approach has been previously reported (Stone *et al.* 2000a).

A p value of <0.05 was considered statistically significant. I was advised and assisted with the statistical analysis by Dr Isabella Butcher, Research Fellow, Public health Sciences, University of Edinburgh using SAS/STAT software, Version 9.1 of the SAS System for Windows. Copyright © 2002-2003 SAS Institute Inc.

8.5 RESULTS

Of the 905 patients who were still alive and on postal follow up, 457 fulfilled the eligibility criteria and were sent the questionnaire package. Seven patients subsequently transpired to have another concurrent cancer diagnosis, two patients were found to have had initial treatment less than a year ago and carers informed me that five patients were demented. These men were deemed ineligible retrospectively and not included in the analysis. Two patients returned the questionnaire declining participation, one patient said he did not understand the questionnaire and one questionnaire was returned as the addressee was unknown. The final eligible patient participation rate was 91% (402/443). There were no demographic or clinical differences between those who did and did not participate (see table 8.1).

Table 8.1 Comparison of demographic and clinical characteristics of recurrence free prostate cancer patients who did and did not participate in the survey.

	Eligible patients				
	Non-participants n=41		Participants n=402		
Variable	%	n	%	n	**P-value**
SIMD group					0.452
1	**39**	16	**40**	159	
2	**15**	6	**21**	81	
3	**22**	9	**19**	76	
4	**15**	6	**13**	51	
5	**10**	4	**7**	27	
Tumour (T) stage at time of treatment					0.583
1	**26**	9	**36**	121	
2	**60**	21	**47**	160	
3	**14**	5	**17**	59	
Prostate Cancer Treatment					0.730
brachytherapy	**5**	2	**6**	25	
radiotherapy	**56**	23	**61**	244	
radical prostatectomy	**39**	16	**33**	133	
Mean age at time of survey (SD)	**72.0** (6.4)		**71.7** (6.3)		0.811*
Months since treatment median (range)	**61.0** (21 to 312)		**54.0** (13 to 233)		0.085**

SD = standard deviation, SIMD= Scottish Index of Multiple Deprivation

All were compared using Chi squared test except * Student t Test ** Mann Whitney test

244 (61%) had received radiotherapy, 133 (33%) had undergone radical prostatectomy and 25 (6%) had had brachytherapy as their initial treatment for prostate cancer. Due to the small number of brachytherapy patients (this has only been available in recent years in Edinburgh) the analysis is focussed on the two largest treatment groups from now on.

The mean age of the sample was 72 years (SD 6.1) and the median time since treatment was 56 months (range 13-233). Only three men were on adjuvant androgen deprivation therapy. The radiotherapy group had more medical comorbidities than the radical prostatectomy group. See tables 8.2 and 8.3

Table 8.2. Continuous variables for the non-cancer group and recurrence free prostate cancer group according to previous treatment received

	Recurrence free prostate cancer group		Recurrence free prostate cancer group initial treatment				Non-cancer group	
			Radiotherapy		Radical Prostatectomy			
	n=377		n=244		n=133		n=63	
	mean	SD	mean	SD	mean	SD	mean	SD
Fatigue								
global fatigue (BFI)	**2.2**	(2.2)	**2.4**	(2.2)	**1.8**	(2)	**1.8**	(1.7)
EORTC fatigue score**	**25**	(23)	**28**	(24)	**20.8**	(21)	**21**	(15)
Age at time of survey	**72**	(6.1)	**72.8**	(5.6)	**70.6**	(6.7)	**66.2**	(6.7)
EORTC QLQc30								
Global Health related QL*	**73**	(20)	**71**	(21)	**77**	(19)	**80**	(15)
Physical Function*	**81**	(21)	**78**	(22)	**86**	(18)	**89**	(15)
Role Function*	**83**	(26)	**79**	(28)	**89**	(22)	**91**	(18)
Cognitive Function*	**79**	(19)	**78**	(20)	**81**	(16)	**80**	(16)
Social Function*	**80**	(27)	**78**	(29)	**83**	(24)	**86**	(22)
Pain**	**14**	(23)	**16**	(25)	**10**	(19)	**13**	(21)
Dyspnoea**	**20**	(28)	**22**	(29)	**15**	(24)	**15**	(19)
Insomnia**	**24**	(29)	**23**	(30)	**24**	(29)	**21**	(26)
Constipation**	**13**	(23)	**13**	(22)	**12**	(25)	**8**	(16)
Diarrhoea**	**9**	(19)	**10**	(20)	**6**	(16)	**6**	(15)

BFI= Brief Fatigue Inventory, EORTC QLQc30 = European Organisation for Research and treatment of cancer core 30, QL = quality of life, SD = standard deviation

* Higher scores = better function, ** Higher scores = worse symptoms

Table 8.3 Categorical variables for the non-cancer group and recurrence free prostate cancer group and according to previous treatment received.

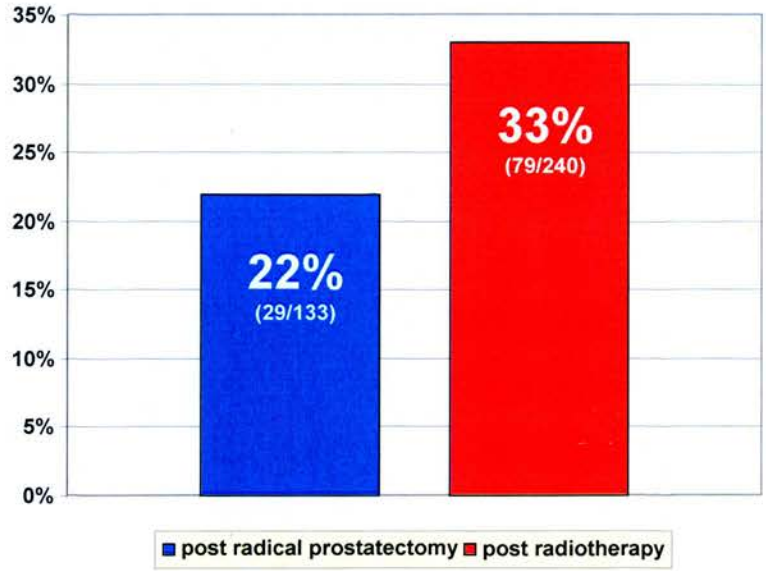
	Recurrence free prostate cancer group		Recurrence free prostate cancer group initial treatment				Non-cancer group	
			Radiotherapy		Radical rostatectomy			
	n=377		n=244		n=133		n=63	
	%	n	%	n	%	n	%	n
Fatigue								
Substantial Global Fatigue (BFI global fatigue >3)	**29**	108	**33**	79	**22**	29	**16**	10
Fatigue is a problem	**29**	107	**34**	81	**20**	26	**-**	-
Fatigue present > 1 month	**30**	110	**35**	83	**21**	27	**-**	-
HADS								
Anxiety ≥ 9	**13**	50	**14**	34	**12**	16	**13**	8
Depression ≥ 8	**14**	52	**16**	39	**10**	13	**8**	5
Depression -Qu8 ≥ 8	**7**	27	**10**	23	**3**	4	**6**	4
moderate/severe urinary symptoms (IPSS > 7)	**37**	139	**41**	99	**30**	40	**69**	43
Other symptoms 'quite a bit' & 'a lot'								
urine incontinence	**7**	25	**5**	12	**10**	13	**-**	-
dysuria	**1**	4	**1**	3	**1**	1	**-**	-
faecal incontinence	**3**	10	**3**	7	**2**	3	**-**	-
rectal bleeding	**3**	11	**5**	11	**0**	0	**-**	-
Erectile Function								
not possible/severely reduc	**79**	287	**76**	177	**85**	110	**45**	28
Serious problem/quite a problem	**30**	107	**30**	69	**48**	38	**46**	13
Comorbidities								
cardiac problems	**31**	114	**37**	86	**21**	28	**46**	29
respiratory problems	**24**	88	**27**	63	**19**	25	**8**	5
diabetes	**11**	40	**15**	35	**4**	5	**10**	6
cerebrovascular accident	**8**	29	**10**	22	**5**	7	**3**	2
depression	**15**	54	**16**	36	**14**	18	**5**	3
musculoskeletal problems	**40**	147	**41**	96	**39**	51	**21**	13
neurological problems	**1**	5	**1**	3	**2**	2	**-**	-
total comorbidities NONE	**29**	106	**24**	59	**35**	47	**40**	25
ONE	**37**	136	**34**	82	**41**	54	**33**	21
TWO +	**36**	133	**42**	101	**24**	32	**27**	17

BFI= Brief Fatigue Inventory, HADS – Qu8= Hospital Anxiety and Depression Scale minus question 8, IPSS= International Prostate Symptom Score, SIMD= Scottish Index of Multiple Deprivation

8.5.1 Prevalence and associations of Substantial Global Fatigue

The estimated prevalence of Substantial Global Fatigue was 29% (108/377) for the whole group. Put in context this is higher than the non-cancer comparison group of men with benign prostatic hypertrophy from studies A and B (16%, 10/63, p=0.031).

Figure 8.1 Proportions of patients with Substantial Global Fatigue who had undergone radical prostatectomy or radiotherapy



There was a significant association between fatigue and treatment received. Patients who had received radiotherapy were 1.8 times more likely to have Substantial Global Fatigue than those who had undergone radical prostatectomy (33% vs. 22%, p= 0.024, figure 8.1)

Men with Substantial Global Fatigue had significantly poorer global health related quality of life, poorer physical, role and social function, more pain and insomnia (see table 8.4). Substantial Global Fatigue was much more likely in men who had depression (odds ratio 18.8, but only 40% of those patients had depression, so did not account for all the fatigue. This dropped to 21% once the confounding fatigue item from the HADS was excluded). Substantial Global Fatigue was also more likely in men with anxiety (odds ratio 8), moderate/severe urinary symptoms (odds ratio 4.5) and concurrent comorbidities (see table 8.5). In addition it was associated with

having "quite a bit/ a lot" of faecal incontinence (8% vs. 1% p=0.001) and urinary incontinence (14% vs. 4% p<0.001). Substantial Global Fatigue was not associated with age, social deprivation category or time since treatment. The majority of men had erectile dysfunction regardless of their fatigue status however men with Significant Global Fatigue more frequently said they regarded this as quite a problem/a serious problem (44.4% vs. 23.5%, p=0.001).

Table 8.4 Univariate associations of continuous variables with Substantial Global Fatigue (p<0.05 in bold)

	Global Fatigue				
	Substantial n=108		None/mild n=265		
Variable	mean	(SD)	mean	(SD)	P-value
Age	**71.8**	(6.4)	**72.1**	(6)	0.600*
Months since treatment					
median (range)	**55**	(23,143)	**54**	(13, 233)	0.515
EORTC QlQc30 scores					
Global health status/QL*	**53**	(20)	**81**	(14)	**<.0001**
Physical function*	**61**	(23)	**89**	(14)	**<.0001**
Role function*	**57**	(30)	**93**	(15)	**<.0001**
Social function*	**56**	(30)	**90**	(18)	**<.0001**
Pain**	**30**	(31)	**7**	(15)	**<.0001**
Insomnia**	**43**	(35)	**16**	(23)	**<.0001**
Diarrhoea**	**16.0**	(25)	**5.8**	(14)	**<0.001**
Constipation**	**20.1**	(29)	**9.3**	(20)	**<0.001**
All compared using Mann Whitney U Tests except * Student t-test					
EORTC QLQc30 = European Organisation for Research and treatment of cancer core 30, QL = quality of life					
* Higher scores = better function, ** Higher scores = worse symptoms					

8.5.2 Independent associations of Substantial Global Fatigue

Treatment received, urinary symptoms, medical comorbidities, anxiety and depression were entered into a multivariate logistic regression. Treatment received was no longer associated with Substantial Global Fatigue once the other factors were controlled for. Depression was the strongest independent predictor with an odds ratio of 10.9 (see table 8.5). When HADS question 8 was removed the odds ratio was still 10.6 with minimal change in the odds ratios of the other variables.

Table 8.5 Univariate and multivariate analysis of categorical variables and association with Substantial Global Fatigue

Variable	Total	Global Fatigue				Univariate analysis			Multivariate analysis*		
		Substantial n=108		None/mild n=265		Odds ratio	95% CI	p-value (Wald Chi Sq. value)	Odds ratio	95% CI	P-value (Wald Chi Sq. value)
	n	%	n	%	n						
Treatment:								**0.024**			**0.1979**
radical prostatectomy	133	**27**	29	**39**	104	1		(5.1)	1		(1.7)
radiotherapy	240	**73**	79	**61**	161	1.8	(1.1, 2.9)		1.5	(0.8, 2.8)	
Urinary Symptoms (IPSS)								**<.0001**			**<0.0001**
None/mild	235	**38**	41	**74**	194	1		(38.9)	1		(18.0)
Moderate/severe	137	**62**	67	**27**	70	4.5	(2.8, 7.3)		3.4	(1.9, 6.0)	
Comorbidities:								**<.0001**			**0.0027**
None	105	**9**	10	**36**	95	1		(32.3)	1		(11.9)
One	135	**35**	37	**37**	98	3.6	(1.7, 7.6)		3.8	(1.7, 8.8)	
Two or more	132	**56**	60	**27**	72	7.9	(3.8, 16.5)		3.9	(1.7, 8.9)	
HADS anxiety ≥ 9								**<.0001**			**0.0109**
no	323	**68**	73	**94**	250	1		(38.3)	1		(6.5)
yes	50	**32**	35	**6**	15	8.0	(4.1, 15.4)		2.9	(1.3, 6.6)	
HADS depression ≥ 8								**<.0001**			**<0.0001**
no	321	**60**	65	**97**	256	1		(56.1)	1		(29.6)
yes	52	**40**	43	**3**	9	18.8	(8.7, 40.6)		10.9	(4.6, 25.9)	
HADS depression - Qu8 ≥ 8								**<.0001**			
no	346	**79**	85	**99**	261	1		(26.7)		See text	
yes	27	**21**	23	**2**	4	17.7	(5.9, 52.5)				

SIMD= Scottish Index of Multiple Deprivation, HADS –Qu 8= Hospital Anxiety and Depression Scale minus question 8 'I feel slowed down', IPSS= International Prostate Symptom Score

* Substantial Global Fatigue n= 107, none/mild n= 264

8.5.3 Fatigue a problem or not

Of those who had Substantial Global Fatigue, 75% (79/106) said it was a problem. These patients were slightly younger (71.2 vs. 73.2years) and had more urinary symptoms (68 vs. 46% moderate/severe urinary symptoms), and a greater proportion had depression (46 vs. 21%, HADS depression minus question 8, 26% vs. 7%). The proportions who had received radiotherapy were similar (75% vs. 69%).

76% (80/106) had experienced fatigue for longer than one month. 66% (70/106) said fatigue was both a problem and had been present for longer than one month.
65/107 patients with Substantial Global Fatigue suggested a possible cause of their fatigue (shown in table 8.6) only four men attributed it to their previous prostate cancer treatment.

Table 8.6. Possible causes of fatigue suggested by 65/107 patients with Substantial Global Fatigue

	Frequency		Frequency
cardiorespiratory problems	13	diabetes	2
stress	6	blood pressure	2
arthritis	6	age	2
sleep problems	5	weather	1
pain	5	weak legs	1
radiotherapy	4	pernicious anaemia	1
infection	4	neuropathy	1
job	3	medication	1
gardening/DIY	3	feelings of weakness	1
stroke	3	bowel frequency	1
nocturia	3	rectal blood loss	1
parkinsons	2	kidney failure	1
operation (non prostate)	2	overweight	1

numbers do not add up to 65 because some patients suggested more than one reason

8.6 DISCUSSION

8.6.1 Main findings

Almost one third of recurrence free prostate cancer survivors had fatigue that interfered with function (Substantial Global Fatigue). Patients who had undergone radiotherapy were more likely to have Substantial Global Fatigue than radical prostatectomy patients but this was no longer the case after controlling for urinary symptoms, depression, anxiety and concurrent comorbidities. Of these, depression was the most strongly associated, even with the confounding HADS fatigue item 8 removed. This suggests fatigue may be more strongly associated with comorbidities and psychological variables than the type of prostate cancer treatment received.

Fatigue was more prevalent in men with a history of prostate cancer than the non-cancer comparison group. This could be because prostate cancer group were older but as age was not an association or a predictor of fatigue this is unlikely. Urinary symptoms are known to be associated with fatigue (Jakobsson *et al.* 2004) but only 37% had moderate to severe urinary symptoms as opposed to 69% in the non-cancer group. The severity of anxiety and depression was similar but a greater proportion of the prostate cancer group had concurrent comorbidities. However the non-cancer group was small so these results must be interpreted with caution.

8.6.2 Limitations

As with all cross sectional studies we can estimate prevalence but not incidence. Prospective studies are required to fully understand the incidence and trajectory of fatigue after differing prostate cancer treatments.

The brachytherapy group was too small to allow robust statistical analysis, consequently any comment can only be limited to patients who have had radiotherapy or radical prostatectomy.

Patient characteristics confound treatment decisions, consequently the treatment groups may have been slightly different at baseline. Men who undergo radical prostatectomy have to be fit enough for a general anaesthetic whereas those who get

radiotherapy tend to be older, have more comorbidity and therefore could be expected to have higher levels of fatigue. However attempts were made to address this by conducting a multivariate analysis.

It should be noted that a small number of men (n=18) in the radical prostatectomy group also had post operative radiotherapy. As a subgroup these patients were found to have slightly higher fatigue scores which may have artificially increased the prevalence of Substantial Global Fatigue in the radical prostatectomy group. It would not have been statistically meaningful to treat these men as a separate group.

The sample may not be fully representative of the whole population of those treated for prostate cancer. Although it is routine for all men to go onto the postal follow up system one year post treatment, patients who are anxious or more symptomatic, or on two years of adjuvant androgen deprivation therapy may continue to attend out patient clinics. However, the number of such cases is estimated by the responsible clinicians to be small.

The historical non-cancer comparison group of Scottish men of a similar age with urinary symptoms was small and statistical power of comparisons is limited. In addition they were not recruited specifically as a comparison group for this study. Ideally I would have compared to a larger group of men without a history of cancer but it was difficult to identify a representative, accessible population from which to recruit. The other option would have been to compare to Brief Fatigue Inventory normative data in men of this age group but there is none available (personal communication with the authors of the BFI in 2003)

Substantial Global fatigue was defined as global fatigue > 3. Work from Study B suggests this does not equate with interview defined clinically significant fatigue (CSF) and this cut off may underestimate the prevalence of CSF in this group. Ideally I would have interviewed all patients to assess whether they were cases of CSF. However this was not feasible.

Using proposed cut offs for continuous variables (such as global fatigue and HADS anxiety and depression), whilst making the results more clinically meaningful can reduce the statistical power of detecting a relationship between a variable and outcome (Altman & Royston 2006). It is appreciated that the HADS cut offs are not the same as an interview defined case definition of depression or anxiety.

Comorbidities were not assessed using a validated scale. In Studies A and B, the Charlson Comorbidity Index was used but in this situation it was not a feasible tool as it depends on reviewing medical case notes. In addition, it was originally devised to predict the likelihood of a patient dying and so only included potentially life threatening medical conditions. From earlier work and talking to patients it quickly became obvious that the Charlson Comorbidity Index did not pick up conditions that may significantly affect a person's life and possibly fatigue e.g. arthritis and Parkinson's Disease. Asking about other medical conditions enabled me to account for these, though relied heavily on the patient's interpretation of the questions and recall/understanding of their medical history.

8.6.3 Other literature

One of the limitations of comparing any study to the other literature is the heterogeneity of fatigue scales used, populations studied and the differing criteria for defining fatigue as being present. Only two studies have specifically examined fatigue in post treatment prostate cancer patients and one of them used the same scale, the Brief Fatigue Inventory (Vordermark *et al.* 2002) . This cross sectional study examined 103 men who had had radiotherapy a median of 2.1 years previously. They used a cut off of 7 or greater to represent 'severe fatigue' on the single item of 'worst fatigue' and found the prevalence was 18.7%. They suggested this was due to late toxicity from radiotherapy however some men still had cancer present and 29% were receiving androgen suppression, both of which may have confounded the findings. Applying the same criteria to my data, the corresponding prevalence was similar in my sample (18.9%). The majority of their remaining analysis focuses on the mean global fatigue score as a continuous variable (overall mean 2.8+/- 2.3 standard deviation). Correspondingly the radiotherapy patients in the present study

sample scored 2.4 +/-2.2 and the radical prostatectomy group were significantly lower at 1.8 +/-2.0 (see table 8.2).

Several papers have compared different prostate cancer treatments using quality of life measures. The majority do not report fatigue findings. Of those that have, one examined patients up to 5 years post treatment and found radiotherapy patients had lower vitality (measured by the SF-36) than radical prostatectomy patients (Bacon *et al.* 2001) whereas others found no difference at 2 or 5 years (Potosky *et al.* 2000;Potosky *et al.* 2004). Those that compared to control data found fatigue/vitality scores were similar regardless of type of treatment received (Lilleby *et al.* 1999;Brandeis *et al.* 2000;Penson *et al.* 2003).

Literature published since October 2003

At the time of designing this study there was no information about fatigue after brachytherapy or radical prostatectomy. Since then, a cross sectional survey has been published that compared the 'psychological functioning' of 861 men who had had either radiotherapy, radical prostatectomy or brachytherapy (Hervouet *et al.* 2005). Fatigue was one of the symptoms assessed and was measured using the Multidimensional Fatigue Inventory. They applied a cut off for 'clinical fatigue' (but did not detail the justification for this) and found the prevalence to be 18.5% overall. Radiotherapy, brachytherapy and radical prostatectomy groups had respective prevalence of 23.6%, 19.8% and 12.7%. They too found radiotherapy patients had significantly higher odds than the other treatments of having clinical fatigue (and depression) but did not compare their findings to a control group. Although a good sized sample, it only represented 56% of the population invited to participate and included those who had relapsed local or metastatic cancer. The present study had a 91% participation rate and specifically focussed on men who were recurrence free.

Another study reported a secondary multivariate analysis of prospectively collected data on 149 patients who under went radiotherapy/brachytherapy (grouped together), radical prostatectomy or watchful waiting. They found that treatment did not predict being fatigued at follow up. While this study is the first to attempt to solely examine predictors of fatigue, it had several shortcomings: fatigue was not measured using a

fatigue specific instrument and the time since treatment was not clear as the follow up data was reported as "6-12 months after prostate biopsy" which can predate treatment by several months (Maliski *et al.* 2005).

A cross sectional study of 249 patients more than 2 years after radiotherapy showed EORTC fatigue scores were very similar to over 70s German normal population data (mean 29.5 vs. 27.8; the mean score for the present study was similar at 25.1). However in this study 34% had relapsed disease which may have confounded fatigue findings (Geinitz *et al.* 2006).

8.6.4 Conclusions

This cross sectional survey is the first study to specifically focus on fatigue in recurrence free prostate cancer survivors. Fatigue that interferes with function was present in approximately one third and was more than a non-cancer comparison group. Fatigue was associated with treatment but not after controlling for depression, comorbidities and urinary symptoms. Care should be focussed on optimising identification and management of these conditions which may improve fatigue.

CHAPTER

9

STUDY D

FATIGUE IN MEN WITH HORMONE CONTROLLED PROSTATE CANCER: A CROSS SECTIONAL SURVEY

Chapter 9,
List of Sections

9.1 INTRODUCTION

The background to this study has been covered in Chapter 2 but is summarised here.

Androgen deprivation therapy ('hormone treatment') is the primary therapy for men with metastatic prostate cancer or those with localised disease who are not suitable for surgery or radiotherapy. For those with high risk, early localised disease, adjuvant hormone treatment is also given for two years after radiotherapy or surgery to reduce the risk of recurrence.

Most commonly long term androgen deprivation is in the form of LHRH (lutinising hormone releasing hormone) analogue injections given every three months. This lowers the levels of circulating testosterone, thus preventing prostate tumour growth. If primary treatment fails, other hormonal treatments can be commenced such as oral antiandrogens (i.e. biclutamide), stilboestrol and prednisolone. Often the cancer can be controlled in this way for several years and treatment is continued until either the disease becomes hormone refractory or the patient dies of other causes.

Androgen deprivation therapy is known to be associated with a number of side effects, most commonly hot flushes, impotence and loss of libido. Others include gynaecomastia (breast enlargement) anaemia, muscle wasting, depression, increase in fat deposition and a decline in cognitive function (Holzbeierlein *et al.* 2004). In my clinical experience patients also commonly complain of fatigue. However there is very little literature that has specifically addressed this symptom in prostate cancer patients. In common with Study A, the only published study that has, found that fatigue increased after three months of androgen deprivation (Stone *et al.* 2000a). To date there are no published data specifically examining the prevalence of fatigue in men receiving long term hormone treatment for prostate cancer.

In other cancers, fatigue is common in advanced disease. Hormone treatment is used to control both localised and metastatic prostate cancer but to my knowledge there are no data comparing fatigue in prostate cancer patients with different stages of disease.

Prostate cancer survival is often in terms of many years and so it is important to identify symptoms that affect patients' quality of life. There is a clear need for a representative study specifically exploring the problem of fatigue and its associations in men with hormone controlled prostate cancer.

9.2 AIMS

To determine the prevalence and associations of Substantial Global Fatigue (Brief Fatigue Inventory global fatigue > 3) in men with hormone controlled prostate cancer.

To determine whether there is any difference in the prevalence of Substantial Global Fatigue between patients who have local or metastatic disease.

To compare the prevalence of Substantial Global Fatigue to a historical non-cancer comparison group of men with benign prostatic hypertrophy (from Studies A and B).

9.3 HYPOTHESES

Substantial Global Fatigue will be associated with poorer quality of life, depression, anxiety and pain.

The prevalence of Substantial Global Fatigue in men with hormone controlled prostate cancer will be higher in men with metastatic disease than local disease.

Men with hormone controlled prostate cancer will have a higher prevalence of Substantial Global Fatigue than a historical non-cancer comparison group.

9.4 METHODS

9.4.1 Design

A cross sectional postal survey supplemented with retrospective clinical data.

9.4.2 Patient Sample

Men with prostate cancer in the county of Fife receive multidisciplinary care from the Urologists based in the District General Hospitals (Queen Margaret Hospital (QMH), Dunfermline and Victoria Hospital, Kirkcaldy) and an Edinburgh Cancer Centre Oncologist who does a weekly clinic at QMH.

In Fife, all LHRH analogue injections are centrally coordinated and delivered by the Clinical Nurse Specialists based at QMH. Men on long term androgen deprivation therapy for prostate cancer receive injections every three months and their PSA (prostate specific antigen) is checked at the same time. This setting provided the ideal opportunity for collecting data from a representative sample of men receiving long term androgen deprivation therapy in a geographically defined area.

Inclusion criteria

- Localised or metastatic prostate cancer
- The patient had been on androgen deprivation therapy for at least three months
- PSA <0.2μg/L within the last three months (indicating their prostate cancer was controlled) or if above 0.2μg/L, then stable at nadir for at least two consecutive readings a minimum three months apart

Exclusion criteria

- On neo-adjuvant androgen deprivation therapy prior to radiotherapy or brachytherapy (these patients only had treatment for three months)
- Hormone refractory prostate cancer (their cancer would not be controlled and may have confounded fatigue findings)
- Another concurrent cancer diagnosis (as other cancers can be associated with fatigue and this may have confounded the findings).

Recruitment

Between November 2005 and February 2006, The Clinical Nurse Specialist identified eligible patients and introduced the survey in a letter which accompanied the patient information sheet, consent form and survey questionnaire. Patients were invited to participate in the survey and post back the questionnaire and consent form in a stamped addressed envelope provided. Potential participants who did not return the questionnaire within one month, were sent another one by post. Demographic and clinical details of non participants were noted.

9.4.3 Non-cancer comparison group

This was a historical comparison group which comprised of the 63 men with benign prostatic hypertrophy recruited for Studies A and B.

9.4.4 Demographic and Clinical Data Collected

- Date of birth
- Postcode, to assess Scottish Index of Multiple Derivation see section 5.1.1.
- Marital status (data from patient questionnaire)
- Most recent PSA result
- Disease status (localised/metastatic) from medical notes or radiological records

9.4.5 Self Rated Questionnaire Measures

- **The Brief Fatigue Inventory (BFI)** As it was not possible to interview patients, a cut off of global fatigue >3 was used to define fatigue of a clinically relevant severity (termed Substantial Global Fatigue), see section 4.1.2.1.

- **Two additional questions** which could be answered,"Yes" or "No"
  - "Has fatigue been a problem for you in the last week?" This was asked because in previous work, although some patients said they felt fatigued, they did not find it a problem because they were able to adjust their lives

accordingly by for example putting things off until the next day because they were retired.

- "Have you felt fatigued for longer than one month?" This was to ascertain whether fatigue was more than an acute problem. A period of one month was chosen as this corresponded to the work that was done regarding the case definition of CSF (clinically significant fatigue).

- **One open question** "If yes, to either of the above, what do you think contributed to it or caused it [fatigue]?"

- **Hospital Anxiety and Depression Scale (HADS)**, see section 5.4.1.

- **European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire core 30 version 3.0 (EORTC QLQc30)**, see section 5.4.2. In order to focus on the most relevant issues for this population only the following subscales and items were selected: physical, role, and social functioning, three symptom scales (fatigue, nausea and vomiting) ,and single items (dyspnoea, insomnia, constipation, diarrhoea). This reduced the patient questionnaire burden and avoided replication of question themes (i.e. using both the HADS and the emotional functioning subscale to measure similar things).

- **International Prostate Symptom Score (IPSS)**, see section 5.4.4, with a preliminary question asking if they had a urinary catheter. If so, they did not fill in the IPSS score as the questions were irrelevant.

- **Likert scales for erectile function** and how much of a problem this is, see section 5.4.3.

- **Likert scales for common side effects** from prostate cancer, androgen deprivation or previous prostate cancer treatment as fatigue may be associated with symptom burden. These side effects were also of particular

interest to the responsible clinicians. Each item related to the past week and is answered on a four point scale; not at all, a little, quite a bit, very much.

- urinary incontinence and dysuria as these are not covered by the IPSS.
- faecal incontinence and rectal bleeding
- hot flushes and sore nipples or breasts which are common side effects of androgen suppression.

- **'Worst pain'** item from the Brief Pain Inventory (Cleeland CS 1989) This cohort included men with metastatic disease so it was decided this symptom should be investigated. Patients were asked to rate their worst pain in the last week on an 11 point scale between 0 ('no pain') and 10 ('pain as bad as you can imagine'). This has been found to be the most sensitive item and is brief and well validated (Serlin *et al.* 1995).

- **Other Comorbidities**

  It was not feasible to obtain copies of all peripheral hospital notes or to ask the GP about each patient's past medical history and comorbidities. Patients were instead asked about the most common comorbidities that may influence fatigue (cardiovascular and respiratory problems, diabetes, stroke, depression, musculoskeletal problems or another cancer diagnosis). There was also an open question allowing them to mention any other medical conditions they thought we should know about and medications they were taking. This approach is similar to that employed by other authors (Lilleby *et al.* 1999).

9.4.6 Ethical Approval

The study was approved by the Fife and Forth Valley Local Research Ethics Committee. Reference number 05/S0501/108.

9.4.7 Statistical Analysis

Data were inspected using histograms and box plots and described using means, medians and percentages of categories as appropriate. To assess whether the data was representative of the eligible sample, data from participants and non participants were compared using Student t-tests and Chi squared tests as appropriate.

Fatigue was described as the global fatigue score and the percentage who had Substantial Global Fatigue (global fatigue score >3). Prevalence of Substantial Global Fatigue was compared to the non-cancer group using Chi squared tests

Univariate associations of Substantial Global Fatigue were examined using binary logistic regression for categorical variables and Student t-tests and Mann Whitney tests as appropriate for continuous variables. Independent associations of Substantial Global Fatigue were examined using multivariate analysis with no selection. Variables such as physical, role and social functioning were not included as these could be regarded as outcomes of fatigue rather than predictors. HADS depression question 8 "I feel as if I am slowed down" may be construed as referring to fatigue. Hence associations between Substantial Global Fatigue and depression were performed both including and excluding this item. This approach has been previously reported (Stone *et al.* 2000a).

A p value of <0.05 was considered statistically significant. I was advised and assisted with the statistical analysis by Dr Isabella Butcher, Research Fellow, Public health Sciences, University of Edinburgh using SAS/STAT software, Version 9.1 of the SAS System for Windows. Copyright © 2002-2003 SAS Institute Inc.

9.5 RESULTS

There were 298 patients with prostate cancer who were on long term androgen deprivation therapy, 211 of which had hormone controlled disease. 204 fulfilled the eligibility criteria and were sent the questionnaire package. Two patients subsequently transpired to have another concurrent cancer diagnosis and carers informed me that four patients had severe cognitive impairment and were unable to fill in the questionnaire. These men were deemed ineligible retrospectively and not included in the analysis. Two patients sent back the blank questionnaire saying they were well and did not think the questions were relevant to them. One questionnaire was returned saying the addressee had moved away. The final eligible patient participation rate was 81% (160/198). There were no statistically significant demographic or clinical differences between those who did and did not participate (see table 9.1).

Table 9.1 Comparison of demographic and clinical details of eligible patients who did and did not participate in the survey.

	Eligible Patients				
	Non-participants n=38		Participants n=160		
Variable	**%**	n	**%**	n	**p-value**
SIMD group					**0.801**
1	**16**	6	**18**	28	
2	**22**	8	**31**	49	
3	**19**	7	**15**	24	
4	**30**	11	**24**	38	
5	**14**	5	**12**	19	
Adjuvant hormones					**0.469****
No	**97**	37	**93**	148	
Yes	**3**	1	**8**	12	
Disease Status					**0.267**
local	**58**	22	**70**	111	
metastatic	**42**	16	**29**	47	
unknown	**0**	0	**1**	2	
Mean age in years (SD)	**79.1** (8.9)		**77.2** (7.5)		**0.173***

All were compared using Chi squared test except * Student t test ** Fishers Exact Test

SD = Standard deviation, SIMD= Scottish Index of Multiple Deprivation

The mean age of the sample was 77.2 years (SD 7.5) and the majority (61%) had local disease. 88% (140/160) were on first line hormonal treatment and 7.5% (12/160) were on adjuvant hormonal treatment. 70% were married or cohabiting, 22% were widowed and 8% were unmarried or divorced. Descriptive continuous and categorical variables are shown in tables 9.2 and 9.3.

Table 9.2 Continuous variables for the non cancer group and hormone controlled prostate cancer group according to disease extent

	Hormone controlled prostate cancer		Hormone controlled prostate cancer				Non-cancer group	
			local disease		metastatic disease			
	n=160		n=111		n=47		n=63	
	mean	**SD**	**mean**	**SD**	**mean**	**SD**	**mean**	**SD**
Fatigue								
global fatigue (BFI)	**3.1**	(2.4)	**3.3**	(2.5)	**2.7**	(2.2)	**1.8**	(1.7)
EORTC Fatigue Score	**35**	(24)	**38**	(25)	**31**	(22)	**21**	(15)
Age in years	**77.2**	(7.5)	**78.1**	(7.5)	**75.4**	(7.0)	**66.2**	(6.7)
EORTC QLQc30								
Global Health Related QL*	**65**	(23)	**63**	(25)	**70**	(20)	**80**	(15)
Physical Function*	**67**	(25)	**65**	(26)	**71**	(21)	**89**	(15)
Role Function*	**68**	(33)	**66**	(34)	**72**	(31)	**91**	(18)
Cognitive Function*	**75**	(23)	**74**	(24)	**76**	(21)	**80**	(16)
Social Function*	**72**	(33)	**67**	(34)	**80**	(29)	**86**	(22)
Nausea**	**5**	(11)	**4**	(12)	**5**	(11)	**3**	(13)
Dyspnoea**	**31**	(33)	**33**	(35)	**25**	(31)	**15**	(19)
Insomnia**	**32**	(32)	**33**	(32)	**30**	(32)	**21**	(26)
Constipation**	**21**	(29)	**20**	(30)	**24**	(27)	**8**	(16)
Diarrhoea**	**9**	(20)	**10**	(22)	**4**	(11)	**6**	(15)

BFI = Brief Fatigue Inventory, EORTC QLQc30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30. QL = quality of life

* Higher scores = better function, ** Higher scores = worse symptoms

Table 9.3 Categorical variables for the non-cancer group and the hormone controlled prostate cancer group according to disease extent

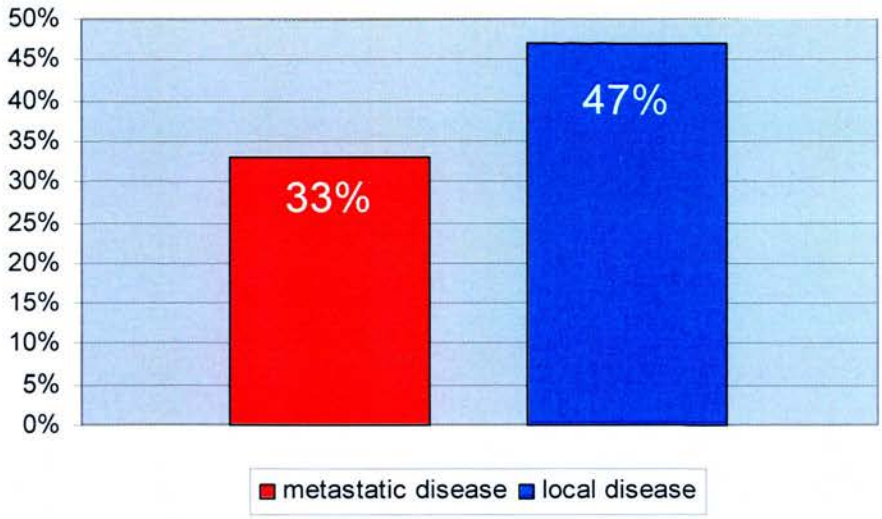
	Hormone controlled prostate cancer		Hormone controlled prostate cancer				Non-cancer group	
			local disease		metastatic disease			
	n=160		n=111		n=47		n=63	
	%	n	%	n	%	n	%	n
Fatigue								
substantial global fatigue (BFI global fatigue >3)	**43**	68	**47**	52	**33**	15	**16**	10
Fatigue is a problem:	**45**	70	**47**	50	**43**	20	-	-
Fatigue present > 1 month	**44**	67	**47**	50	**39**	17	-	-
Pain								
BPI worst pain ≥ 4	**28**	42	**32**	34	**19**	8	-	-
HADS								
Anxiety ≥ 9	**19**	30	**19**	21	**20**	9	**13**	8
Depression ≥ 8	**28**	44	**28**	31	**29**	13	**8**	5
Depression -Qu8 ≥ 8	**12**	18	**12**	13	**11**	5	**6**	4
moderate/severe urinary symptoms (IPSS)	**48**	74	**51**	53	**46**	21	**68**	43
Other symptoms 'quite a bit' & 'a lot'								
urine incontinence	**4**	6	**6**	6	**0**	0	-	-
dysuria	**1**	1	**0**	0	**2**	1	-	-
faecal incontinence	**3**	4	**3**	3	**2**	1	-	-
Hot flushes	**35**	55	**36**	39	**33**	15	-	-
Sore breasts	**8**	13	**8**	8	**11**	5	-	-
Erectile Function								
not possible/severely reduced	**97**	150	**95**	102	**100**	46	**45**	28
Serious problem/quite a problem	**22**	34	**21**	22	**24**	11	**21**	13
Comorbidities								
cardiac problems	**39**	61	**42**	46	**30**	14	**46**	29
respiratory problems	**37**	57	**39**	43	**30**	13	**8**	5
diabetes	**13**	20	**15**	16	**9**	4	**10**	6
cerebrovascular accident	**9**	13	**10**	10	**7**	3	**3**	2
depression	**17**	25	**18**	18	**16**	7	**5**	3
musculoskeletal problems	**58**	91	**59**	64	**60**	27	**21**	13
neurological problems	**2**	3	**3**	3	**0**	0	**0**	0
total comorbidities NONE	**15**	24	**16**	17	**15**	7	**40**	25
ONE	**33**	53	**28**	31	**43**	20	**33**	21
TWO +	**52**	82	**56**	62	**43**	20	**27**	17

BFI = Brief Fatigue Inventory, BPI= Brief Pain Inventory, HADS= Hospital Anxiety and Depression Scale minus question 8, IPSS= International prostate symptom score.
Not all rows add up to 160 because 2 patients' disease status was unclear

9.5.1 Prevalence and associations of Substantial Global Fatigue

The estimated prevalence of Substantial Global Fatigue in men with hormone controlled prostate cancer was 43% (68/160). Put in context this is higher than the non-cancer comparison group of men with benign prostatic hypertrophy from studies A and B (16%, 10/63, p=0.0002). Men with locally advanced prostate cancer had a higher prevalence of Substantial Global Fatigue than those with metastatic disease but sample numbers in the latter group were small and this did not achieve statistical significance (47 vs. 33%, p= 0.10, figure 9.1)

Figure 9.1 Prevalence of Substantial Global Fatigue in men with hormone controlled metastatic and locally advanced prostate cancer



Men with Substantial Global Fatigue had poorer global health related quality of life, poorer physical, role, and social function and higher insomnia scores (see table 9.4). It was significantly more likely in men who had depression (odds ratio 9.8, dropping to 8.4 once HADS question 8 was excluded), anxiety (odds ratio 5.0), worst pain ≥ 4 (odds ratio 9.2), moderate/severe urinary symptoms (odds ratio 3.3) and concurrent comorbidities (see table 9.5). Substantial Global Fatigue was not associated with age or deprivation category.

Table 9.4 Univariate associations of continuous variables with Substantial Global Fatigue (p<0.05 in bold)

Variable	Global Fatigue				P-value
	Substantial n=68		None/mild n=91		
	mean	SD	mean	SD	
Age	77.3	(8.7)	77.1	(6.6)	0.8823 *
EORTC QLQc30 scores					
Global health related QL*	52	(21)	74.7	(20)	**<.0001**
Physical function*	50	(21)	79.6	(20)	**<.0001**
Role function*	47	(34)	84.5	(22)	**<.0001**
Social function*	49	(33)	88.6	(22)	**<.0001**
Insomnia**	38	(35)	26.6	(29)	**0.0466**

All compared using Mann Whitney U test except * Student t-test

EORTC QLQc30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire core 30, QL = quality of life

* Higher scores = better function, ** Higher scores = worse symptoms

9.5.2 Independent associations of Substantial Global Fatigue

Urinary symptoms, comorbidities, anxiety, depression, disease status and 'worst pain' scores were entered into a multivariate logistic regression. Worst pain ≥ 4 and depression were the only independent associations of Substantial Global Fatigue (odds ratios 3.0 and 4.9 respectively) after controlling for the other factors. In case HADS depression question 8 "I feel slowed down" was confounding the relationship with fatigue, a second regression was performed excluding this question. This resulted in worst pain ≥ 4 being the only independent association with Substantial Global Fatigue (odds ratio 4.4, see table 9.5).

Table 9.5 Univariate and multivariate associations (with and without HADS depression question 8) of Substantial Global Fatigue

Variable	Global Fatigue		Univariate		Multivariate		Multivariate with HADS depression –Qu 8	
	Substantial %	one/mild %	Odds ratio (95% CI)	p-value Vald Chi Sq value)	Odds ratio (95% CI)	p-value (Wald Chi Sq value)	Odds ratio (95% CI)	p-value (Wald Chi Sq value)
Disease status				**0.1028**		**0.1906**		**0.317**
Local	78	66	1	(2.7)	1	(1.7)	1	(1.0)
Metastatic	22	34	0.5 (0.3, 1.1)		0.5 (0.2, 1.4)		0.6 (0.2, 1.6)	
BPI worst pain ≥ 4				**<.0001**		**0.0359**		**0.0034**
No	48	90	1	(26.5)	1	(4.4)	1	(8.6)
Yes	52	10	9.2 (4.0, 21.5		3 (1.1, 8.6)		4.4 (1.6, 11.8)	
Urinary Symptoms (IPSS):				**0.0005**		**0.2593**		**0.2625**
None/mild	34	64	1	(12.3)	1	(1.3)	1	(1.3)
Moderate/severe	66	36	3.3 (1.7, 6.6)		1.6 (0.7, 3.9)		1.6 (0.7, 3.8)	
Comorbidities:				**<.0001**		**0.1784**		**0.1172**
None	3	23	0.1 (0.0, 0.3)	(21.1)	0.2 (0.0, 1.2)	(3.4)	0.2 (0.0, 1.2)	(4.3)
One	24	41	0.3 (0.1, 0.6)		0.6 (0.2, 1.5)		0.5 (0.2, 1.3)	
Two or more	74	36	1		1		1	
HADS anxiety ≥ 9				**0.0004**		**0.2194**		**0.0809**
No	67	91	1	(12.7)	1	(1.5)	1	(3.0)
Yes	33	9	5 (2.1, 12.2)		2.3 (0.6, 8.8)		3 (0.9, 10.7)	
HADS depression ≥ 8				**<.0001**		**0.0047**		-
No	48	90	1	(28.5)	1	(8.0)	-	-
Yes	52	10	9.8 (4.3, 22.8		4.9 (1.6, 14.7)		-	
HADS depression-Qu8 ≥ 8				**0.0012**		-		**0.1475**
No	78	97	1	(10.5)	-	-	1	(2.1)
Yes	22	3	8.4 (2.3, 30.3		-		3 (0.7, 13.1)	

BPI = brief pain inventory, CI = confidence interval, HADS= Hospital anxiety and depression scale, IPSS = International prostate symptom score

9.5.3 Fatigue a problem or not

Of those who had Substantial Global Fatigue, 82% (51/62) said it was a problem. These patients were older (78.1 vs. 73.8years), had more moderate to severe urinary symptoms (68 vs.54%), more comorbidities (78 vs. 54% had two or more comorbidities) more pain ('worst pain' ≥ 4, 55 vs.33%) and a greater proportion had depression (59 vs. 23%).

81% (50/62) had experienced fatigue for longer than one month. 74% (46/62) said fatigue was both a problem and had been present for longer than one month. 38/68 patients with Substantial Global Fatigue suggested a possible cause of their fatigue but only four men attributed it to their hormone treatment or prostate cancer. The other causes suggested by patients are in table 9.6.

Table 9.6 Possible causes of fatigue suggested by 38/68 patients with Substantial Global Fatigue

Reason for fatigue suggested by patient	Frequency
other medications	7
cardiorespiratory problems	5
musculoskeletal problems	5
old age	5
infection	2
stress	2
sleep problems	2
prostate cancer	2
pain	2
hormone injections	2
inactivity	1
job	1
other health problems	1
caring for relatives	1
diabetes	1

9.6 DISCUSSION

9.6.1 Main findings

The prevalence of Substantial Global Fatigue in men with hormone controlled prostate cancer was 43%. Of those that were fatigued, 82% said it was a problem and had significantly worse quality of life, poorer role, social and physical functioning. Substantial Global Fatigue was also associated with higher pain scores, depression, anxiety, concurrent comorbidities and more urinary symptoms. After controlling for these factors, the only independent associations of Substantial Global Fatigue were depression and pain. However HADS depression item 8 did confound the relationship and once this was excluded only pain was independently associated.

These results should be interpreted with caution, because the effect of removing the contribution of HADS item 8 to the HADS depression score made the definition of depression more stringent and consequently the depression group became smaller (17 patients). However this would still be an acceptable cut off as other authors have used case definition thresholds for depression as high as 11 (Bjelland *et al.* 2002).

The prevalence of Substantial Global Fatigue was higher than a small non-cancer comparison group of men with benign prostatic hypertrophy. These results must be interpreted with caution as the latter were younger, had less comorbidities and a lower prevalence of depression. In addition they were not recruited specifically as a comparison group for this study. Ideally I would have compared to a group of older men without a history of cancer but it was difficult to identify a representative, accessible population from which to recruit. The other option would have been to compare to Brief Fatigue Inventory normative data in men of this age group but there is none available (personal communication with the authors of the BFI in 2003). It is also noteworthy that this hormone controlled group of prostate cancer patients had a higher prevalence of Substantial Global Fatigue than the recurrence free men in study C (43 vs. 29%).

There is the clinical impression that patients with greater tumour burden experience higher levels of fatigue. This was not confirmed by this study as there was no

statistically significant difference between the prevalence of Substantial Global Fatigue in men with localised or metastatic disease. This was not surprising as by definition, cancer is assumed not to be the cause of fatigue because this cohort had hormone controlled prostate cancer. However, it is interesting to note that there was a counterintuitive trend for those with local disease to have higher fatigue. They also had higher pain scores (presumably not cancer related) and lower role, social and physical functioning. This could be partially explained because they were older and had more comorbidities than the metastatic group. The severity of anxiety and depression were similar regardless of disease stage and so appear not to contribute to the difference in fatigue.

9.6.2 Limitations

The prevalence of Substantial Global Fatigue may be an underestimate. This is because some of the non participants' addresses were in nursing homes and it is possible that these men did not participate because they were too ill or fatigued to do so. However, there was a good response rate to the survey (81%), and no statistical differences between the demographic and clinical characteristics of those who did and did not participate.

As with all cross sectional studies we can estimate prevalence but not incidence. Prospective studies are required to fully understand the incidence and trajectory of fatigue on long term hormone treatment.

The other limitations relate to the measures: (a) The cut off on the BFI global fatigue scale of >3 was applied to define Substantial Global Fatigue. Work from Study B suggests this did not equate to interview defined clinically significant fatigue (CSF) and so may underestimate this. Ideally I would have interviewed all patients to assess whether they were cases of CSF, however this was not feasible (b) The HADS could have also been analysed as a continuous measure but this causes difficulties in interpreting odds ratios which become less clinically meaningful. It is appreciated that the cut offs are not the same as an interview defined case definition of depression or anxiety (c) Comorbidities were not assessed using a validated scale. In

Studies A and B, the Charlson Comorbidity Index was used but in this situation it was not a feasible tool as it depends on reviewing medical case notes. In addition, it was originally devised to predict the likelihood of a patient dying and so only included potentially life threatening medical conditions. From earlier work and talking to patients it quickly became obvious that the Charlson Comorbidity Index did not pick up conditions that may significantly affect a person's life and possibly fatigue e.g. arthritis and Parkinson's Disease. Asking about other medical conditions enabled me to account for these though relied heavily on the patient's interpretation of the questions and recall/understanding of their medical history.

Lastly, some studies found that men on androgen deprivation therapy for three months had a drop of haemoglobin (Strum *et al.* 1997;Ornstein *et al.* 1999). The patients in this study had been on treatment for longer than that. We were unable to check the haemoglobin of our sample due to the postal nature of our survey. However, anaemia is a recognised association of fatigue and should be considered in future investigations.

9.6.3 Other literature

There are no other studies to compare to that have specifically examined fatigue in men with long term hormone controlled prostate cancer. The most similar one prospectively examined fatigue in 62 men receiving androgen deprivation therapy over three months (Stone *et al.* 2000a). These men had various stages of disease and were either receiving hormonal therapy as their primary treatment or as neo-adjuvant treatment before radiotherapy. The authors used four different fatigue scales, one of which was also used in this study (the EORTC fatigue subscale). They reported a significant increase in fatigue scores of three of the scales used but not the EORTC fatigue subscale. This remained unchanged at median of 22/100 (range 0-89) which is lower than the men in this study (median 33, range 0-100) who had been on long term treatment.

Other studies have examined quality of life in men with locally advanced or lymph node positive prostate cancer comparing men who had hormone treatment vs. no

treatment. None of these used a fatigue specific instrument but found SF-36 vitality was lower and EORTC fatigue was statistically significantly higher in those who had androgen deprivation therapy (Herr & O'Sullivan 2000;Potosky *et al.* 2002;Van Andel & Kurth 2003). Fatigue and pain were found to be the most severe symptoms in men with bone metastases prior to hormone treatment (Jonler *et al.* 2005) but there is a lack of studies addressing what happens to fatigue after treatment starts.

9.6.4 Conclusions

To my knowledge this cross sectional study of the first to focus on fatigue in men with hormone controlled prostate cancer. Almost half this population had fatigue of a clinically relevant severity that impaired ability to function and quality of life. For some men with local disease, there is debate about whether they should have hormone treatment at all or just be on active monitoring in view of the detrimental effect on quality of life and limited survival benefit.

Most clinicians (and patients) regard fatigue as an inevitable and untreatable side effect of androgen deprivation therapy. Perhaps this does not have to be the case. Pain was an independent predictor of fatigue, suggesting attention needs to be paid to ensure adequate pain management (of presumably non malignant conditions seeing as their prostate cancer was controlled). In view of the possibility of anaemia developing during treatment, it may be worthwhile haemoglobin being prospectively monitored. Finally, it is recognised that androgen deprivation causes muscle wasting. Exercise may help maintain muscle bulk and has been shown to attenuate fatigue in cancer patients (Windsor *et al.* 2003;Courneya *et al.* 2007). Prospective studies of men on long term androgen deprivation therapy using a fatigue specific measurement instrument are required to fully understand the incidence, impact and possible treatment of fatigue.

CHAPTER

10

CONCLUSION

Chapter 10

List of Sections

10.1 FATIGUE AND PROSTATE CANCER

10.1.1 Why I set out to examine fatigue in prostate cancer

I set out to examine fatigue in prostate cancer patients because there was little published data regarding fatigue in this population despite it being the commonest male cancer. In addition, amongst health professionals involved in the care of prostate cancer patients, there was a difference of opinion about the severity and trajectory of fatigue during and after treatment. Survival of prostate cancer can be in terms of many years and could be considered to be a chronic disease. Consequently survivorship issues and long term side effects of treatment are now attracting increasing recognition and concern amongst oncologists.

10.1.2 What I set out to do

I wanted to explore fatigue in men with prostate cancer from several different perspectives. These included examining fatigue during and after treatment for localised disease and also patients on treatment for more advanced and metastatic disease. Additionally, it was planned to assess fatigue using not only recognised fatigue specific questionnaire measures but an interview defined case definition of clinically significant fatigue that would be devised. Finally I wanted to integrate these subjective assessments with objective biological measures such as cytokines to assess any possible correlates of fatigue.

10.1.3 What was done

After exploring the feasibility of doing several prospective studies in the time available, it became clear I would have to focus on specific areas and some studies would have to be cross sectional.

In total four studies were carried out. Study A was three month pilot prospective study that concentrated on men having radiotherapy, brachytherapy or neo-adjuvant androgen deprivation therapy for localised prostate cancer. Results of this led to Study B which focussed on men having brachytherapy and followed them up for 12 months. Study C was a postal survey examining fatigue in recurrence free survivors more than a year after having radiotherapy or radical prostatectomy. Finally, men

with more advanced disease were examined in Study D, a postal survey of men with hormone controlled prostate cancer. Throughout all this work, fatigue was assessed using a recognised fatigue specific questionnaire. In addition, an interview based case definition of clinically significant fatigue (CSF) was devised and applied in Studies A and B. Potential biological correlates of fatigue were also explored in both these studies.

10.1.4 Main findings

Study A

The pilot study found that examining fatigue in men with early prostate cancer was feasible. Preliminary results indicated that CSF increased in both the radiotherapy and brachytherapy groups one month after treatment but returned to baseline levels in the radiotherapy group, whilst there was the suggestion of prolonged fatigue in the brachytherapy group. Fatigue was not associated with changes in markers of systemic inflammation (CRP and IL-6).

Study B

Following on from the above, Study B focussed on brachytherapy and found that cases of CSF significantly increased between baseline and one month (6 vs. 29%, p=0.001). The prevalence at one and three months was significantly greater than that of men without cancer who were of a similar age (29% vs. 4% p=0.001 and 16% vs. 4% p=0.049 respectively). Those who were cases of CSF at baseline tended to remain so for the 12 months afterwards whereas there were no baseline factors that predicted who developed CSF at one month. Cases of CSF had poorer health related quality of life, poorer physical functioning, poorer role functioning and higher depression scores than non cases. Most cases of CSF had resolved by six months after treatment but those who were cases at baseline tended to remain so. Fatigue was not related to CRP.

For both studies A and B, in contrast to cases of CSF, when fatigue was measured as a continuous global fatigue score, there were no significant changes over time.

Study C

This postal survey found the prevalence of fatigue (a cut off on the Brief Fatigue Inventory >3 and called Substantial Global Fatigue in this thesis) was 29% in recurrence free survivors previously treated for prostate cancer more than one year ago. Fatigue was associated with poorer quality of life and worse role, social and physical functioning. Univariate analysis showed a significant association with treatment received but this was no longer the case after controlling for depression (with and without HADS item 8), anxiety, urinary symptoms, and medical comorbidities. Of all these factors, the strongest independent association with fatigue was depression.

Study D

This postal survey found 43% of men with hormone controlled prostate cancer had Substantial Global Fatigue. There were no statistically significant differences in the prevalence for those with metastatic and local disease. Independent associations of fatigue were worst pain > 4 and depression. However in a second multivariate analysis when HADS depression item 8 was removed, only worst pain >4 was independently associated.

Both recurrence free prostate cancer survivors and men with hormone controlled prostate cancer had a higher prevalence of fatigue than the non-cancer group of men with benign prostatic hypertrophy (16%).

10.1.5 General Conclusions

This research has produced new information about fatigue and prostate cancer. To my knowledge it includes the first studies that have specifically examined fatigue (a) after brachytherapy (b) in recurrence free prostate cancer survivors and (c) in men with hormone controlled prostate cancer.

Although fatigue was a common side effect of brachytherapy, it did not impair patients' functioning as much as had been anticipated. Nor did it appear to be related to markers of systemic inflammatory response such as CRP. The two cross sectional

surveys found the prevalence of fatigue in recurrence free survivors was higher than that of a non-cancer comparison group but the relationship with type of treatment received was not strong. Not surprisingly, men with more advanced hormone controlled disease had a higher prevalence of fatigue. Fatigue was associated with depression but generally HADS scores were low in men with prostate cancer and the association does not appear to be as strong as for women with breast cancer. Fatigue findings varied according to the assessment tool used (interview or questionnaire) and this raises doubts about the validity of the use of scale based questionnaires in fatigue research as a whole (discussed further below).

10.1.6 General Limitations

Fatigue and prostate cancer

The majority of patients studied during this project either had localised prostate cancer or were recurrence free. There would have probably been a greater proportion of CSF in men with metastatic hormone refractory prostate cancer. I tried to set up a study of these men but identifying them was surprisingly difficult. Generally they were not attending the outpatient clinics, nor were they inpatients in the oncology wards. The responsible clinicians were under the impression that once patients had got to that stage they were referred to the palliative care services. Consequently I went to the two hospices in Edinburgh (St. Columbas and Marie Curie Centre) but in fact, according to their records they only had one or two such patients a month. Bearing in mind some of these men would not have been well enough to participate in a study it was decided on balance this was not feasible.

Although there were some changes after radiotherapy and brachytherapy in biological measures such as haemoglobin, lymphocyte count, IL-6 and CRP indicating a systemic effect of localised treatment, there was little evidence that these changes were associated with fatigue. It had been originally planned to perform more extensive proinflammatory cytokine testing but the available information did not justify this and financial resources were limited. Had it been possible to study men with more advanced prostate cancer in detail, ideally I would have liked to have assessed biological parameters in those patients.

There were no data available regarding fatigue scores on the Brief Fatigue Inventory for the general male population. Instead, a group of men with benign prostatic hypertrophy were recruited as a non-cancer comparison group. Comparisons with the prostate cancer group would have been more robust if the non-cancer sample was larger. It is possible this group of men with benign prostatic hypertrophy had a higher level of fatigue than the general population as has been shown in a Swedish Study (Jakobsson *et al.* 2004). I had looked into the possibility of locating a representative sample of men over 60 years of age without cancer (e.g. recruiting from bowling clubs) but it was difficult to do this without introducing sampling bias.

The differences in methods of fatigue assessment

Several issues that have hampered fatigue research in the past remain. Firstly, there is still a problem of defining what fatigue really is. To some extent this is a problem of colloquial language and the word meaning different things to different people. Despite the various research definitions of fatigue, patients do not think in convenient research categories and some authors argue the best definition is similar to that of pain; it is what the person experiencing it says it is (Cleeland & Wang 1999;Holley 2000a;De Groot *et al.* 2003). The second issue is measuring fatigue and defining when it becomes a clinically significant problem. Most clinicians and patients agree when fatigue is severe. However at other times a patient's interpretation of fatigue severity can depend on their expectations and can vary from patient to patient. In turn a clinician's impression may also be different to that of the patient.

There were some interesting findings with regards to different methods of assessing fatigue. In studies A and B, fatigue was examined using both a continuous scale measure and the interview based case definition of CSF which produced different findings. Possible reasons for this have been discussed in detail in Chapter 7 but in summary could be partly explained by a combination of factors: (a) some patients rated an increase in the fatigue scores and others, a decrease, which averaged out the mean group fatigue score (b) patients adjusted their internal standards and expectations (response shift) (c) some patients said different things on paper to when

they were interviewed. The interview was more rigorous and questionnaires should never be used as a substitute for talking to patients. However, as suggested by the NCCN, questionnaires may be a useful screening tool to identify who may need more in depth clinical assessment (Mock 2005).

In addition from a methodological point of view, ideally the CSF criteria would have been applied to a larger number of fatigued and non fatigued people (such as those who participated in the postal surveys) to assess its relationship to the Brief Fatigue Inventory more comprehensively. However due to limitations of time and personnel this was not feasible.

Since starting this project, further work has been conducted using the ICD 10 proposed definition of the syndrome of Cancer Related Fatigue (Cella *et al.* 2001;Sadler *et al.* 2002;Van Belle *et al.* 2005;Andrykowski *et al.* 2005;Young & White 2006;Murphy *et al.* 2006;Fernandes *et al.* 2006) but further work is required because as discussed in Chapter 4, the criteria are impractical to apply in full.

10.2 FATIGUE AND CANCER

Fatigue is a real and serious problem for many cancer patients. There is a natural tendency to race ahead to investigate possible treatments for this distressing symptom. Since embarking on this thesis, more evidence for different approaches to managing fatigue has emerged but none have demonstrated substantially effective changes in fatigue. Helpful reviews have been published summarising these findings (Ahlberg *et al.* 2003;Mustian *et al.* 2007;Carroll *et al.* 2007). So far most data relates to exercise, but this has to be defined carefully according to the fitness of the patient and it remains unclear what is the most effective prescription. Haematopoetic agents have shown some benefit in anaemic chemotherapy patients but the effects may be confounded by disease stage. Pharmacological interventions such as psychostimulants, antidepressants, corticosteroids and L-carnitine have been examined in small samples of mixed cancer samples for times ranging from 7 days to 2 months. However, most studies that have shown benefit to date are open label and

of the few that have progressed to blinded randomised controlled trials, no improvement in fatigue has been found. Monoclonal antibodies to block proinflammatory cytokines have been shown to help fatigue in patients with Rheumatoid Arthritis (Omdal & Gunnarsson 2005), this may also help cancer patients. With any of these medications there are side effects and so other interventions have been attempted such as advising patients to rest, providing information about the possible development of fatigue, cognitive behavioural therapy, sleep interventions, or complementary therapies such as acupuncture, yoga and aromatherapy.

10.2.1 What still needs to be done

Fatigue is a distressing problem for many cancer patients and despite the difficulties associated with its research, it is an important issue that is deserving of more study.

In prostate cancer, further prospective studies of fatigue in men with advanced prostate cancer who are receiving androgen deprivation therapy or chemotherapy are required. It may be worthwhile to build on published work and try a gentle exercise intervention in these men.

With regards to other cancers, more prospective studies of specific clinical groups receiving similar treatments are required to give clinically meaningful information to enable clinicians to inform patients of the likelihood of fatigue. In addition, biological factors should be appropriately measured which may shed light on potential mechanism or correlates of fatigue. Follow up needs to extend for several years to assess the trajectory of post treatment fatigue and this will also enable the identification of pre-treatment risk factors which may help prevent the development of fatigue in the first place. This is especially important where the aim of treatment is cure. With a growing number of cancer survivors and given the substantial adverse physical, psychosocial and economic consequences of post cancer treatment fatigue, rehabilitation and treatment is critical. Better still that fatigue is prevented in the first place.

For fatigue research as a whole, further work needs to be done to agree a definition of clinically significant fatigue and a measurement tool. The evaluation of potential treatments will remain difficult in view of the lack of these. Fatigue is a symptom of many other medical conditions and it may be appropriate for a case definition of clinically significant fatigue to be applied outwith cancer. This would enable comparisons of prevalence and associations and evaluation of possible shared mechanisms of fatigue development.

10.3 PERSONAL REFLECTION

I have learned much along the journey of working towards this thesis (amongst other things, having conducted two small prospective studies I now appreciate why there are relatively few out there - they are hard work!). I am very grateful to all the patients who took part for enabling me to gain deeper insight into the issues they face. That was a privilege for me and I hope in the process, this work has made a small contribution to the understanding of fatigue in prostate cancer patients. In general, patients are living longer with cancer and oncologists are increasingly recognising the adverse impact of fatigue on the patients they treat. Research into this important symptom is gaining momentum. I hope that in the near future, advances in the understanding and management of fatigue will mirror progress made with pain and nausea in previous years. Useful steps forward have been made, but many still lie ahead.

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APPENDICES

List of Appendices

1. Proposed ICD-10 Criteria for Cancer Related Fatigue

A. Six (or more) of the following symptoms have been present every day or nearly every day during the same 2 week period in the last month, and at least one of the symptoms is (1) significant fatigue.

1. Significant fatigue, diminished energy,or increased need to rest, disproportionate to any recent change in activity level.
2. Complaints of generalized weakness or limb heaviness.
3. Diminished concentration or attention
4. Decreased motivation or interest to engage in usual activities
5. Insomnia or hypersomnia.
6. Experience of sleep as unrefreshing or nonrestorative.
7. Perceived need to struggle to overcome inactivity.
8. Marked emotional reactivity (eg sadness,frustration, or irritability) to feeling fatigued.
9. Difficulty completing daily tasks attributed to feeling fatigued.
10. Perceived problems with short term memory.
11. Post exertional malaise lasting several hours.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. There is evidence from the history, physical examination, or laboratory findings that the symptoms are a consequence of cancer or cancer therapy.

D. The symptoms are not primarily a consequence of co-morbid psychiatric disorders such as major depression, somatization disorder, somatoform disorder or delirium.

All criteria (A to D) need to be fulfilled for cancer related fatigue to be diagnosed

2. Charlson Comorbidity Index

Comorbidity	Present	Points
Myocardial Infarct		1
Congestive Heart Failure		1
Peripheral Vascular Disease		1
Cerebrovascular Disease		1
Dementia		1
Chronic Pulmonary Disease		1
Connective Tissue Disease		1
Ulcer Disease		1
Mild Liver Disease		1
Diabetes (without Complications)		1
Diabetes with end organ damage		2
Hemiplegia		2
Moderate or severe renal disease		2
2^{nd} solid tumour (non metastatic)		2
Leukeamia		2
Lymphoma, multiple myeloma		2
Moderate or severe liver disease		3
2^{nd} metastatic solid tumour		6
AIDS		6

3. Karnofsky Performance Status Index

Normal, no complaints	100
Able to carry out normal activities, minor signs of disease	90
Normal activity but with effort	80
Self-caring but unable to carry out normal activity or work	70
Requires occasional assistance but able to care for most needs	60
Requires considerable assistance and frequent medical care	50
Disabled, requires special care and assistance	40
Severely disabled, hospitalization indicated although death not imminent	30
Very sick, requires hospitalization. Active supportive treatment necessary	20
Moribund	10
Dead	0

4 Hospital Anxiety and Depression Scale

Patients are asked to tick the box (not shown) for the response that applies best to them in relation to eth past week. The scores and details of which subscale the items belong to are shown for completeness

Item		Score	Scale
(1)	**I feel tense or 'wound up':**		*Anxiety*
	Most of the time.....	*3*	
	A lot of the time.....	*2*	
	Time to time, occasionally.....	*1*	
	Not at all.....	*0*	
(2)	**I still enjoy the things I used to enjoy**:		*Depression*
	Definitely as much.....	*0*	
	Not quite so much.....	*1*	
	Only a little.....	*2*	
	Hardly at all.....	*3*	
(3)	**I get a sort of frightened feeling as if something awful is about to happen:**		*Anxiety*
	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*	
(4)	**I can laugh and see the funny side of things**:		*Depression*
	As much as I always could.....	*0*	
	Not quite so much now.....	*1*	
	Definitely not so much now.....	*2*	
	Not at all.....	*3*	
(5)	**Worrying thoughts go through my mind**:		*Anxiety*
	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*	
(6)	**I feel cheerful**:		*Depression*
	Not at all.....	*3*	
	Not often.....	*2*	
	Sometimes.....	*1*	
	Most of the time.....	*0*	
(7)	**I can sit at ease and feel relaxed**:		*Anxiety*
	Definitely.....	*0*	
	Usually.....	*1*	
	Not often.....	*2*	
	Not at all.....	*3*	

Item		Score	Scale
(8)	**I feel as if I am slowed down**:		*Depression*
	Nearly all the time.....	*3*	
	Very often.....	*2*	
	Sometimes.....	*1*	
	Not at all.....	*0*	
(9)	**I get sort of frightened feelings like 'butterflies in the stomach'**:		*Anxiety*
	Not at all.....	*0*	
	Occasionally.....	*1*	
	Quite often.....	*2*	
	Very often.....	*3*	
(10)	**I have lost interest in my appearance**:		*Depression*
	Definitely.....	*3*	
	I don't care as much as I should.....	*2*	
	I may not take quite as much care.....	*1*	
	I take just as much care as ever.....	*0*	
(11)	**I feel restless as if I had to be on the move**:		*Anxiety*
	Very much indeed.....	*3*	
	Quite a lot.....	*2*	
	Not very much.....	*1*	
	Not at all.....	*0*	
(12)	**I look forward with enjoyment to things**:		*Depression*
	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*	
(13)	**I get sudden feelings of panic**:		*Anxiety*
	Very much indeed.....	*3*	
	Quite a lot.....	*2*	
	Not very much.....	*1*	
	Not at all.....	*0*	
(14)	**I can enjoy a good book or radio or TV programme**:		*Depression*
	Often.....	*0*	
	Sometimes.....	*1*	
	Not often.....	*2*	
	Very seldom.....	*3*	

5 EORTC QLQc30 version 3.0

Your health in general		**Not at all**	**A little**	**Quite a bit**	**Very much**
1)	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or suitcase?	*1*	*2*	*3*	*4*
2)	Do you have any trouble taking a long walk?	*1*	*2*	*3*	*4*
3)	Do you have any trouble taking a short walk outside of the house?	*1*	*2*	*3*	*4*
4)	Do you need to stay in bed or a chair during the day?	*1*	*2*	*3*	*4*
5)	Do you need help with eating, dressing, washing, yourself or using the toilet?	*1*	*2*	*3*	*4*
During the past week:					
6)	Were you limited in doing either your work or other daily activities?	*1*	*2*	*3*	*4*
7)	Were you limited in pursuing your hobbies or other leisure time activities?	*1*	*2*	*3*	*4*
8)	Were you short of breath? … … …	*1*	*2*	*3*	*4*
9)	Have you had pain? … … … … …	*1*	*2*	*3*	*4*
10)	Did you need to rest? … … … …	*1*	*2*	*3*	*4*
11)	Have you had trouble sleeping? … …	*1*	*2*	*3*	*4*
12)	Have you felt weak? … … … … …	*1*	*2*	*3*	*4*
13)	Have you lacked appetite? … … …	*1*	*2*	*3*	*4*
14)	Have you felt nauseated? … … … …	*1*	*2*	*3*	*4*
15)	Have you vomited? … … … … …	*1*	*2*	*3*	*4*
16)	Have you been constipated? … … …	*1*	*2*	*3*	*4*
17)	Have you had diarrhoea? … … … …	*1*	*2*	*3*	*4*
18)	Were you tired? … … … … … …	*1*	*2*	*3*	*4*
19)	Did pain interfere with your daily activities?	*1*	*2*	*3*	*4*
20)	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	*1*	*2*	*3*	*4*

	Not at all	A little	Quite a bit	Very much
21) Did you feel tense? … … … … …	*1*	*2*	*3*	*4*
22) Did you worry? … … … … … …	*1*	*2*	*3*	*4*
23) Did you feel irritable? … … … … …	*1*	*2*	*3*	*4*
24) Did you feel depressed? … … … …	*1*	*2*	*3*	*4*
25) Have you had difficulty remembering things?	*1*	*2*	*3*	*4*
26) Has your physical condition or medical treatment interfered with your family life?	*1*	*2*	*3*	*4*
27) Has your physical condition or medical treatment interfered with you social activities?	*1*	*2*	*3*	*4*
28) Has your health or medical treatment caused you financial difficulties?	*1*	*2*	*3*	*4*

For the following questions please circle the number between 1 and 7 that best applies to you

29) How would you rate your overall health during the past week?

1 *2* *3* *4* *5* *6* *7*
Very poor Excellent

30) How would you rate your overall quality of life during the past week?

1 *2* *3* *4* *5* *6* *7*
Very poor Excellent

Subscales	Items	Subscales	Items
		Symptoms	
Global Health status/quality of life	29,30	Fatigue	10,12,18
		Nausea and Vomiting	14,15
		Pain	9,19
Functional Subscales		Dyspnoea	8
Physical function	1-5	Insomnia	11
Role function	6,7	Appetite loss	13
Emotional function	21-24	Constipation	16
Cognitive function	20,25	Diarrhoea	17
Social function	26,27	Financial difficulties	28

6 International Prostate Symptom Score

Scores are shown in italics

DURING THE PAST MONTH	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
Incomplete emptying How often have you had the sensation of not emptying your bladder completely after you finish urinating?	*0*	*1*	*2*	*3*	*4*	*5*
Frequency How often have you had to urinate again less than two hours after you finished urinating?	*0*	*1*	*2*	*3*	*4*	*5*
Intermittency How often have you found you stopped and started again several times when you urinated?	*0*	*1*	*2*	*3*	*4*	*5*
Urgency How often have you found it difficult to postpone urination?	*0*	*1*	*2*	*3*	*4*	*5*
Weak Stream How often have you had weak stream?	*0*	*1*	*2*	*3*	*4*	*5*
Straining How often have you had to push or strain to begin urination?	*0*	*1*	*2*	*3*	*4*	*5*
DURING THE PAST MONTH	**None**	**1 time**	**2 times**	**3 times**	**4 times**	**5 times or more**
Nocturia How many times did you most typically get up to urinate overnight?	*0*	*1*	*2*	*3*	*4*	*5*

7 DSM IV Structured Clinical Interview for Major Depression

To make a diagnosis of MDD, **five** or more of the following criteria must have been present during the **same 2 week period in the past month** and represent a **change from previous functioning.** At least one of the five symptoms must be either question **1** or **2** (core symptoms).

	CORE SYMPTOMS		
1	**Depressed mood most of the day, nearly every day** as indicated either by subjective report (feels sad or empty) or observation (tearful).	**Y**	**N**
2	Markedly **diminished interest or pleasure** in all, or almost all activities most of the day, nearly every day, representing a significant change from previous functioning	**Y**	**N**
3	**Significant weight loss** when not dieting, or **weight gain** (a change of more than 5% in 1 month) OR decrease or increase in appetite nearly every day	**Y**	**N**
4	**Insomnia** or **hypersomnia** nearly every day	**Y**	**N**
5	Psychomotor **agitation or retardation** nearly every day (must be **observable by others**)	**Y**	**N**
6	**Fatigue** OR **loss of energy** nearly every day	**Y**	**N**
7	**Feelings of worthlessness OR excessive or inappropriate guilt** nearly every day (not merely self-reproach about being sick or low self-esteem)	**Y**	**N**
8	Diminished ability to **think** or **concentrate** or **indecisiveness**, nearly every day	**Y**	**N**
9	**Recurrent thoughts of death** (not just fear of dying) Recurrent **suicidal ideation without a specific plan,** OR a **suicide attempt** or a **specific plan** for committing suicide (Does not need to be present every day)	**Y**	**N**

8 Modified activity Score

Rate activity over **last week**. Grade maximum activity **each day.** Total activity rating is sum of grade x days/7.Rating for day:

0 = MINIMAL: i.e. Bed bound with minimal walking

1 = MINOR: i.e. walking (indoors or out) for less than 1 hour in total

2 = MODERATE: i.e. walking (indoors or out) for 1 – 3 hours in total

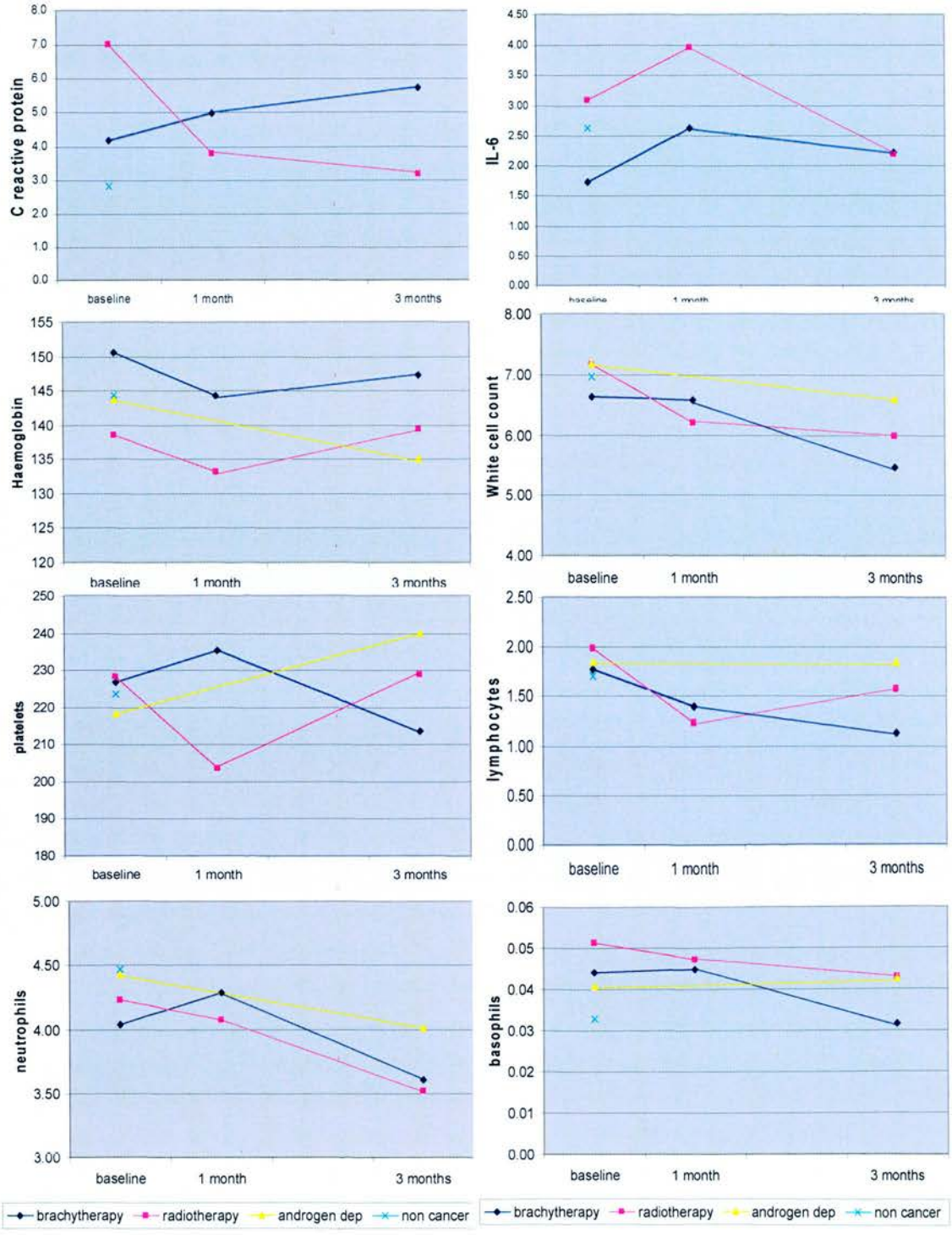
3 = HEAVY: i.e. walking (indoors and out) for more than 3 hours in total
Or short period (less than 20 mins) of running / swimming / cycling or similar vigorous exercise

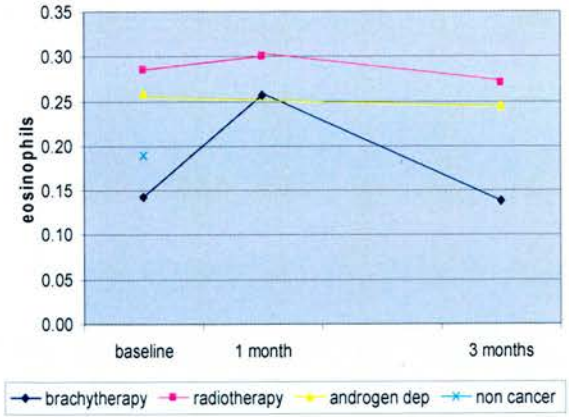
4 = VERY HEAVY: i.e. longer periods (more than 20 mins) of vigorous exercise

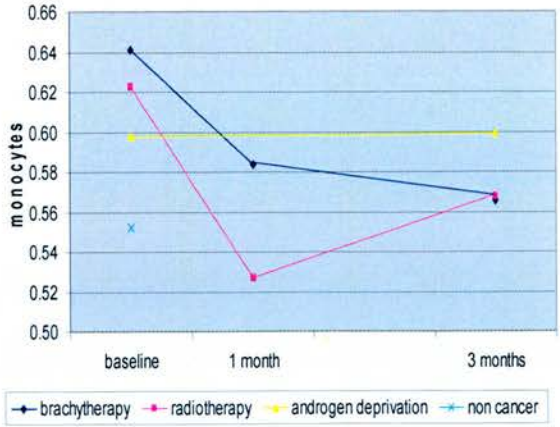
Day	**Grade**
1	....
2	....
3	....
4	....
5	....
6	....
7	....
Total =	-----

9 Study A. Changes in biological measures

after brachytherapy, radiotherapy and androgen deprivation therapy




0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
eosinophils
baseline
1 month
3 months
brachytherapy
radiotherapy
androgen dep
non cancer


0.66
0.64
0.62
0.60
0.58
0.56
0.54
0.52
0.50
monocytes
baseline
1 month
3 months
brachytherapy
radiotherapy
androgen deprivation
non cancer

10 ASCO Annual Meeting June 2007 abstract

Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement), 2007: 9044

Title: Clinically significant fatigue in recurrence free prostate cancer survivors

Authors: D. J. Storey, D. McLaren, M. Shipway, I. Butcher, S. Liggatt, R. O'Dea, J. F. Smyth, M. Sharpe. University of Edinburgh Cancer Research Centre, Edinburgh, UNITED KINGDOM.

Background
In the absence of definitive evidence of best disease control, treatment decisions for early prostate cancer should consider likely long term side effects and quality of life. Fatigue is an acute side effect of treatment but there are no data about long term clinically significant fatigue (CSF) in recurrence free prostate cancer survivors. This study presents the prevalence, associations and predictors of CSF after radical prostatectomy (RP) or radiotherapy (XRT).

Methods
A postal questionnaire survey of 416 recurrence free men treated at a regional cancer centre >1 year previously. CSF was defined as global Brief Fatigue Inventory score >3. Other measures: Hospital Anxiety and Depression Scale (HADS), International Prostate Symptom Score (IPSS), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, clinical and demographic information. Relationships between these factors and CSF were explored in univariate and then multivariate logistic regression analyses.

Results
91% (377/416) of questionnaires were analyzable. Mean age was 72 years (SD 6.1) and median time since treatment was 56 months (range 13-233). The prevalence of CSF was 29% (108/377) overall; 22% (29/133) post RP and 33% (79/244) post XRT. Univariate and multivariate associations of CSF predictors are shown below. Patients with CSF also had poorer quality of life, physical, role, and social function (all $p<0.001$). CSF was not associated with age, social deprivation category or time since treatment.

		Univariate odds of CSF (95% CI)	p value	Multivariate odds of CSF (95% CI)	p value
Treatment	RP	1	**0.024**	1	**0.1979**
	XRT	1.8(1.1, 2.9)		1.5(0.8, 2.8)	
IPSS>7 (moderate or worse urinary symptoms)		4.5(2.8, 7.3)	**<.0001**	3.4(1.9, 6.0)	**<.0001**
Comorbidities (n)	0	1	**<.0001**	1	**0.0027**
	1	3.6(1.7, 7.6)		3.8(1.7, 8.8)	
	≥2	7.9(3.8, 16.5)		3.9(1.7, 8.9)	
HADS anxiety ≥9		8(4.1, 15.4)	**<.0001**	2.9(1.3, 6.6)	**0.0109**
HADS depression ≥8		18.8(8.7, 40.6)	**<.0001**	10.9(4.6, 25.9)	**<.0001**

Conclusions

Almost a third of recurrence free prostate cancer survivors have CSF. RP is associated with less CSF post treatment than XRT but treatment type did not remain statistically significant in a multivariate analysis controlling for other factors. Depression at outcome had the strongest association with CSF. Other associated variables were IPSS>7, comorbid medical conditions and anxiety. Care should focus on optimising the identification and management of these conditions to improve fatigue.