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AN INVESTIGATION OF WEAKNESS, FATIGUE, STRENGTH, FUNCTION AND QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER

by

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A Thesis Submitted for the Degree of

Doctor of Medicine

to

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From Research Carried Out as Gabriel Blane Research Fellow in

Palliative Medicine at Strathcarron Hospice, Denny, Stirlingshire

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CONTENTS **Page**

APPENDIX 3 (continued) **Page**

LIST OF TABLES

LIST OF TABLES (continued) **Page**

LIST OF TABLES (continued)

LIST OF TABLES (continued) **Page**

LIST OF FIGURES

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DECLARATION

I declare that all the work in this thesis was carried out by myself, except where indicated below.

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I dedicate this thesis to Miss Campbell, without whom this work would not have been possible, and to my wife for her patience.

SUMMARY

Weakness and fatigue are the commonest symptoms in patients with advanced cancer. They are symptoms which have largely eluded precise definition, but have been reported to seriously affect quality of life and ability to perform basic daily activities. Reduced muscle bulk due to cancer cachexia and alteration in intrinsic muscle function have been suggested as causes of both reduced muscle strength and subjective weakness and fatigue. It has been reported that anxiety/depression, anaemia, deranged biochemistry and the inflammatory response may contribute to weakness and fatigue. However, the relationship between subjective weakness and fatigue and objective strength in cancer patients is not clear. To date, such relationships have not been studied in cancer patients.

The aims of the present work were twofold. First, to investigate the importance of weight loss, altered body composition, the inflammatory response, haematological and biochemical parameters in the experience of weakness and fatigue in patients with advanced cancer. The second aim of this work was to examine the relationships between objective tests of strength and function and measures of weakness and fatigue and patient-related quality of life in patients with advanced cancer.

In chapter 5, a typical hospice population was studied retrospectively, to provide a background and baseline to the prospective studies. A heterogeneous group of 229 cancer patients, who had died in the preceding 6 months, was described. Of these patients, more than half had the presence of weight loss documented in the casenotes. Weakness, fatigue and tiredness were documented as important symptoms in some patients, but not as frequently as in previous prospective studies. Many patients had

increased difficulty in performing the activities of daily living. The difficulties of establishing symptom prevalence retrospectively from casenotes is discussed. Many of the patients were taking drugs implicated in the aetiology of weakness and fatigue, such as opioids, benzodiazepines, antidepressants and corticosteroids.

In chapter 6, a group of patients with advanced cancer was compared with an age, sex and healthy body mass index matched healthy control group. The cancer group were clearly more unwell, having lost weight including both fat and muscle. The cancer patients also had a lower performance status and had significantly more weakness and fatigue. The correlations obtained between the weakness scale and the two fatigue scales suggested that weakness and fatigue tend to co-exist and that patients tend to use the terms weakness and fatigue synonymously.

The cancer patients were more anaemic and had evidence of an inflammatory response. Correlations with the weakness and fatigue scales suggest that anaemia and the inflammatory response may be aetiological factors in the pathogenesis of weakness and fatigue. It was of interest that patients taking benzodiazepine drugs had higher fatigue scores than those not receiving such drugs.

Those cancer patients who had lost greater than 5% of their body weight were compared with those who were weight-stable. The weight-losers had lost muscle mass, had more weakness and fatigue and reported greater difficulty in carrying out activity than the weight-stable patients. The weight-losers had a more marked inflammatory response, suggesting that the inflammatory response is involved in ongoing weight loss in patients with advanced cancer.

In chapter 7, it was observed that in addition to having more weakness and fatigue, the cancer patients had lost physical strength, compared with the healthy controls, as well as performing less well in the chair, stair and walking functional tests. The cancer group also had poorer levels of self-rated functioning, an increased symptom burden and poorer quality of life. Although there was no apparent relationship between the weakness score and the strength measures, multivariate analysis suggested that muscle bulk may be an important factor in determining muscle strength.

The fatigue and weakness scale scores in the cancer group were related to objective function, and handgrip strength was related to chair stand time. The relationship between strength and function was not as striking as in previous work in the healthy elderly. However, it was clear that cancer patients were a more rapidly changing group than the healthy elderly. Moreover, small decrements in strength could lead to a large deterioration in function as the patient crosses the threshold of ability to inability.

Patient-rated global quality of life was correlated with fatigue, weakness, the chair stand and depression. Therefore, it is likely that poor quality of life, in part, is the result of weakness and fatigue and poorer functioning. Depression was strongly correlated with fatigue scores and was the strongest single predictor for fatigue on multivariate analysis.

When the weight-losing patients were compared with the weight-stable patients, the weight-losers had lower handgrip strength, poorer self-assessed function and poorer performance in the chair and stair tests. The weight-losing patients had more anxiety and depression as well an increased symptom burden. Many of the symptom scores of the EORTC questionnaire were correlated with the weakness and fatigue scores. This

may be because more unwell patients often have multiple symptoms at the same time, but it is also possible that other symptoms may contribute to the pathogenesis of weakness/fatigue.

In chapter 8, the characteristics of those patients who were followed up to 6 weeks were compared with those who were not followed up due to death or disease progression. Patients without follow-up had lost more of their healthy weight, had lower performance status, poorer self-assessed and actual function, increased anxiety and depression, more dyspnoea and reduced appetite compared to the group with follow-up. It is likely, therefore, that weight-losing patients are a group with more advanced disease than weight-stable patients.

The follow-up patients were reassessed after 6 weeks and those who had lost weight over that period were compared with those who had remained weight-stable. At baseline, those patients who subsequently lost weight had a lower performance status, performed less well in the functional tests and had a more marked inflammatory response. In longitudinal study there was an increase in mid-arm circumference in the weight-stable patients as well as an improvement in fatigue scores and in the functional tests. The weight-losing patients had a reduced mid-arm circumference and far fewer patients were able to complete the functional tests than in the weight-stable group. Performance status did not change over time, but performance in the various functional tests did, suggesting that the latter may be more sensitive indicators of a patient's ability to function than performance status. Although fatigue scores improved in the weight-stable patients, there was no alteration in depression scores, suggesting that it is likely that fatigue precedes a lowering in mood rather than vice versa.

In conclusion, this work has confirmed that weakness and fatigue are common problems in patients with advanced cancer who are not receiving active anti-cancer therapy. Patients tend to use the terms weakness and fatigue synonymously. Weakness/fatigue become more severe with increasing weight loss and illness progression. Weight-losing cancer patients are more unwell than weight-stable patients and lose muscle mass, muscle strength and are more functionally disabled. Weight-losers have poorer quality of life and more anxiety and depression. It is evident that these parameters change together, but the longitudinal relationships between strength, function, weakness/fatigue, weight loss and quality of life require further study. The relationship between depression and fatigue is strong and understanding the nature of this relationship merits further investigation.

1. INTRODUCTION AND AIMS

1.1 Cancer and the Development of Specialist Palliative Care Services

One in three people will develop cancer in the United Kingdom and one in four will die of the disease (Richards, 1997). Many patients will, therefore, not be cured of their cancer.

Palliative care has been defined as "the active total care of patients whose disease is not responsive to curative treatment." This includes the control of physical symptoms as well as dealing with psychological, social and spiritual problems. The ultimate goal of palliative care is to achieve the best quality of life possible for patients and their families (Doyle, Hanks and MacDonald, 1998).

The modern hospice movement has done much to promote a whole person orientated approach to patient care. In the United Kingdom, the Marie Curie Memorial Foundation and St. Christopher's hospice were at the forefront of this movement (Saunders, 1998). It has been recognised that there are many important components to the provision of good palliative care, of which in-patient care is only part. Home care services, Day Care Units, hospital palliative care teams and bereavement care have all become integral to the provision of specialist palliative care. Palliative care services have developed in recent years and, as well as cancer care, are increasingly providing care for patients with other non-malignant, incurable conditions (Twycross, 1980; Addington-Hall, 1998).

One of the cornerstones of specialist palliative care is good symptom control. However, there is comparatively little evidence-based research into the symptoms experienced by patients with advanced cancer (Wilkinson, 1993).

The ethics of research in this patient group has been a matter of some debate, with some claims that research in a vulnerable patient population is not desirable, and that many patients may feel obliged to participate in a project even though it will not directly benefit themselves (de Raeve, 1994).

There are, however, compelling counter arguments in favour of research in this patient group. Speck (1996) argues that there is an ethical obligation to undertake clinical research in order to improve the knowledge base against which clinical decisions are made. Bruera (1994) argues that we cannot afford not to perform research, given the increasing number of patients dying with cancer and the fact that many of the symptoms which cause patients significant distress have, as yet, no effective treatment.

It is, of course, important that patients understand the nature of any research in which they participate, so that consent is properly informed. Patients also need to be assured that they are free to withdraw from the study at any time, without prejudicing their future care (Wilkinson, 1993; Bruera, 1994; Speck, 1996). There is often a high attrition rate in studies involving patients with advanced cancer, because patients become too unwell or die before study completion (Loprinzi et al., 1990).

1.2 The Problem of Weakness and Fatigue

In a survey of 1000 patients with advanced cancer, Donnelly and Walsh (1995) reported that the ten most frequently observed symptoms were pain, fatigue, weakness, anorexia, weight loss, lack of energy, dry mouth, constipation, dyspnoea and early satiety. When these symptoms were present, 60-80% of patients rated them as moderate or severe. In this study, pain was reported to be the commonest symptom. However, recently, some researchers have concluded that weakness and fatigue are actually the commonest symptoms faced by this patient group (Lichter, 1990; Glaus, Crow and Hammond, 1996; Vogelzang et al., 1997; Pater et al., 1997).

Although there has been a significant amount of research into pain control in cancer patients, there has been comparatively little research into weakness and fatigue. One study of weakness in the elderly suggested that weakness was often a symptom that was accepted as inevitable (Gordon, 1986). It has been suggested that pain and pain control gain much more attention from oncologists than fatigue, perhaps because effective treatments exist for pain control (Vogelzang et al., 1997). The very vagueness of the concepts of weakness and fatigue, and the fact that patients often use different terms such as tiredness, exhaustion, lethargy and loss of energy to describe how they are feeling, make them difficult symptoms to research (Lichter, 1990; Regnard and Mannix, 1992). Many researchers agree that weakness and fatigue are difficult terms to define clearly (Dunlop, 1989; Nail and Winningham, 1995). The different prevalences noted in the literature for weakness and fatigue may be due to inconsistent definitions, variable patient populations or the lack of appropriate control groups (Richardson and Ream, 1996; Loge and Kaasa, 1998).

Published studies suggest that between 40 and 82% of hospice or hospital patients with advanced cancer experience weakness (Dunlop, 1989; Donnelly and Walsh, 1995). Copp and Dunn (1993) reported that hospice and community nurses found weakness to be the most difficult symptom to manage in dying patients. Rhodes, Watson and Hanson (1988) reported that tiredness and weakness were the two symptoms that interfered most with patients' abilities to care for themselves. They also observed that it was difficult to disentangle the two concepts of tiredness and weakness. Dunlop (1989) reported that weakness was not only the commonest symptom experienced by cancer patients (reported by 82% of patients), but was also their most distressing symptom. Pater and colleagues (1997) cited fatigue as the commonest and most distressing symptom faced by patients with cancer. Meyerowitz, Sparks and Spears (1979) reported that, in a study of 50 patients with breast cancer, 96% of patients experienced fatigue related to chemotherapy. However, this study had no control group. It has been suggested that up to 100% are fatigued after radiotherapy (Nail and King, 1987). More recently, Richardson (1995) commented that fatigue was the most distressing side effect of chemotherapy.

The terms weakness and fatigue are often used interchangeably by staff and patients alike (Piper, Lindsey and Dodd, 1987) and it has been suggested that they may well be aspects of the same phenomenon (Morant et al., 1993; Nail and Winningham, 1995). Some researchers prefer to use the term asthenia to describe the combination of weakness and fatigue thought to co-exist in many patients (Bruera and MacDonald, 1988; Morant, 1996). However, some effort has been made to discriminate between these two concepts.

1.2.1 Definition of Weakness

The term weakness has, in the past, often been associated with strokes, neuromuscular disorders and immobility (Nail and Winningham, 1995) and some suggest that weakness is predominantly a neurological problem (Pickard-Holley, 1991). Various definitions in the cancer and palliative care literature include both subjective and objective dimensions. Weakness has been defined as a deficiency in strength or power (Lichter, 1990) or a reduction in muscle strength or endurance below a baseline level (Nail and Winningham, 1995). Other definitions include: an inability or difficulty in starting an activity (Morant et al., 1993) and physical inability to perform a task (Dunlop, 1989; Barnish, 1994).

Glaus and colleagues (1996), reporting on a study of subjective experiences of fatigue/tiredness, suggested that weakness is a pathological component of tiredness, not found in the healthy subjects, and reported that tiredness was often expressed as a reduction in physical strength or reduced physical performance, for example an inability to walk as far as before. These researchers hypothesised that strength might be a key dimension to be isolated and studied further. In this study, weakness was defined as "an anticipatory, subjective sensation of difficulty in initiating a certain activity" which did not include localised or regional weakness from neurological or muscular disorders, thus distinguishing between weakness from neurological damage and weakness with normal neurological function.

1.2.2 Definition of Fatigue

On the other hand, fatigue has, primarily, been described as a subjective, multidimensional phenomenon which is variable in severity and has physical,

emotional, mental, functional and spiritual components (Irvine et al., 1991; Irvine et al., 1994; Nail and Winningham, 1995; Glaus et al., 1996). A recent study developed a definition of fatigue from analysis of concepts raised by cancer patients at interview: "a subjective, unpleasant symptom which incorporates total body feelings ranging from tiredness to exhaustion, creating an unrelenting overall condition which interferes with individuals' ability to function to their normal capacity" (Ream and Richardson, 1996). Other patient complaints are of a complete lack of energy, lethargy, tiredness and sheer exhaustion, feeling "slowed down", cognitive problems such as loss of motivation and poor concentration, and also a decreased ability to perform simple tasks (Meyerowitz et al., 1979; Rhodes et al., 1988; Pickard-Holley, 1991; Winningham et al., 1994; Irvine et al., 1994; Ream and Richardson, 1997). Many patients complain of associated low mood, loss of control of their lives and loss of independence (Irvine et al., 1991; Ream and Richardson, 1997). It has also been suggested that depression, as well as resulting from fatigue, can also be a cause of fatigue (Vogelzang et al., 1997).

In the study carried out by Vogelzang and colleagues (1997), patients reported that fatigue was something they had "to endure". One third of patients reported that fatigue affected their hope of fighting their illness, or of survival, and 12% felt that they would rather die than face fatigue.

Some researchers distinguish between acute and chronic fatigue. Ream and Richardson (1997) describe acute fatigue as a phenomenon experienced by normal individuals as a response to physical activity, mental effort or lack of sleep. It is transient and will generally respond to rest or a change of lifestyle, hence the term acute fatigue. It appears to be part of normal body functioning, protecting the individual from various stresses,

physical, emotional, mental and spiritual (Piper et al., 1987; Nail and King, 1987; Barnish, 1994).

Chronic fatigue, however, is not present in normal individuals and is present in a variety of disease states, particularly in malignancy and chronic infection (Morant et al., 1993). Tiredness occurs with only mild or moderate physical or mental effort and rest fails to adequately relieve this symptom, which may relate to chronic stress, either directly or indirectly related to the disease process. This may lead to avoidance of activity (Aistars, 1987; Piper et al., 1987; Barnish, 1994; Ream and Richardson, 1997).

Fatigue is particularly reported in relation to cancer therapy, such as chemotherapy, radiotherapy and biological response modifiers, such as interferon. Many patients discontinue treatment as a result of distressing fatigue (Winningham et al., 1994; Richardson, 1995). However, the prevalence estimates for fatigue in many studies need to be interpreted with caution, as fatigue is present in the healthy population and a lot of studies do not include a healthy control group.

1.2.3 Comparison of Weakness and Fatigue

Is there a relevant and useful difference between weakness and fatigue? In the study by Glaus and colleagues (1996), the patients stated that there was a physical dimension to their experience of tiredness, often describing this as loss of strength. It was hypothesised that it might be possible to isolate the physical component of tiredness and that, perhaps, this could be regarded as weakness as opposed to fatigue.

Morant and co-workers (1993) hypothesised that there was a difference between weakness and fatigue by suggesting that weakness constituted difficulty in initiating activity, but that fatigue was a lack of strength to continue activity once started. Many patients find that they are able to perform activity during a crisis or given the appropriate stimulus, that they would otherwise have found difficult to do (Nail and Winningham, 1995). Glaus and co-workers suggested that there must be a voluntary component to fatigue, since an individual can still push himself/herself to perform certain tasks (Glaus et al., 1996). Motivational factors may therefore be important in distinguishing between fatigue and weakness, fatigue having a motivational component, but weakness a disability which cannot be overcome by mental effort. The presence of an anxiety disorder or depression may, however, affect the mental effort needed for activity (Glaus et al., 1996). It is, therefore, likely to be difficult to disentangle the physical and emotional factors involved in the performance of activity.

Weakness could, therefore, be regarded as a difficulty or absolute inability in initiating activity, which cannot be overcome by mental effort, making it a largely objective and physical problem. Fatigue could be considered to be an inability to continue activity once started, due to tiredness, but which has a motivational component, i.e., the patient can keep going, given the appropriate stimulus or mental effort.

The difficulties in separating these two symptoms are multiplied by the fact that weakness and fatigue are likely to co-exist and may interact with each other. Patients who are tired are likely to reduce their activity levels, leading to muscle disuse and muscle weakness. Patients who are weak are likely to have more difficulty in performing activity: more strength will be needed to perform that activity and they will

tire more easily. A downward spiral may be difficult to arrest (Nail and Winningham, 1995; Glaus et al., 1996).

Although, theoretically, it may be possible to distinguish between weakness and fatigue, it has to be acknowledged that patients are likely to use the terms synonymously to mean either an objective difficulty in doing something or a subjective experience of tiredness. It is likely that weakness and fatigue represent two overlapping components of a bigger problem, which has been termed asthenia. However, there is value in trying to tease out these components if it will influence management of the patient's symptoms. What is, therefore, most important is not which words the patient is using to describe how they are feeling, but the problems that the patient is experiencing which prevent him/her from functioning normally.

Although there are studies which have considered the subjective experience of patients with weakness/fatigue (Dunlop, 1989; Glaus et al., 1996; Krishnasamy, 1997), there are no prospective studies to date which have attempted to investigate the relationship between these subjective elements and objective physical strength and performance in daily activities. There are also no prospective controlled studies to date which have investigated the experiences of weakness/fatigue in cancer patients who are not receiving active cancer treatment.

In the subsequent sections of this chapter, possible aetiological factors in the pathogenesis of weakness/fatigue will be considered, paying particular attention to possible causes of muscle weakness and dysfunction in cancer patients. The terms

weakness, fatigue and asthenia will be used, where this is the term used by the author quoted.

1.3 Cancer Cachexia

The syndrome of cancer cachexia is often suggested as an aetiological factor for the symptoms of weakness and fatigue (Theologides, 1979; Lichter, 1990; MacDonald, Alexander and Bruera, 1995; Billingsley and Alexander, 1996). An often profound weight loss, with consequent loss of muscle mass and adipose tissue, is the major feature of this debilitating syndrome (Nelson, Walsh and Sheehan, 1994a; Toomey, Redmond and Bouchier-Hayes, 1995). It is hypothesised that the loss of muscle mass leads to loss of muscle strength, hence weakness (Lichter, 1990).

1.3.1 Weight Loss in Cancer Patients

It has been recognised for many years that cancer patients who lose weight have a poorer prognosis than those who remain weight-stable (DeWys et al., 1980; Kern and Norton, 1988). As well as having a shorter survival time, patients who have lost a considerable amount of weight tolerate anticancer therapies, such as chemotherapy or radiotherapy, less well than weight-stable patients (Loprinzi, 1995).

The majority of patients with advanced cancer lose weight (Nixon et al., 1980), although this varies according to tumour type. Patients with lung and gastrointestinal cancers tend to lose large amounts of weight early on in their illness, whereas patients with breast and haematological malignancies frequently maintain their weight until late in the illness (MacDonald et al., 1995; Billingsley and Alexander, 1996).

The syndrome of cancer cachexia is not merely weight loss, but includes anorexia, and often early satiety and nausea (possibly secondary to gastric stasis caused by autonomic

insufficiency) (Brennan, 1977; Theologides, 1979; Calman, 1982; Nelson et al., 1994a; Falconer et al., 1994).

Patients with cachexia are more prone to infection, and infection is probably a common cause of death in those cancer patients who have lost a substantial amount of weight (Klastersky, Daneau and Verhest, 1972). However, Warren (1932), in a large post-mortem study, concluded that cachexia, in the absence of other factors, was the sole cause of death in 22% of patients. Other researchers have concluded that cachexia is a major factor in the death of up to 50% of cancer patients (Toomey et al., 1995; Espat, Moldawer and Copeland, 1995; Billingsley and Alexander, 1996).

It is important to know the nature of the tissue being lost in weight-losing cancer patients. There is loss of both skeletal muscle and adipose tissue, and one group of researchers found a reduction in total body fat of 85%, and in muscle tissue of 75%, in a group of lung cancer patients who had lost 30% of their original pre-illness weight (Preston et al., 1995). Although both adipose tissue and muscle mass are lost, it is suggested that the loss of muscle accounts for most of the morbidity and mortality (Nelson et al., 1994a; Toomey et al., 1995). In cachectic patients, muscle protein synthesis appears to be reduced and muscle breakdown increased (Emery et al., 1984; Toomey et al., 1995). In a study by Heymsfield and colleagues (1985), it was noted that in weight-losing cancer patients there was no alteration in visceral tissue and non-muscle protein. In contrast, in a group of patients with anorexia nervosa, there was a reduction in the weight of these tissues. These results were later confirmed by Preston and colleagues (1995). This suggests that the weight loss in cancer patients is not merely due to starvation.

1.3.2 Aetiology of Cancer Cachexia

Weight loss does not appear to be related merely to altered digestion or mechanical disruption, e.g., in oesophageal or gastric tumours, as patients with lung cancer often lose significant amounts of weight (Stanley, 1980). The degree of weight loss does not appear to correlate with the cancer type or site, or the tumour bulk (Kern and Norton, 1988; Tisdale, 1991).

Weight loss results from an energy imbalance between energy intake and energy expenditure. This negative energy balance may, thus, be related to a reduced food intake, increased energy expenditure, or a combination of both.

Food intake does appear to be reduced in cachectic cancer patients, and anorexia is a common symptom in cancer patients (DeWys, 1979; Bruera, 1997; O'Gorman, McMillan and McArdle, 1998). Although some patients do have mechanical causes for reduced food intake, and some patients complain of nausea and altered taste sensation (Theologides, 1972; Calman, 1982; Kern and Norton, 1988), many patients lose weight disproportionately to their reduction in food intake (DeWys et al., 1980).

Studies of resting energy expenditure in cancer patients have found that in weight-losing patients resting energy expenditure is inappropriately high. The body's normal adaptive response to weight loss is a reduction in energy expenditure, yet many studies have found either normal, or increased, resting energy expenditure, suggesting that metabolism in these patients is abnormal (Theologides, 1979; Calman, 1982; Fearon and Carter, 1988). Falconer and colleagues (1994) found that an elevated energy expenditure

in pancreatic cancer patients was associated with the presence of an acute phase response.

It has been suggested that cytokines such as the interleukins 1 and 6 and tumour necrosis factor are mediators of cancer cachexia (Scott et al., 1996; Billingsley and Alexander, 1996). Cytokines are polypeptide molecules produced by inflammatory cells, in particular macrophages, monocytes and lymphocytes, in response to tumour growth, infection and trauma (Billingsley and Alexander, 1996). Cytokines redirect protein metabolism away from the peripheral tissues to the liver, with a consequent increase in hepatic acute phase protein synthesis. Acute phase proteins, such as C-reactive protein, are produced by the liver in response to inflammation and appear to be a reliable measure of the acute phase response (Thompson, Milford-Ward and Whicher, 1992). Tumour necrosis factor and interleukin-1 are not consistently found in the serum, but may act at a tissue level (Billingsley and Alexander, 1996). However, raised serum levels of interleukin-6 have been frequently detected in the serum of some groups of weight-losing cancer patients (Espat et al., 1995; Scott et al., 1996).

Increasing C-reactive protein levels have been associated with disease progression (Milano et al., 1978) and a correlation between C-reactive protein and fatigue severity has been previously reported (Morant, 1996). Elevation of C-reactive protein concentrations have been reported in association with weight loss in non-small cell lung cancer patients (Scott et al., 1996). Although not all weight-losing cancer patients have elevated C-reactive protein levels (Fearon, 1992; McMillan et al., 1994a), some studies have reported that elevated C-reactive protein is a strong predictor of reduced survival (Fearon, 1992; Falconer et al., 1995). Fearon (1992) has reported that an acute phase

response is associated with a reduction in body cell mass, the component of body fat free mass where most of the important metabolic processes, such as energy production, are carried out (Heymsfield, Tighe and Wang, 1994). It has also been reported that a reduction in the acute phase response in animals can improve anorexia and lead to weight gain (Gelin and Lundholm, 1992).

1.3.3 Treatment of Cachexia

Given that cancer cachexia is such a significant problem in cancer patients in terms of morbidity and mortality, the reversal of this process would seem to be of considerable importance. However, the definitive method of treating cachexia, i.e., removal, or other curative treatment of the tumour (Kern and Norton, 1988; Fearon and Carter, 1988), is not an option in a large number of patients.

Supplementary nutrition has been considered as a means of increasing caloric intake (Burke, Bryson and Kark, 1980). It has been suggested that supplementing nutrition by intravenous (parenteral) or enteral routes may improve the outlook in this patient group, particularly in terms of responsiveness to cancer therapy (Copeland et al., 1975).

However, a meta-analysis of 28 randomised trials of total parenteral nutrition (TPN) has reported no significant improvement in tolerance of, or response to, anti-neoplastic therapy, nor in survival for those receiving TPN (Klein, Simes and Blackburn, 1986), although some trials have reported patient weight gain (Popp et al., 1981). There have also been significant complications in some patients, including thrombosis and infection. An increase in weight following enteral feeding via nasogastric or gastrostomy tube has previously been reported (Keymling, 1994; Bozzetti, 1994).

However, it would appear that the increase in weight was due to a disproportionate increase in body fat compared with lean body tissue (Bozzetti, 1994).

Given that cancer cachexia appears to be the result of complex metabolic processes (Billingsley and Alexander, 1996), it is likely that the solution to weight loss in cancer patients will involve more than simply increasing the calorie intake (DeWys and Kubota, 1981).

There have been many attempts to influence cancer cachexia through pharmacological measures, using drugs such as cyproheptadine, pentoxifylline and hydrazine sulfate. However, few controlled trials exist and there is little objective evidence to support their use (Kardinal et al., 1990; Loprinzi et al., 1994a; Loprinzi et al., 1994b; Loprinzi, 1995; Goldberg et al., 1995).

Other drugs such as thalidomide, melatonin, β-2 adrenoceptor agonists and the cannabinoids have been suggested as possible therapies for cancer cachexia, but no large trials have yet been published (Nelson et al., 1994b; Gagnon and Bruera, 1998). However, there is some evidence that the use of the polyunsaturated fatty acid eicosapentanoic acid may affect the acute phase response and lead to weight gain in pancreatic cancer patients (Wigmore et al., 1997).

Corticosteroids are widely used as appetite stimulants (Willox et al., 1984), but there is no clear evidence of muscle mass gain, or improved survival, and they have significant side-effects. The role of steroids in cancer patients is further discussed in section 1.9.

Megestrol acetate is a synthetic progestogen which has been used in the treatment of breast cancer. It had also been noted to cause an increase in appetite and weight in some patients unrelated to tumour response (Ansfield et al., 1974; Ansfield et al., 1976). Several randomised double-blind placebo-controlled studies in cancer patients of mixed, mainly non-hormone responsive tumour types have shown increased appetite, some weight gain and improved mood (Loprinzi et al., 1990; Bruera et al., 1990; Tchekmedyian et al., 1992; Strang, 1997). However, weight gain in cancer patients receiving megestrol acetate appears to be mainly fat with little increase in fat free mass (Loprinzi et al., 1993).

Medroxyprogesterone acetate is a progestational agent with additional endocrine effects. Johnson and co-workers (1984) reported weight gain in 53% of patients with advanced breast cancer, although it is possible that this is because the medroxyprogesterone acetate was acting as an anti-tumour agent. Downer and colleagues (1993) studied a group of cancer patients, with non-hormone responsive tumours, in a randomised double blind placebo controlled trial and found no evidence of weight gain, although there was a significant improvement in appetite.

Ibuprofen is a non-steroidal anti-inflammatory drug which has been reported to moderate the acute phase response and reduce the circulating concentrations of acute phase proteins (Preston et al., 1995; McMillan et al., 1995). It has also been reported to reduce resting energy expenditure in pancreatic cancer patients (Wigmore et al., 1995). A recent study has suggested a role for ibuprofen, in combination with megestrol acetate, in promoting weight gain in weight-losing patients with an acute phase response (McMillan et al., 1997).

It is clearly important that further study of the acute phase response, in relation to cachexia and fatigue, is carried out.

1.4 Neuromuscular Disorders

The term weakness has often been used to denote a neurological or neuromuscular problem (Nail and Winningham, 1995). Indeed, there are a number of reasons why these problems occur in cancer patients. Focal limb weakness may be the result of a cerebrovascular accident, a haemorrhage into a primary or secondary brain tumour, or directly related to cerebral metastases. Clinicians should also be wary of the patient complaining of being "off his legs", or reporting leg weakness, as this may represent a potentially treatable spinal cord compression .

Radiculopathies, due to spread of the primary tumour - particularly breast, lung, gastric, melanoma and lymphoma - to the leptomeninges, may present with a variety of motor and sensory deficits, particularly a lower motor neurone type weakness (Chad and Recht, 1991).

Brachial plexopathy is due to damage to the brachial plexus from disease spread to the axillary lymph nodes - usually from a breast or lung carcinoma - or due to previous radiotherapy, often many years before. Weakness is, however, far less common than pain. The distribution of the weakness will relate to the part of the brachial plexus involved. Lumbosacral plexopathy may relate to direct invasion of the lumbosacral plexus from an intra-abdominal neoplasm or, less commonly, due to metastatic spread - usually from a primary breast carcinoma - or previous radiotherapy. Pain and weakness co-exist, although weakness is the more prominent in radiotherapy induced lesions and is usually bilateral, symmetrical and distal in distribution (Chad and Recht, 1991; Stubgen, 1995).

Paraneoplastic syndromes are uncommon, but should be considered as a cause of muscle weakness. Symptoms can precede the cancer diagnosis by a period of months to years and many of these syndromes can be partially reversible with treatment of the tumour (McEvoy, 1994). Table 1.1 lists some of the paraneoplastic syndromes which may present with muscle weakness (Richardson, 1982; Chad and Recht, 1991; Dalmau et al., 1992; Stubgen, 1995). The commonest of these is the Lambert-Eaton myasthenic syndrome (LEMS) which is present in about 3% of patients with small cell lung cancer (McEvoy, 1994; Stubgen, 1995). LEMS is caused by antibodies against voltage-gated calcium channels, which prevent the release of acetylcholine from peripheral nerve terminals, and presents with predominantly proximal muscle weakness. Weakness tends to affect the lower limbs and is associated with easy muscle fatiguability, hyporeflexia and autonomic dysfunction (McEvoy, 1994; Anderson, 1995; Stubgen, 1995).

Myasthenia gravis is associated with thymoma in 30% of patients. When thymoma is present it is generally poorly responsive to thymectomy (Stubgen, 1995).

Drugs used as anti-cancer therapy can also lead to iatrogenic muscle weakness, notably vincristine and other vinca alkaloids, etoposide, paclitaxel and cytosine (Stubgen, 1995).

Table 1.1 Paraneoplastic Syndromes Which May Present With Muscle Weakness

Paraneoplastic syndrome	Associated malignancy
Motor neurone disease:	
Amyotrophic lateral sclerosis	Non-Hodgkin's lymphoma
Subacute motor neuronopathy	Hodgkin's disease
Lambert-Eaton myasthenic syndrome	Small-cell lung cancer in up to 80% of patients
Myasthenia gravis	Thymoma
Polymyositis/dermatomyositis	Lung, breast, gastrointestinal and ovarian malignancies are most common
Carcinoid myopathy	Carcinoid syndrome
Acute necrotising myopathy	Small-cell lung cancer, breast, gastrointestinal and bladder malignancies
Paraneoplastic encephalomyelitis	Mainly small-cell lung cancer (Anti-Hu antibody associated)
Sensorimotor polyneuropathies:	
Acute inflammatory demyelinating (Guillain-Barré syndrome)	Hodgkin's disease, lung cancer
Chronic inflammatory demyelinating	Lymphoma
Acute/chronic axonal	Lung cancer
Carcinomatous myelopathy	Mainly lung cancer (very rare)

1.5 Aetiology of Impaired Muscle Function

Cachexia causes a reduction in muscle quantity. In the review of weakness in cancer patients by Lichter (1990), cachexia was considered to be the major cause of muscle weakness. However, not all patients who complain of feeling weak have lost weight and Theologides (1982) speculated as to why some patients with asthenia maintained their muscle bulk and strength until death. Most clinicians will have known patients who were able to self-care despite their marked cachexia, and some who became dependent and were unable to function despite maintaining their weight.

1.5.1 Inactivity

Many cancer patients are far less active than their healthy counterparts and some researchers have commented on the role of inactivity in the production of muscle weakness in cancer patients (Winningham et al., 1994; Nail and Winningham, 1995). It has been estimated that a third or more of the reduction in ability to carry out physical activity in cancer patients can be attributed to prolonged physical inactivity (MacVicar, Winningham and Nickel, 1989). Excessive bedrest is thought to be partly responsible for weakness and reduced exercise tolerance (Lichter, 1990). Immobility is known to reduce muscle strength more than muscle area, with the quadriceps being the muscle most severely affected (Nørregaard et al., 1994). The quadriceps muscle is functionally very significant and is used in many important daily activities, such as rising from a chair and stair climbing (Bassey et al., 1992).

Inactivity may be an inevitable result of advancing cancer and increasing ill-health. It may, however, be partly related to altered role. Tasks previously performed by the

patient may become delegated to carers, either at the patient's instigation or by the well-meaning intervention of carers. This may have knock-on effects and the patient may suffer from loss of role, poor self-esteem and greater dependence (Aistars, 1987). It is not clear whether the previous fitness or activity level of the patient affects the rate of any subsequent decline in muscle function or strength.

1.5.2 Cytokines and Muscle Metabolites

It has been hypothesised that circulating humoral factors may cause changes to muscle and its function (Theologides, 1982). More recently fatigue has been associated with the local and circulating effects of cytokines on muscle function. St. Pierre, Kasper and Lindsey (1992) hypothesised that tumour necrosis factor, either produced by the body in response to the cancer, or used as anti-cancer therapy, may contribute to generalised muscle weakness via reduced muscle protein stores, leading to reduced muscle bulk and metabolic abnormalities within the muscle. It is thought that this may lead to reduced contractile ability in the muscle and impaired neuromuscular transmission. It is suggested that both the qualitative and quantitative effects on muscle will limit the patient's ability to exercise and that increased effort will be required to generate adequate contractile force. Ability to exercise may, therefore, be impaired in cachectic cancer patients because of increasingly abnormal skeletal muscle metabolism.

During exercise, particularly in those who are inactive, like many cancer patients, there may be an accumulation of some muscle metabolites, such as hydrogen ions, and a reduction in others, such as muscle phosphocreatinine. These changes may contribute to the patient's experience of fatigue (Newsholme, Blomstrand and Ekblom, 1992; St. Pierre et al., 1992).

1.5.3 Other Causes of Impaired Muscle Function

Muscle biopsies have shown that cancer patients, even those who have not lost weight tend to lose type 2 muscle fibres preferentially to type 1 fibres. Type 2 fibres are used more in short duration activity, e.g., stair climbing, and this may explain some of the functional problems faced by non weight-losing cancer patients (Gomm et al., 1990; St. Pierre et al., 1992).

Vitamin D deficiency (osteomalacia) is common in medically ill patients, and one study of 290 consecutive patients on a general medical ward reported that 57% were vitamin D deficient (Thomas et al., 1998). One feature of vitamin D deficiency is proximal muscle weakness, which can be marked (Forbes and Jackson, 1993). Vitamin D deficiency relates to a combination of dietary deficiency and lack of sunlight exposure (Ainsleigh, 1993; Forbes and Jackson, 1993). Vitamin D concentrations have not previously been studied in patients with advanced cancer.

1.5.4 Muscle Electrical Activity

It can often be difficult to determine how much of an apparent muscle weakness is truly organic (has a physical cause) and how much is functional (no obvious physical cause) (McComas, Kereshi and Quinlan, 1983). Patients may complain of muscle weakness and the reduced strength could be related to a loss of muscle tissue, a change in muscle function, or an inability or reluctance to activate fully all of the muscle (Rutherford, Jones and Newham, 1986).

The technique of twitch interpolation by electrical stimulation has a long tradition in the scientific literature. It has been used to study the electrical activity of muscles and to try

and distinguish between the voluntary and involuntary components of muscle force production (Denny-Brown, 1928; Merton, 1954). The principle is that if a subject can activate a muscle fully during a muscle contraction then a superimposed electrical stimulus will not produce any additional force (Merton, 1954; McComas et al., 1983).

It has been shown that by stimulating the quadriceps muscle, the extra force generated by the interpolated twitch decreases with increasing levels of voluntary muscle force, (Chapman et al., 1984). This has been confirmed in other muscle groups (Belanger and McComas, 1981). Thus, an electrical stimulus delivered when the subject is producing a sub-maximal effort will produce a twitch tracing, the height of which is inversely related to the strength of the muscle contraction. The size of the superimposed twitch falls off linearly with increasing muscle tension and when the muscle is fully activated, i.e., true maximum voluntary contraction, then no twitch will be visible. A series of twitches related to muscle contractions of varying strengths may be graphed and the extrapolated value of muscle force for zero twitch corresponds to the maximal voluntary muscle force achievable (Merton, 1954; Chapman et al., 1984; Nørregaard et al., 1994).

The technique can be used to decide whether a subject, when asked to produce a maximum voluntary muscle contraction has in fact done so (Chapman et al., 1984). One study reported a large functional component to reported muscle weakness in two patients. Large twitches were observed, superimposed on the force tracing, indicating that both patients had performed sub-maximal efforts (McComas et al., 1983). Sub-maximal efforts may be related to poor motivation, pain, fear of pain and psychological factors (Rutherford et al., 1986). It is possible that subjects may feel "weak", without any detectable, objective muscle weakness.

Rutherford, using this technique to study quadriceps muscle activation, was able to identify three patient groups: those with pain and incomplete activation of muscle due to pain, those with no pain and incomplete activation and those with loss of muscle tissue and full activation. (Rutherford et al., 1986).

Several groups have studied muscle strength and activation in patients with chronic fatigue syndrome. Two studies reported muscle strength to be normal in this patient population and similar to that of the healthy controls (Lloyd, Hales and Gandevia, 1988; Stokes, Cooper and Edwards, 1988). Stokes and colleagues commented that abnormalities in performance occurred only during voluntary activity and concluded that central impairment causing a sub-maximal effort was the cause of weakness, rather than intrinsic muscle weakness. Lloyd and co-workers (1988), however, suggested that the problem was an abnormality of perception of muscle force by the subject rather than of actual force production, i.e., the subject was unable to tell he had produced a sub-maximal effort. In contrast, Nørregaard's study reported that muscle strength was reduced per unit area of the quadriceps muscle in patients with fibromyalgia - which is related to chronic fatigue syndrome - and found no difference in central activation between patients and controls (Nørregaard et al., 1994).

The clinical studies involving twitch interpolation have generally studied isometric muscle contractions (see section 1.6) in different patient groups, although one study has looked at isokinetic contractions (Westing, Seger and Thorstensson, 1990).

The above principles may well be applicable to cancer patients. Although a few studies have reported abnormal muscle electrophysiology in cancer patients (Bruera et al.,

1988; Monga et al., 1997), there appear to be no studies of twitch interpolation in cancer patients. Many patients will have lost muscle quantity, but may be able to fully activate their muscles and may be weak purely due to loss of muscle bulk. However, some patients may have normal muscle bulk and still have reduced strength due to failure to use their muscles properly. Some cachectic patients may also have an element of abnormal muscle function. More work needs to be done in looking at the involuntary and voluntary components of muscle strength in cancer patients.

1.6 Strength and Functional Ability

Although weakness has been defined as a reduction in muscle strength, and many have commented at the difficulty cancer patients with weakness or fatigue have in the performance of ordinary activity, to date there appear to be few studies which have measured strength and quantified functional ability in cancer patients, or have examined their relationship. Having concluded that muscle function and muscle electrophysiology were abnormal in cancer patients, Bruera and co-workers hypothesised that abnormal muscle function may be a major component of asthenia/fatigue. It was suggested that attempts should be made to correlate the severity of asthenia with muscle function (Bruera et al., 1988, 1989).

In physiological terms, strength is the ability of a muscle to generate force. Force is more difficult to define as in itself it cannot be seen. What can be seen is the effect of that force, for example an object falling to the ground under the effect of gravity. If a force is applied to an object it will move and accelerate, unless an opposing force acts upon it (Jones and Round, 1990a). Measurement of muscle force has been important for exercise scientists and for those involved in rehabilitation medicine, to assess the effects of exercise or training programmes (Perrin, 1993a).

The capacity of a muscle to generate force can be assessed through either static or dynamic contraction. Isometric (constant length) contractions are static muscle contractions. In isometric assessment, the amount of force a muscle can generate against a resistance permitting no overall joint movement is measured. The resistance is in direct ratio to the force applied (Perrin, 1993a).

Testing of isometric force has traditionally been performed with techniques such as handgrip dynamometry (Perrin, 1993a). Handgrip dynamometry has been used extensively in a variety of patient settings (Kallman, Plato and Tobin, 1990; Watters et al., 1993; Cress et al., 1995). The main advantage of isometric resistance is that it can be used to test muscles around a joint which cannot move, for example due to joint pathology (Perrin, 1993a). It is also an easy concept for the patient to understand. The major disadvantage of isometric strength assessment is that it allows measurement only at a specific point in a joint's range of motion and, therefore, does not directly relate to usual daily activities.

Isotonic (constant load) assessment is a dynamic method of measuring muscle force and involves the application of force through all or part of a joint's range of movement. A muscle can produce dynamic tension whilst either shortening or lengthening (Perrin, 1993a). In isotonic muscle contraction the level of resistance against joint movement remains constant (Thistle et al., 1967). If the joint movement is in a direction opposite to that of gravity and the force produced by the muscle exceeds the external resistance encountered, the contraction is described as shortening (or concentric) in nature (Perrin, 1993b). If the joint motion is in the direction of the gravity and the external resistance encountered exceeds the muscle's ability to generate force, the contraction is described as lengthening (or eccentric) in nature. Isotonic force can be measured using dumbbells or weight machines and force is often measured by testing the amount of weight that can be lifted through a joint's range of movement for a number of repetitions. Isotonic measures have the advantages of being able to assess multiple joints simultaneously and of assessing a more natural form of movement. However, isotonic assessment is limited in that the muscle can be overloaded only by the amount of weight that can be lifted

through the weakest part of the exercised range of motion. There may also be difficulties in isolating a specific muscle group without contribution from accessory muscle groups.

An isokinetic contraction is also a dynamic contraction, but the angular velocity of joint motion is held constant. The concept of isokinetic contraction and exercise is a relatively recent development (Thistle et al., 1967; Hislop and Perrine, 1967). Isokinetic dynamometers allow individuals to exert as much force and angular movement (movement through a joint's natural range of motion) as they can up to a predetermined velocity and through a pre-determined range of movement (Perrin, 1993a). When a limb's angular rate of movement equals or exceeds the pre-set velocity limit, the dynamometer produces an equalling counterforce to ensure constant movement rate (Thistle et al., 1967; Perrin, 1993a). The limb being studied is attached to the lever arm of the dynamometer. As force is being measured about a joint's axis of rotation it is technically known as torque (Perrin, 1993b). Measurement of isokinetic resistance has the advantage that a muscle group can be exercised to its maximum potential throughout a joint's entire range of motion and therefore it more closely mimics ordinary daily activity (Thistle et al., 1967). It is also safer than isotonic exercise because the dynamometer's resistance mechanism disengages when pain or discomfort is experienced by the patient. As in isotonic assessment, it can be difficult to isolate one muscle group, without contributions from accessory groups.

Although what is measured in strength testing is muscle force or torque, because strength is a term often used interchangeably with force (Jones and Round, 1990a) and because strength is the more commonly used term in general speech, the word strength will generally be used throughout this thesis.

1.6.1 Strength and Ageing

In contrast to the lack of cancer literature, there is a wealth of literature regarding the measurement of strength and function in the healthy population and in particular in the elderly population. Muscle strength is known to decline with age and appears to be related to muscle mass and fat free mass (Larsson, Grimby and Karlsson, 1979; Kallman et al., 1990; Frontera et al., 1991; Fiatarone et al., 1994). Fiatarone and colleagues (1990, 1994) suggest that the decline in muscle strength and mass during ageing is related to physical frailty, functional decline and impaired mobility.

Kallman and co-workers (1990) reported that although handgrip strength correlated with muscle mass, there was a stronger association with age and suggested that other factors, such as ageing effect on the muscle, or reduced activity might be important. However, Frontera and colleagues (1991) found no significant difference between strength in patients of different ages when controlled for muscle mass (measured by urinary creatinine excretion) and fat free mass (measured by hydrostatic weighing) and concluded that muscle mass was the major determinant of age related skeletal muscle strength. It has also been reported that reduction in muscle strength is related to type 2 muscle fibre atrophy, which is found in the elderly (Gomm et al., 1990).

1.6.2 Relationships Between Strength and Function

Although the cancer literature does comment on the role of the multidisciplinary team in the rehabilitation of cancer patients and in particular on the role of the physiotherapist in maintaining muscle strength and function, or in providing aid to activity (Fulton and Else, 1998), there appear to be no studies which have specifically examined the relationship between muscle strength and the ability to carry out daily activities in

cancer patients. However, a relationship between self-perceived fatigue and self-perceived function - as measured using the Sickness Impact Profile (Bergner et al., 1981) - has previously been reported in cancer patients (Irvine et al., 1994).

Much more work has been done in care of the elderly research in the last 20 years, although as recently as 1986, Young commented that few studies had attempted to correlate measures of muscle strength, or of exercise tolerance, and performance in the activities of daily living. However, subsequent to this, it has been reported that in the elderly there is a correlation between self-perceived physical function - using the Sickness Impact Profile physical dimension summary score - and handgrip strength, as well as with physical performance measures such as time to stand from a chair and walking gait speed (Cress et al., 1995).

One study reported correlations between muscle strength, climbing onto variable step heights and walking speed in healthy 70 year old men and women, and also reported a relationship between strength in gripping a key and manual dexterity (Aniansson, Rundgren and Sperling, 1980). Bassey and colleagues (1992) reported a positive correlation between leg extensor power and short-term performance measures: speed of stair climbing, rising from a chair and walking. Power is the amount of work done by a muscle producing force over a period of time (Jones and Round, 1990a).

1.6.3 The Role of Strength and Functional Training

Several studies in various patient groups have looked specifically at trying to improve strength and ability to perform functional activities.

Fulcher and White (1997) reported that, in a patient population with chronic fatigue syndrome, isometric quadriceps strength and aerobic capacity - as measured by time on a treadmill - could be increased using a graded exercise programme.

Several trials have been carried out in the healthy elderly. Using an exercise programme McMurdo and Burnett (1992) reported improvements in perceived health status and life satisfaction, increased physical exertion levels and improved spine flexion. However, no significant improvement in handgrip strength was found. In another study of strength training in nonagenarian females, increased mid-thigh muscle area and increased walking speed were reported, but there was no improvement in stair climbing (Fiatarone et al., 1990). A later study by the same group, a randomised placebo-controlled trial of progressive resistive exercise in the elderly, reported that muscle strength increased by 13% in the training group and only 3% in the control group who participated in ordinary recreational activities (Fiatarone et al., 1994). Walking speed and stair climbing power, as well as the level of spontaneous activity, were also found to improve significantly. They found no relationship between the degree of muscle hypertrophy and the relative strength gains and concluded that some of the strength gain related to improved neural recruitment pattern within the muscle rather than merely improved muscle bulk.

Another group studied stair climbing as a means of improving quadriceps strength in middle-aged women, the rationale being that climbing stairs required an individual to vertically lift body weight and thus might improve leg strength. It was reported that those who took part in the stair climbing exercises developed increased isokinetic quadriceps strength (Loy et al., 1994).

One randomised trial of strength training in elderly women to try and improve functional ability reported only an improvement in highest step height achievable and time to rise from a kneeling position - but not other functional tests - despite an improvement in knee extensor and elbow flexor muscle strength (Skelton et al., 1995). It was concluded that task dependent increases in strength and power can only produce limited improvement in functional ability. It is thought that gains from strength training may be specific to the type of exercise used during a training programme and that isolation of one muscle, e.g. the quadriceps, will not necessarily lead to functional improvement. Training may improve performance by increasing neural activation of the muscle units, leading to better muscle co-ordination and more skilful execution of activity (Gillies et al., 1999). The study by Gillies and colleagues set out to test the hypothesis that elderly patients could improve their ability to perform simple daily functional activities by practising those activities. They speculated that muscle decline might in part be due to lack of practice. The exercise group improved in stair ascent/descent, chair rise, triple chair rise and walking, and controls in only stair ascent and chair rise. Only the walking test was significantly different between the two groups, but study numbers were small (n=20) (Gillies et al., 1999).

As poor functional ability is often a factor in patients with advanced cancer, there is a need for studies to examine the relationship between strength and function in cancer patients. Formal assessment of ways of improving ability to perform daily activities is also needed.

1.7 Exercise and Fatigue

The traditional approach to the management of fatigue/tiredness in cancer patients has been to advise patients to rest as much as possible. It has previously been assumed that cancer patients would be unable to tolerate exercise (Aistars, 1987; MacVicar et al., 1989). However, there is some evidence that regular aerobic exercise may have important physiological and psychological benefits, including reduced fatigue (Aistars, 1987). Graydon and colleagues (1995) reported that sleep and exercise were the two most effective patient-reported strategies for the relief of fatigue in patients receiving chemotherapy or radiotherapy for cancer.

In a review of the role of exercise in the rehabilitation of cancer patients, Friedenreich and Courneya (1996) identified nine studies of exercise in cancer patients, including four randomised controlled trials, three quasi-experimental studies and two retrospective studies. All of the studies involved breast cancer patients, mainly those of good performance status and mostly patients who were receiving active anti-cancer therapy. In most of the studies exercise was carried out on a bicycle ergometer in a controlled laboratory setting. Overall, it was concluded that exercise produced improvements in functional capacity, defined as improvement in the body's maximal uptake of oxygen. It was also concluded that exercise led to increased lean tissue, decreased body fat, reduction in nausea and fatigue and improved psychological well-being and quality of life.

The rationale for aerobic exercise is that, because there is a direct relationship between oxygen uptake and the performance of physical activity, aerobic exercise will improve

oxygen uptake by skeletal muscle (MacVicar et al., 1989). MacVicar and co-workers (1989) suggested that, even in advanced disease states, an exercise programme may minimise loss of functioning and prevent muscle disuse in cancer patients.

The role of exercise has been challenged by St. Pierre and colleagues (1992) who feel that exercise may increase muscle weakness in cachectic cancer patients. It is certainly true that studies to date have included mainly breast cancer patients at early stages of disease and it is difficult to extrapolate from the findings in these studies to patients with advanced disease. A recent study has suggested that exercise may reduce fatigue in patients with different cancer types (Dimeo, Rumberger and Keul, 1998), but this study included only five patients. Larger studies of the role of exercise in cancer patients - both weight-stable and weight-losing - are needed.

1.8 Anaemia

Anaemia has been implicated as a cause of weakness, fatigue and asthenia (Lichter, 1990; Morant, 1996; Cella, 1997). One study reported a correlation between the level of weakness, as measured on a linear analogue scale, and the haemoglobin concentration, and a later study by the same researcher found a weak correlation between haemoglobin concentration and a linear analogue scale measurement of fatigue (Morant et al., 1993; Morant, 1996).

In a study of transfusion in anaemic cancer patients, weakness was one of the reasons for transfusion in 91% of patients (Gleeson and Spencer, 1995). A significant improvement in patient-rated weakness score - as scored on a linear analogue scale - was found after transfusion as well as improvements in dyspnoea and general well-being scores. The researchers' definition of weakness equated with loss of strength. Not all patients benefited from transfusion. The absolute level of haemoglobin did not appear to correlate with the level of weakness, nor was there more benefit from transfusion in those with the lowest initial haemoglobins.

In 2 studies, Irvine and colleagues (1991, 1994) found no consistent relationship between the level of fatigue and haemoglobin concentration. Bruera and colleagues (1989) found no correlation between haemoglobin level and an asthenia score and concluded that anaemia was probably not that important as an aetiological factor for weakness and fatigue in patients with advanced cancer.

However, a recent study using the Functional Assessment of Cancer Therapy Fatigue (FACT-F) questionnaire (Yellen et al., 1997) has reported that patient scores of fatigue were able to distinguish between different haemoglobin categories (< 11.0 g/dl, 11.0-13.0 g/dl and > 13.0 g/dl). A further study has reported that administration of erythropoietin to non-haematological cancer patients caused an increase in haemoglobin and also in quality of life and ability to carry out daily activity (Demetri et al., 1998).

Weakness and fatigue, therefore, would appear to be associated with anaemia, but there has been no consistent, strong, linear relationship established between degree of anaemia and the severity of weakness and fatigue.

1.9 Other Abnormalities

Various biochemical abnormalities may contribute to the aetiology of generalised weakness in cancer patients, some of which are potentially treatable, such as hypercalcaemia and hypokalaemia, uraemia and hypomagnesaemia (Regnard and Mannix, 1992). Hyponatraemia may be related to the syndrome of inappropriate anti-diuretic hormone secretion, which is a feature of some cancers, such as small cell lung cancer and can relate to drug therapy, such as opioids and antidepressants (Regnard and Mannix, 1992; Morant, 1996; Bower, Brazil and Coombes, 1998). Low albumin levels are often found in patients with advanced cancer and Morant and colleagues (1993) reported a correlation between albumin levels and patient-rated weakness.

Drug therapy is thought to contribute to the aetiology of weakness and fatigue, in particular opioids, anti-emetics, benzodiazepines, diuretics and psychotropic drugs, all of which are widely used in cancer patients (Bruera and MacDonald, 1988; Lichter, 1990; Regnard and Mannix, 1992; Barnish, 1994).

Endocrine abnormalities are a less common cause of weakness. They may predate and not be related to the cancer, for example diabetes, Addison's disease or hypothyroidism, or may be directly related to the cancer, such as Cushing's syndrome, hypopituitarism or hypoadrenalism secondary to adrenal metastases (Bruera and MacDonald, 1988; Lichter, 1990). Infection may also contribute to weakness in patients, who are often immunosuppressed as a result of progressive disease or chemotherapy (Bruera and MacDonald, 1988; Regnard and Mannix, 1992).

1.10 Corticosteroids

Corticosteroids (steroids) are one of the most frequently used groups of drugs in the palliation of the symptoms of advanced cancer and may be used in up to two-thirds of in-patients in cancer or palliative care units (Hanks, Trueman and Twycross, 1983; Batchelor et al., 1997).

Indications for the use of steroids include spinal cord compression, raised intracranial pressure secondary to primary or metastatic cerebral malignancy and superior vena caval obstruction. Steroids are also sometimes used as co-analgesics to reduce pain in association with hepatic metastases or due to nerve compression. They are also frequently used in the treatment of anorexia, to improve mood and promote feelings of general well-being, particularly in those who complain of feeling weak or tired (Hanks et al., 1983; Popiela, Lucchi and Giongo, 1989; Robustelli Della Cuna, Pellegrini and Piazzi, 1989; MacDonald, Hagen and Bruera, 1994; Batchelor et al., 1997).

Little is yet known about the mode of action of steroids when used for treatment of anorexia and to enhance well-being. They may work partly through a central euphoriant effect and partly through effects on prostaglandins and pro-inflammatory cytokines (Bruera et al., 1985; Yanagawa et al., 1996; Gagnon and Bruera, 1998).

There have been few randomised controlled trials investigating the value of steroids in cancer patients. The Methylprednisolone Pre-terminal Cancer Study Group reported on two trials studying the efficacy of an eight week, 125mg/day intravenous course of methylprednisolone sodium succinate (MPSS), compared to placebo, in a heterogeneous

group of patients with advanced cancer (Robustelli Della Cuna et al., 1989; Popiela et al., 1989). The first study reported that the patients receiving MPSS had significantly higher quality of life ratings than the placebo group, although this was rated by the health professionals and not by the patients (Robustelli Della Cuna et al., 1989). They also reported a significant improvement in patient-rated appetite, pain, vomiting and general well-being over the study period in the steroid treated group. However, there was no improvement in weakness scores and there was a significantly higher death rate in female patients receiving MPSS. In light of this, Popiela and colleagues performed a similar study in female cancer patients (Popiela et al., 1989). In this study, there was a non-significant trend towards earlier death in the steroid treated patients. They did, however, report an improvement in appetite, well-being, nausea and anxiety scores throughout the study period and also a significant improvement in weakness scores in the first two weeks of the study.

Steroids do, however, have significant side effects. Gastrointestinal symptoms are probably the commonest side effects, including dyspepsia, oropharyngeal candidiasis and upper gastrointestinal haemorrhage (Hardy, 1998). Steroid treated patients are generally more prone to infection. Raised serum glucose is also common and some patients develop psychiatric complications, including frank psychosis. (Hanks et al., 1983; MacDonald et al., 1994; Batchelor et al., 1997).

A recent small study of fifteen cancer patients treated with dexamethasone (a synthetic steroid) reported that nine (60%) developed clinically detectable proximal muscle weakness (myopathy), which in five patients was severe enough to interfere with the activities of daily living (Batchelor et al., 1997). All patients were receiving high doses

of dexamethasone (16-100 mg/day of dexamethasone in those most disabled). The development of myopathy was significantly related to the cumulative dose of steroid, although not with the duration of steroid treatment. A decline in respiratory function was also reported, mainly affecting the group with proximal myopathy, and was thought to be due to respiratory muscle weakness.

The incidence of steroid myopathy has been reported as 10-60% (MacDonald et al., 1994). However, one study documented myopathy in only 2% of patients (Hanks et al., 1983), although in this study steroid doses were lower (starting dose of 10-30 mg of prednisolone or 4-16 mg of dexamethasone) than in the study by Batchelor and co-workers (1997).

The muscle damage caused by steroids is thought to be related to alterations in muscle protein metabolism, with increased protein breakdown and reduced synthesis. Atrophy of type 2 muscle fibres has been found even in patients on low doses of corticosteroids, although this finding has also been reported in cancer patients generally (Warmolts et al., 1975; Gomm et al., 1990; St. Pierre et al., 1992; MacDonald et al., 1994). Anecdotal reports suggest that the incidence of steroid myopathy is highest in those treated with fluorinated steroids, such as dexamethasone, and that muscle weakness may improve over time with stopping the steroids, reducing the steroid dose or changing to a non-fluorinated steroid, such as prednisolone or hydrocortisone (MacDonald et al., 1994; Batchelor et al., 1997). Isometric exercise may help to preserve muscle bulk (Horber et al., 1985; MacDonald et al., 1994).

Steroids, therefore, although having some beneficial effects in cancer patients, have significant side effects, including steroid myopathy, which may lead to muscle weakness and may interfere with daily activities.

1.11 Quality of Life

The World Health Organisation (1947) defined health as "a state of complete physical, mental and social well-being and not merely the absence of disease." However, in the care of patients with cancer, traditionally the primary outcome variables have been tumour response to treatment and disease free survival (Aaronson et al., 1993; Hjermstad et al., 1995).

It is increasingly accepted that a significant proportion of patients with cancer will not be cured and that to aim to improve patient's well-being is a critical component of good patient care (Ahmedzai, 1990; Hjermstad et al., 1995). It has been stated that the primary aim of palliative care is to optimise the quality of life of patients with advanced incurable illness through the control of physical symptoms and attention to their psychological and spiritual needs (Richards and Ramirez, 1997).

Quality of life, or health related quality of life has been defined as "the extent to which one's usual or expected physical, emotional and social well-being are affected by a medical condition and its treatment" (Cella, 1995). This definition is extended by Ahmedzai to include the impact of the disease and treatment on the patient's family (Ahmedzai, 1993).

It is now widely accepted that a number of dimensions, or domains, contribute to quality of life, but that the relative importance of each dimension will vary between individuals and with time. The dimensions which are generally assessed are physical symptoms, emotional well-being, cognitive well-being, functional activity and social functioning.

Also included in some assessment tools are family relationships, occupational functioning, spirituality, perception of the future, treatment satisfaction, sexuality and body image (Ahmedzai, 1990; Hjermstad et al., 1995; Richards and Ramirez, 1997).

A number of questionnaires have been developed specifically to measure quality of life and a number of articles review these different measurement tools (Clark and Fallowfield, 1986; Moinpour et al., 1989; Cella, 1995). Any questionnaire should be valid (i.e., it should measure what it claims to measure) and reliable (i.e., on re-testing it should give the same result). However, validity can only be assessed indirectly as no gold standard of quality of life exists for comparison. Clearly, each patient will define their own quality of life differently (Hjermstad et al., 1995; Richards and Ramirez, 1997).

There has been debate as to who should measure quality of life. There is some consensus that because quality of life is subjective and individual for each patient, the patient should measure it where possible (Slevin et al., 1988; Richards and Ramirez, 1997). In the study by Slevin and colleagues (1988) it was suggested that doctors failed to adequately assess patients' quality of life. However, it has been suggested that there may be situations where it is necessary for others, whether professional carer or a relative, to measure quality of life when the patient, for whatever reason, is unable to do so themselves (Ahmedzai, 1990; Cella, 1995). It could be argued that all quality of life assessment tools are flawed in that they presuppose the relevant areas of quality of life to be studied (Ahmedzai, 1993). The SEIQoL (schedule for evaluation of individual quality of life) tool has been recently developed (Hickey et al., 1996) and allows respondents to nominate the areas of life which are most important, rate their level of

satisfaction with each area, and indicate the relative importance of each to their overall quality of life. However, to date, this tool has not been validated in cancer patients.

Given the importance of quality of life to patients with a short life expectancy, it is vital that studies involving this patient group include some measure or assessment of quality of life. In preference, any measure should be assessed by the patient, using simple tools which can be easily completed.

SUMMARY

A significant proportion of patients with cancer will not have curable disease and, consequently, symptom control and improvement of all aspects of quality of life are priorities. Weakness and fatigue are two of the commonest symptoms in patients with advanced cancer, yet little is known about their aetiology and less about how to manage them. They are often felt to be merely an inevitable consequence of advancing disease.

It is known that patients with weakness and fatigue complain of reduced strength and ability to perform simple daily activities. It is clear, from studies comparing cancer patients with healthy controls, that patients often express a physical dimension to their feelings of tiredness, which could possibly be understood as "weakness". There is very little research into the relationship between the subjective experience of weakness and actual measures of strength and functional ability in cancer patients.

Many patients with advanced cancer have lost weight and this is reported to be an aetiological factor in weakness and fatigue. However, the exact role of cancer cachexia, and the inflammatory response associated with cachexia, in the production of these symptoms, and in loss of physical strength and functional ability, is unclear.

Anaemia, biochemical abnormalities and certain drugs commonly used in cancer patients have also been implicated in the aetiology of weakness and fatigue, although the relative importance of these is not known. Psychological distress has also been reported to be related to weakness and fatigue.

Clearly, weakness and fatigue are important symptoms in cancer patients, and a greater understanding of their aetiology and impact is important. The relationships of weakness and fatigue to strength, function, blood parameters, psychological distress and other aspects of quality of life require further investigation.

AIMS OF THIS WORK

The aims of the work which follows were:

1. To investigate the importance of weight loss, altered body composition, the inflammatory response, haematological and biochemical parameters in patients with advanced cancer.

2. To examine the relationships between objective tests of strength and function, and measures of weakness and fatigue and patient-related quality of life in patients with advanced cancer.

CHAPTER 2 : METHODS : BODY COMPOSITION

2.1 Introduction

2.1.1 Body Composition

As has previously been discussed in section 1.3, many cancer patients lose weight. Weight loss in itself in cancer patients confers a poorer prognosis, in terms of survival, and leads to significant morbidity (DeWys et al., 1980; Nixon et al., 1980). Certainly, weight is often used as a measure of nutritional status in cancer studies (Heymsfield and McManus, 1985; Heymsfield et al., 1994; Burman and Chamberlain, 1996). The severity of weight loss in an individual is determined by two factors: the rate of weight change over time and the total reduction in weight. It is important to note the patient's usual weight by history or from previous measurements as obese patients may have lost weight and be malnourished, although they are still overweight compared to the average population (Heymsfield et al., 1994). Weight is simple to measure, but it does have its disadvantages as a measure of nutritional status. The presence of ascitic fluid or peripheral oedema, a large tumour mass or organomegaly can mean that a patient may well have lost little weight, but has lost significant amounts of fat and skeletal muscle (Heymsfield and McManus, 1985; Heymsfield et al., 1994; Burman and Chamberlain, 1996).

Body mass index (BMI) is often used in diagnosis of both malnutrition and obesity (Garn, Leonard and Hawthorne, 1986). It is calculated by dividing the patient's weight in kilograms by the square of their height in metres and is clinically more relevant than an absolute value of weight. However, body mass index also has some limitations.

Although BMI has a relatively strong correlation with body fat, some athletic individuals may have a large skeletal muscle mass and a high BMI, but are not obese (Smalley, 1990). Weight and BMI are clearly important indicators of nutrition and prognosis, but as they have limitations, additional approaches to assessing body composition were employed in the present work.

Keys and Brozek (1953) pointed out that "the human body may be analysed in many ways; the best way will depend on the end sought and the practical possibilities". The present work adopted this approach of using methods which were practical, simple and acceptable to patients.

The human body can be considered to be made up of several compartments and several models have been used to describe these components. The simplest of these is one which divides the body into fat and fat free mass, which contains muscle and visceral tissue, non-muscle lean tissue and minerals. Given that weight loss in cancer patients involves loss from both compartments (Cohn et al., 1981; Heymsfield and McManus, 1985; Preston et al., 1995), then it should be possible to measure alterations in both. Previous work has reported that fat-free mass consists of approximately 73% water (Pace and Rathbun, 1945) and, consequently, if body weight and total body water are known, this percentage can be used to estimate both fat mass and fat-free mass. A number of methods have been used to measure these two compartments.

Underwater, or hydrostatic, weighing involves the complete submersion of the patient in water, the weight underwater being subtracted from that in air. The weight of the patient is then divided by their volume to calculate their density. This method involves the

assumption that both fat and fat-free mass have known and constant densities (0.9 kg/l for fat and 1.1 kg/l for fat-free mass) (Jones and Norgan, 1974; Durnin and Womersley, 1974; Jebb and Elia, 1993). Although inexpensive and non-hazardous, this technique requires considerable patient co-operation and is generally not considered to be suitable for frail and elderly patients (Jebb and Elia, 1993). It was, therefore, not considered suitable for use in this work.

Body composition can also be assessed by isotope dilution (Moore, 1980; Shizgal, 1981; Hannan et al., 1995). This method involves the injection or ingestion of stable isotopes, such as deuterium oxide, 18-oxygen, or tritiated water. After a time to allow the isotope to disperse throughout body water, the concentration of the isotope is measured in blood, urine, breath or saliva and is used to calculate total body water (Moore, 1980; Jebb and Elia, 1993; Burman and Chamberlain, 1996). It is assumed that the isotope has the same distribution volume as water and that fat is anhydrous, although this may not be strictly true (Szeluga et al., 1984). Fat-free mass is calculated from total body water by assuming that fat free mass is, on average, 73% water (Heymsfield et al., 1994; Burman and Chamberlain, 1996). Fat mass is calculated, by subtracting fat free mass from body weight. Disadvantages of the technique include possible exposure to radiation, lack of easy availability of isotopes, often complex analytical procedures and, in some cases, serial blood sampling. It was therefore not felt to be suitable for the patients in this work.

Measurement of skinfold thickness is a technique widely used for the estimation of body fat (Jebb and Elia, 1993; Burman and Chamberlain, 1996). A series of regression equations have been developed which allow prediction of total body fat and fat-free

mass from a combination of four skinfold measurements (Womersley and Durnin, 1973). Skinfold thickness is measured by pinching a fold of skin and subcutaneous fat between the jaws of a pair of calipers, which exert a standard pressure over a standard area (Burkinshaw, Jones and Krupowicz, 1973; Jebb and Elia, 1993; Burman and Chamberlain, 1996). The method makes the assumption that subcutaneous fat is a reflection of total body fat and that the average thickness of fat is the same as at the selected skinfold sites (Jebb and Elia, 1993; Burman and Chamberlain, 1996). It is an inexpensive and convenient technique, which requires minimal patient co-operation. However, it has been reported to have considerable potential for error with a variation of 6-24% (Burkinshaw et al., 1973). Skinfold compressibility can vary according to age and with the presence of oedema, although the latter is likely to be minimal if only the upper arm is used. There can be substantial inter-observer variation in measurements, but with a single observer more reproducible results have been reported (Womersley and Durnin, 1973). It is recommended that for longitudinal studies the measurements should be made by the same observer and the average of three readings taken (Jebb and Elia, 1993; Burman and Chamberlain, 1996). Despite some of the limitations of this technique, it has been used to detect differences between weight-losing and non weight-losing patients with and without malignant disease (Watson and Sammon, 1980; Bozzetti et al., 1982; Hansell, Davies and Burns, 1986). Its ease and convenience make it ideal for use in frail cancer patients and it was adopted for use in this work.

Limb circumferences can also be used in conjunction with skinfold thicknesses to calculate limb fat and limb muscle area (Heymsfield et al., 1982, 1994). By themselves they may be useful in quantifying changes in an individual over time (Jebb and Elia, 1993). As they are very easy to measure, they were used in this work.

Bioelectrical impedance has been used to estimate total body water, intracellular and extracellular water. In this technique a small alternating current (usually 800 microamps) is passed between electrodes on the hand and foot and the voltage drop allows calculation of resistance (impedance). The current passes through the water and electrolyte component of fat-free tissue; fat is a poor conductor (Jebb and Elia, 1993; Hannan et al., 1994; Burman and Chamberlain, 1996). At low frequencies (around one kilohertz (kHz)) the current is unable to penetrate the cell membranes and thus passes mainly through extracellular fluid, whereas at higher frequencies (500-800 kHz) it passes through the intra- and extracellular water and, thus, total body water can be calculated (Lukaski et al., 1985; Hannan et al., 1995). By assuming the hydration fraction of lean tissue to be 73%, fat free mass can be calculated (Burman and Chamberlain, 1996).

Multi-frequency bioelectrical impedance analysers have been developed which provide a simple, portable and non-invasive means of estimating body composition (Hannan et al., 1994; Hannan et al., 1995). Minimal undressing is required, and little patient co-operation is needed. It is, therefore, a suitable technique for use in frail cancer patients. As with the other body composition measures, there is error involved with the use of this technique. Much of the data for the use of bioelectrical impedance comes from studies of healthy volunteers. Many ill patients retain fluid into the extracellular space and this expansion in total body water means that fat-free mass is over-estimated (Hannan et al., 1995). Simons and colleagues (1995) reported that total body water was significantly overestimated in cachectic cancer patients when compared with predicted values obtained through the use of isotope dilution. However, because of the simplicity

of the technique and the absence of observer bias, this technique was also chosen for this work.

As weight-losing cancer patients tend to lose significant amounts of muscle, it would be useful to estimate the degree of muscle lost. Muscle circumference and area estimates can be derived from skinfold thickness and limb circumference (Heymsfield et al., 1994). However, another indirect method of estimating muscle bulk is through 24 hour urinary creatinine excretion. Ninety eight per cent of urinary creatinine is derived from creatinine phosphate located in skeletal muscle. Therefore, muscle mass can be estimated by measuring 24 hour urine creatinine excretion (Heymsfield et al., 1983; Burman and Chamberlain, 1996). Heymsfield and colleagues (1982) reported a strong correlation between arm muscle area and creatinine excretion and Forbes and co-workers (1976) reported a strong correlation between fat-free mass and creatinine excretion.

There are several factors which affect the validity of measuring creatinine excretion. Creatinine is filtered and secreted in the kidney and the patient must therefore have normal renal function. There is a large intra-individual variability in creatinine excretion and excretion is affected by ingestion of red meat (Heymsfield et al., 1983; Burman and Chamberlain, 1996). A dietary history is therefore important. The 24 hours must be accurately timed or a large margin of error is introduced (Forbes and Bruining, 1976) and, therefore, not all patients will be able to comply with the practicalities of the measurements. Three consecutive collections are recommended but are impractical for out-patients. It is, however, a non-invasive test and is cheap to perform.

Dual photon absorptiometry (DPA) and dual energy X-Ray absorptiometry (DEXA) are now being used more frequently to evaluate body composition. Photons are generated either from a gadolinium source (DPA) or an X-Ray source (DEXA). These are scanned over the patient at 2 different energy levels and the differential absorption of photons is measured. These techniques can determine the percentage of fat in non-bone tissue and, thus, with the addition of appropriate computer software, the fat-free mass can be calculated (Burman and Chamberlain, 1996). Unfortunately, it is an expensive technique and involves a small exposure to radiation (Jebb and Elia, 1993). It was also not readily available for use by the patients in this work.

Computerised tomography, magnetic resonance imaging and ultrasound can directly visualise both fat tissue and non-fat tissue and allow quantification of fat and muscle (Heymsfield et al., 1982; Burman and Chamberlain, 1996). However, they require a significant amount of time and expense and would have been practically very difficult for this work.

In this work, body composition was estimated using the following techniques: height, weight, body mass index, skinfold thickness, limb circumference, bioelectrical impedance analysis and 24 hour urine creatinine excretion. Serum creatine kinase concentrations were also measured as another indirect guide to muscle mass (Giltay et al., 1999). These procedures were felt to be minimally invasive and most likely to be acceptable to a group of cancer patients. The techniques used are described in the following sections.

2.1.2 Blood Tests

As previously discussed in section 1.8, anaemia has been reported to be an aetiological factor for weakness, fatigue and asthenia (Lichter, 1990; Morant, 1996; Cella, 1997) and Morant (1993, 1996) reported significant correlations between linear analogue scale measurements of weakness and fatigue and haemoglobin levels.

As discussed in section 1.9, different biochemical abnormalities have been suggested as causes for weakness or fatigue, including hypercalcaemia, hypokalaemia, hyponatraemia, uraemia and hypomagnesaemia (Regnard and Mannix, 1992; Barnish, 1994). Low albumin concentrations have also been associated with weakness (Morant, 1996) and have been reported in weight-losing cancer patients (Scott et al., 1996). Low albumin may be related to the acute phase response (Fearon et al., 1998). C-reactive protein concentrations - a marker of the acute phase response - have been reported to be elevated in weight-losing cancer patients (Scott et al., 1996) and correlations have been found between C-reactive protein and fatigue levels (Morant, 1996). White cell count has also previously been reported as elevated in weight-losing cancer patients with an acute phase response (Scott et al., 1996). It has been reported that in cancer patients serum zinc concentrations are often decreased and serum copper concentrations increased (Catalano et al., 1993; Sattar et al., 1997). Sattar and colleagues found a significant positive correlation between concentrations of C-reactive protein and copper in patients with non-small cell lung cancer ($p < 0.001$), and a significant negative correlation with zinc ($p < 0.05$). They concluded that alterations in trace elements were associated with the presence of an acute phase response.

Vitamin D deficiency can be associated with proximal muscle weakness (Forbes and Jackson, 1993). Reduced vitamin D concentrations have also been reported in a large proportion of hospital inpatients (Thomas et al., 1998), although this has not previously been investigated in patients with advanced cancer.

2.2 Body Composition Measurements

2.2.1 Height, Weight and Body Mass Index

Height was measured with the patient standing upright in stockinged feet. In patients studied at Stobhill Hospital, a wall mounted stadiometer was used. In patients studied at Strathcarron Hospice, Hunter's Hill Marie Curie Centre and at home, where there was no stadiometer available, the patient was asked to stand against a door or wall, their height marked and measured using a centimetre tape measure. Height in all patients was measured to the nearest 0.5 cm.

Weight was measured on a set of Seca scales (Seca, Vogel & Halke GmbH & Co, Hamburg, Germany), with patients wearing indoor clothing and no shoes. Weighing took place on a flat non-carpeted surface. Weight was recorded to the nearest 0.25 kg. Previous weights were recalled by the patient or, where appropriate, taken from the casenotes.

Body mass index was calculated using the formula:

$$\text{Body mass index } (kgm^{-2}) = \frac{\text{Weight (kg)}}{\text{Height}(m)^2}$$

2.2.2 Skinfold Thicknesses and Limb Circumferences

Skinfold thickness was measured using Harpenden skinfold calipers (British Indicator Ltd., West Sussex, United Kingdom). A stretch resistant measuring tape was used to accurately measure limb circumference and to locate sites for skinfold thickness measurements. Traditionally, body fat has been estimated by using the four site method

which uses equations developed by Durnin and Womersley (1974). The four skinfolds normally measured are biceps, triceps, subscapular and suprailiac. O'Gorman (1997) recently reported a significant direct correlation between the sum of biceps and triceps skinfold thicknesses and fat mass calculated from the four site method ($p < 0.001$). To minimise patient inconvenience, subscapular and suprailiac measurements were not used in this work. To provide an estimate of lower limb fat thigh skinfold thickness measures were also carried out. All skinfold thickness measurements and circumferences were measured on the right side of the body except in patients with lymphoedema, where the left side was used.

The triceps skinfold thickness was measured over the triceps muscle at the midpoint between the acromion process of the scapula and the olecranon of the ulna with the arm relaxed and extended (Figure 2.1). The biceps skinfold thickness was measured at the same level as the triceps skinfold thickness over the biceps muscle, again with the arm relaxed and extended. For each of the skinfold thicknesses, the average of three measurements was taken and rounded to the nearest 0.5mm. The mid-upper arm circumference was measured at the midpoint between the acromion process and the olecranon, i.e., at the same point as the skinfold thickness measurements. The tape was maintained in a horizontal position, touching, but not compressing, the underlying skin. Thigh skinfold thickness was measured on the anterior aspect of the thigh at the midpoint between the anterior superior iliac spine and the middle of the patella. Thigh circumference was measured at this point in a similar way to the upper arm. All measurements were carried out by the same investigator.

2.2.3 Bioelectrical Impedance

Bioelectrical impedance measurements were carried out using a Xitron 4000B multi-frequency bioimpedance analyser (Xitron Technologies, Inc., San Diego, California, USA). Before each set of patient measurements the analyser was calibrated using a test resistor (422 ohms) provided by the manufacturer. The patient was asked to lie supine on a bed, or couch if in their own home, or occasionally if lying down was not practicable then the measurement was completed with the patient semi-supine in a recliner chair. The patient was asked to lie with legs slightly apart and with arms and hands not touching the body. The leads connecting the patient to the analyser did not touch each other nor did they touch any metal. The electrodes were consistently placed according to the same anatomical landmarks (Figure 2.2). The current source electrodes were placed on the right foot and right hand across the metatarsophalangeal joints and metacarpophalangeal joints respectively. The detection electrodes were sited on the right ankle between medial and lateral malleoli and on the right wrist between the distal ends of the ulna and radius. The left side was used if the patient had lymphoedema. The electrodes were disposable, self-adhesive, pre-gelled electrodes designed for use with multi-frequency bioimpedance analysers (Bodystat Limited, Douglas, Isle of Man).

Resistance and reactance was measured at 50 frequencies between 5 kHz and 1 MHz. Analysis was performed by a computer modelling program provided by the manufacturer, on a laptop computer connected to the analyser. The program obtains the best fit to the data and predicts resistance (impedance) at frequencies zero and infinity, which correspond to the resistance of extracellular fluid and total body water, respectively. The program combines this data along with the patient's height, weight and

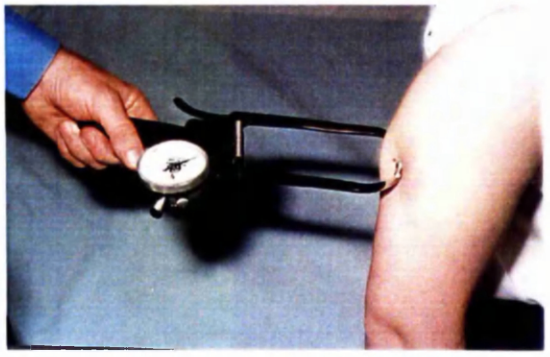
sex to calculate extracellular, intracellular and total body water volumes (Hannan et al., 1995).

2.2.4 Twenty Four Hour Urinary Creatinine Excretion

Urine was collected in a large plastic container, with a 2,500 ml capacity, and containing a small amount of thymol as a preservative. All urine passed in a period of 24 hours was collected in the container. If the container was filled, then the remainder of the collection was collected in a second container. The patients were asked to set a start time for the collection, e.g., 9 a.m. and asked to empty their bladder at that time but not collect that sample. Every time thereafter that the patient needed to go to the toilet, all urine passed was collected in the container. At the exact end of the 24 hour period, the patient was asked to empty their bladder and collect this urine in the container. To take into account the effect of diet on creatinine estimation, patients were asked to recall what they had eaten in the previous 48 hours prior to and during the urine collection. Urine creatinine was assayed from a 20 millilitre aliquot of the complete urine collection using a Roche Cobas Mira analyser (Hoffman-La Roche Ltd., Basel, Switzerland).

2.3 Blood Tests

In this work, haemoglobin was measured using the Syanmet method on a SYSMEX NE 8000 analyser (TOA Medical Electronics Co. Ltd, Kobe, Japan). White cell count was also measured by the SYSMEX NE 8000 analyser using direct current and radiofrequency methods. Urea and electrolytes, albumin, calcium, creatine kinase and C-reactive protein were assayed on an OLYMPUS AU5200 analyser (Olympus Optical Ltd., Tokyo, Japan) using standard methods. Serum magnesium was assayed by Atomic Absorption Spectrophotometry on a Perkin-Elmer 1100B analyser (Perkin-Elmer Ltd, Norwalk, CT., USA). In this work, zinc and copper were assayed by Atomic Absorption Spectrophotometry on a Perkin-Elmer 1100B analyser (Perkin-Elmer Ltd, Norwalk, CT., USA). Serum 25-hydroxy-cholecalciferol (the major circulating metabolite of vitamin D (Marshall, 1988)) was assayed by an Equilibrium Radio-Immunoassay procedure using Incstar ^{125}I-RIA Kit (Diasorin Ltd., Stillwater, Minnesota, USA) and a Packard Cobra 5005 γ-counter (Packard Instrument Co., Meriden, CT, USA).



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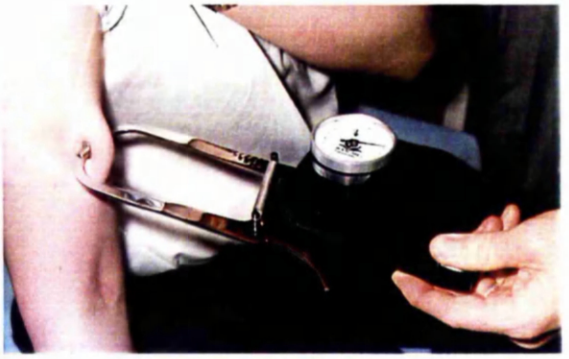

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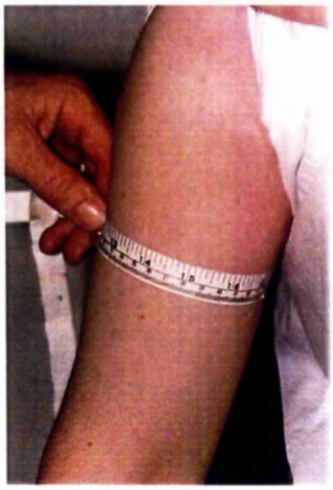

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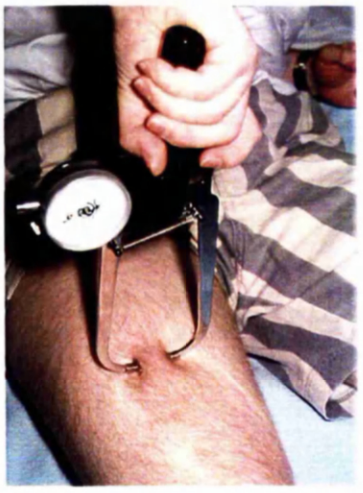

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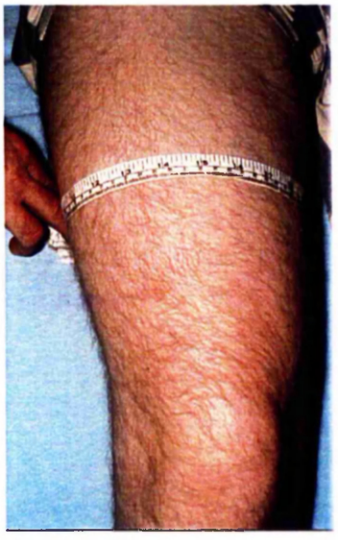
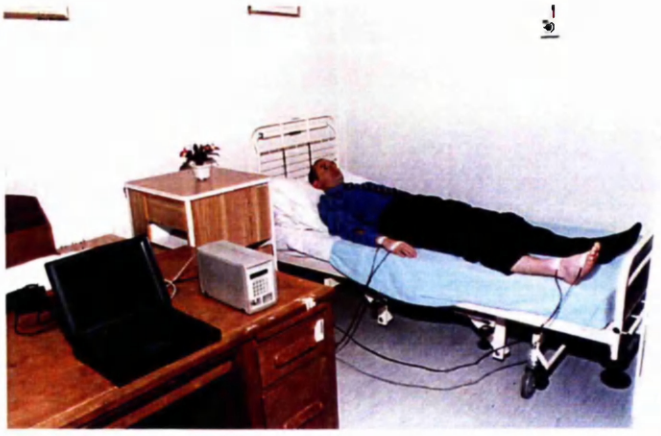


e

Figure 2.1 Anthropometric Measurements

a) Triceps Skinfold Thickness
b) Biceps Skinfold Thickness
c) Mid-Arm Circumference
d) Thigh Skinfold Thickness
e) Mid-Thigh Circumference



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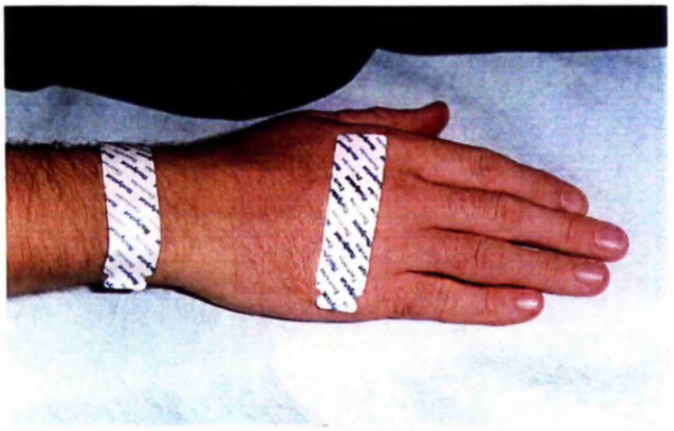

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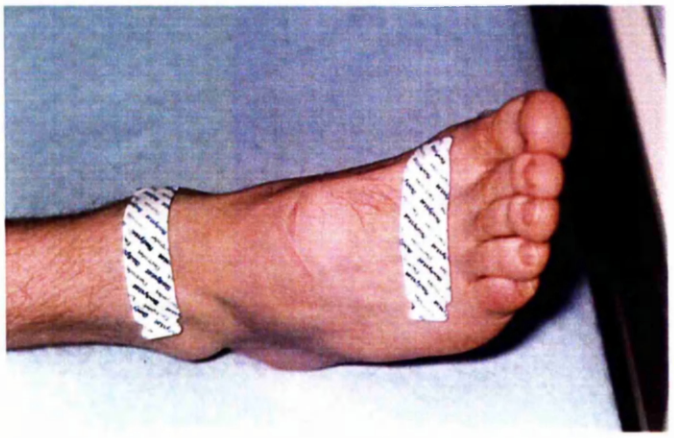


c

Figure 2.2 Bioelectrical Impedance Analysis Apparatus

a) Patient Connected to Xitron 4000B Multi-Frequency Analyser

b) Position of Electrodes on Right Hand

c) Position of Electrodes on Right Foot

CHAPTER 3 : METHODS : STRENGTH AND FUNCTION

3.1 Introduction

As previously discussed in section 1.6, there have been many studies of strength and function in the elderly. However, there has been little published work examining these issues in cancer patients.

Although the literature suggests that handgrip strength has been used in studies involving cancer patients (Burman and Chamberlain, 1996), there appear to be no prospective controlled studies using this technique in this patient group. However, this is a simple technique which has been used extensively in other patient groups (Kallman et al., 1990; Watters et al., 1993; Cress et al., 1995).

As the quadriceps muscle is so important to daily activity, a measure of quadriceps strength was included in this work. To allow direct comparison of an isometric upper limb strength measure (handgrip) and a lower limb strength measure, isometric quadriceps strength was measured in patients fit enough to participate in the test. To study a strength measure more naturally related to ordinary activity, isokinetic quadriceps strength was also measured. A kinetic communicator (Kin-Com) dynamometer was used in this work. The mechanical reliability and the reliability and reproducibility of strength data obtained using the Kin-Com has previously been established (Farrell and Richards, 1986; Tredinnick and Duncan, 1988; Harding et al., 1988). The Kin-Com has also been used to carry out isokinetic and isometric strength measures in cancer patients (Monga et al., 1997), although in other muscle groups other

than the quadriceps. The quadriceps muscle has been tested on the Kin-Com in other patient groups (Tredinnick and Duncan, 1988; Harding et al., 1988).

The technique of twitch interpolation was used to study the voluntary and involuntary components of quadriceps strength, i.e., whether a "maximal effort" by the patient was in fact a true maximal effort. This technique was used during isometric testing to allow comparison to previous work (Gibson et al., 1993; Nørregaard et al., 1994) and also during isokinetic testing.

Many cancer patients report difficulty in carrying out daily activities (Rhodes et al., 1988; Dunlop, 1989). There are no prospective studies which have examined the ability of cancer patients to carry out the activities of daily living. Rising from a chair, stair ascent and descent and walking ability have all been used frequently as short term measures of performance in geriatric research, due to their importance in maintaining an independent lifestyle (Aniansson et al., 1980; Fiatarone et al., 1990; Cress et al., 1995). Their usefulness in assessment of functional ability in other patient groups is not clear. However, clearly these activities are also important to cancer patients.

The chair stand test (ability to rise from a seated to standing position) appears to be a reliable and reproducible test, with a coefficient of variation of only 6.8% over ten trials previously reported in a group of healthy subjects of diverse ages (Csuka and McCarty, 1985). This test has also been used by other investigators, studying the elderly population (Bassey et al., 1992; Skelton et al., 1995; Cress et al., 1995) and has been used to distinguish between young, elderly and hemiparetic subjects (Yoshida, Iwakura and Inoue, 1983). Gillies and colleagues (1999) found, in their longitudinal study, that

many patients produced single chair rise times which left little room for improvement and introduced a triple rise test (standing up from a chair three times in a row).

Stair climbing tests have been also been used as assessments of physical functioning in the elderly (Bassey et al., 1992; Gillies et al., 1999) and also as means of strength training (Loy et al., 1994). Bassey and colleagues (1992) used four stairs, each of 15 centimetres in height with sturdy banister rails on each side and around the top platform. The test was repeated after a "short rest". She studied only stair ascent, whereas Gillies and co-workers (1999) studied ascent and descent with a two minute seated rest at the top and in between tests. However, their stairs were slightly higher at 17 centimetres each.

Walking tests have often been used by investigators as measures of physical function. In a study in the elderly, subjects were asked to walk at a self-selected speed over distances which varied between 6 and 40 metres (Cress et al., 1995). It was reported that self-selected walking gait speed was the greatest single predictor of self-perceived physical function. Aniansson and colleagues (1980) asked patients to walk at their comfortable walking speed over a distance of 30 metres in a corridor. Gillies and co-workers (1999) used a 15 second time period to assess how far patients could walk over a carpeted 6 metre course.

Six and 12 minute walking tests have become part of standard exercise assessment for patients with chronic heart failure and chronic lung disease (Guyatt et al., 1985; Lipkin et al., 1986; Meyer et al., 1997). They measure distance covered in that time and are used because they are simple and inexpensive tests which are familiar to the patient. In

this work, twelve minutes was felt to be too long a test for an advanced cancer patient grouping and, as well as a 6 minute test, a 2 minute test was used.

3.2 Strength Measures

3.2.1 Handgrip Strength

Dominant isometric handgrip strength was measured using a Takei Kiki Kogyo grip dynamometer (Takei and Company, Tokyo, Japan). Handgrip strength was measured to the nearest 0.5 kilogram watts (kgW). The handle was adjusted according to the size of the patient's hand. While standing, the patient held the dynamometer in the dominant hand, with the arm extended by their side (see Figure 3.1). In those unable to stand, the dynamometer was held out in front of them. The patient was asked to squeeze the handle as hard as possible. Three trials were allowed, with a 30 second rest between attempts. The highest of the three values obtained was recorded as the definitive value. Non-dominant handgrip strength was also recorded in later tests.

3.2.2 Quadriceps Strength and Twitch Interpolation Technique

Quadriceps peak force was measured in patients of good performance status (Karnofsky score $\geq$ 70) in the physiotherapy department at Stobhill Hospital on a Kin-Com isokinetic dynamometer (Chattanooga Group, Inc., Hixson, Tennessee, USA; see Figure 3.1). Both isokinetic and isometric quadriceps force were measured. Quadriceps torque was calculated by multiplying the measured force by the length of the lever arm from the centre of rotation to the attachment point at the ankle. Electrical stimulation of the quadriceps muscle, during both isokinetic and isometric testing, was carried out to try and distinguish between voluntary and involuntary muscle force.

Prior to testing, each patient warmed up for 2 minutes on an exercise bicycle with no external resistance, to allow patients to pedal at their own pace. They were then seated

on the movable seat of the Kin-Com apparatus, with their dominant (kicking) leg adjacent to the central section of the machine. Seat back position was adjusted to allow for different statures. The knee joint was aligned with the axis of rotation of the dynamometer lever arm. To try to restrict the contraction to the quadriceps muscle, restraining straps were fastened about the patient's waist and distal thigh. Patients were also asked to keep their arms folded during the testing to prevent the possible extra leverage obtained by pushing down with the arms on the seat. The tested leg was attached to the lever arm by means of a heavy duty strap, secured near the ankle, five centimetres above the medial and lateral malleoli.

Gravity compensation was included in each test, by weighing the leg while attached to the lever arm in a position as close to horizontal as the patient could comfortably allow. The stop angle - the angle measured from the horizontal position to which the patient could move the lever arm comfortably without assistance - was set to provide the limit for the upward movement of the lever arm during the test. The start angle was set at 90° from horizontal for each patient. The 90° was measured with a goniometer as the angle made by the leg in relation to the greater trochanter of the femur, with the lateral joint line of the knee as the central point. The central point was aligned with the point of attachment of the lever arm. The forward and backward speed was set at 60°/sec for each patient. In previous work (Horber et al., 1985), this was identified as the best single speed for assessment.

The purpose of the test was explained. The patient was instructed to push against the shin strap as quickly and smoothly as possible to move the lever arm to the stop angle (concentric contraction) and then to continue to push up against the strap to allow the

machine to push the leg back to the start angle (eccentric contraction). The patient was frequently reminded of the need to push "fast and smooth" to prevent the machine hydraulics from cutting out. Several warm-up contractions were allowed to help the patient become accustomed to the machine. The patient was encouraged to experiment with different amounts of force in preparation for the actual measurements.

The patient was allowed a brief rest period after the warm-up on the machine. During this time the purpose of the electrical stimulation apparatus was explained. The voltage limit was set on the stimulator (Digitimer Stimulator, Welwyn Garden City, Hertfordshire, UK) to 400 volts, although in practice this voltage is rarely reached. The stimulator was connected to the trigger box. The stimulator was connected to two round patch electrodes which were fixed to the patient's anterior thigh (see Figure 3.1), proximally and distally, to allow the stimulus to be given to the peripheral branches of the femoral nerve as they entered the muscle (Jones and Round, 1990b). The trigger box was connected to a small magnet, which was fixed to an adjustable metal retort stand positioned on the floor. Another magnet was fixed to the side of the lever arm adjacent to the centre of the machine. The two magnets were adjusted such that, during testing, the magnet on the lever arm passed close (about 0.5-1.0 cm) to the magnet on the retort stand - triggering the stimulus - at a fixed angle. This angle was originally set at 70° because of pilot work suggesting that the peak of the force curve would be reached at this angle. Test stimuli were given to the patient to assess the current required to produce a visible muscle twitch. The strength of the stimulus was limited by patient tolerance. For the test itself, the current was maintained at around 3 times this level as exercising muscles tolerate higher currents than resting muscles. The current used in the test varied between patients from 30.0 to 70.0 milliamps.

The patient was asked to produce 4 efforts of varying strengths, increasing progressively from gentle ("about a quarter strength") to half and three quarter strength then finally "as hard as you can". The patient was reminded not to equate gentle with slow and to continue to produce efforts that were fast. There was a 30 second break between efforts. The patient was asked to judge the strength of their effort without visual feedback from the monitor screen, based on their experience in the warm-up. This was done to ensure that the patient produced what they believed to be a maximal contraction. If, when asked to push "as hard as you can", the patient felt that they had not produced their best effort, they were allowed another attempt. Eccentric contractions were used to return the lever arm to the start angle, but were not included in the analyses as patients found it more difficult to produce consistent smooth eccentric contractions compared to the concentric contractions. Electrical stimuli were only used during the concentric contractions.

Following a brief rest, to allow the machine set-up to be changed, several graded isometric contractions were recorded (see section 1.6). The same gravity correction values as for the isokinetic testing were used. The test was set up for contractions at fixed lever arm angles of 90° and 60° from horizontal, as previously used in isometric testing (Aniansson et al., 1980). Several warm-up contractions of varying force were allowed, to familiarise the patient with the concept of isometric exercise. The patient was asked to produce three graded efforts (gentle, medium and "as hard as you can") at both 90° and 60°. They were asked to hold that contraction, without relaxing, for 5 seconds. No visual feedback was given as in the isokinetic contractions. An electrical stimulus, identical to that given in the isokinetic testing, was delivered by pressing by the stimulator button at a stable point in the contraction. A thirty second break was

allowed between contractions. The highest force produced at either 90° or 60° was taken to be that patient's peak force.

The data obtained during the Kin-Com tests was downloaded as ASCII (American Standard Code for Information Interchange) files onto pre-formatted floppy disks and analysed and graphed on a personal computer using Microsoft Excel version 7.0a (Microsoft Corporation, Redmond, Washington, USA).

3.3 Functional Tests

3.3.1 Chair Tests

Chair-stand time was measured using a chair of square design, with a firm seat and arm rests. The seat height was 43 centimetres, which is one centimetre higher than the height of the average British toilet (Gillies et al., 1999) and is therefore a functionally significant height. The patient was asked to rise from a seated position to a fully upright position as fast as possible, without using the arm rests. The time taken to complete this manoeuvre was measured on a hand-held digital stopwatch (Lorus Watches, Austin, Texas, USA) to the nearest 0.01 seconds. If the patient was incapable of rising without using the arm rests, then they were allowed to use them and this fact noted. Three trials were allowed, with a 30 second break between attempts. The fastest of the 3 attempts was recorded as the patient's definitive attempt. Sixty seconds after the third attempt, the patient was asked to complete the triple chair rise test. The patient was asked to stand up from the chair 3 times in a row, as fast as possible, and without a break in between each time, given the instruction "Up-down-up-down and finishing on the third up". The time for this test was recorded to the nearest 0.01 seconds on the digital stopwatch. The test was omitted in those who felt unable to complete it. The chair was portable and was used at Stobhill Hospital, Strathcarron Hospice, Hunter's Hill Marie Curie Centre and also in patients' homes.

3.3.2 Stair Tests

A flight of four stairs with banisters on either side was used for this test. The stairs were each 15 centimetres high. For patients seen at home the test was omitted. The test was also omitted in those who were unable to complete the test.

Patients were asked to stand at the foot of the stairs and to climb to the platform at the top of the stairs as quickly as possible, one step at a time. They were then immediately asked to turn around and descend the same stairs as quickly as possible, one at a time. The patient was allowed to use the banisters if they would normally use banisters at home. The time to complete the test was measured to the nearest 0.01 seconds using the same stopwatch as in the chair tests. The stair ascent and descent were performed three times with a thirty second rest between each ascent/descent. Previous studies have used "a short rest" (Bassey et al., 1992) between tests and thirty seconds was felt to be an appropriate rest period. The fastest ascent and fastest descent were recorded as the patient's definitive attempt.

3.3.3 Walking Test

The walking test was performed in a carpeted corridor in which a 20 metre length had been measured off. Suitable corridors were found in all three sites, although this test was not possible in those patients seen at home. The patient was asked to start walking at their ordinary walking pace towards the end of the 20 metres and when they reached this point to turn and come back to the beginning. Patients were asked to continue to do this for as long as they could comfortably do so. They were allowed to stop if they became tired, breathless or had any other significant discomfort. The test was continued for a maximum of 6 minutes when the test was stopped. The distance walked in 2 minutes and 6 minutes was documented, to the nearest metre.

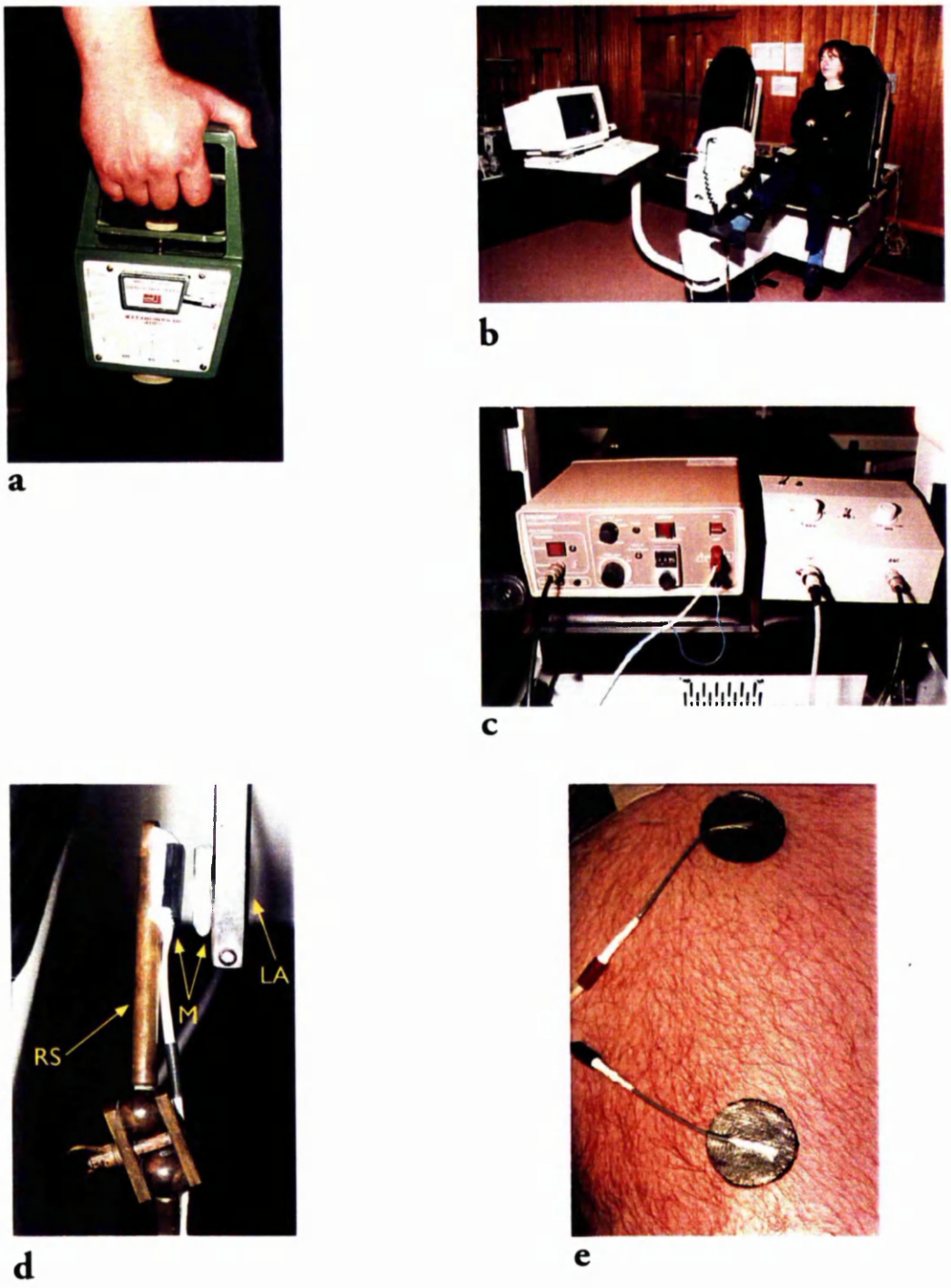


Figure 3.1 Equipment Used in Strength Testing and Electrical Stimulation Apparatus

a) Handgrip Dynamometer **b)** Kin-Com Isokinetic Dynamometer **c)** Digitimer Stimulator and Trigger Box **d)** Position of Magnets (M) on Lever Arm (LA) and Retort Stand (RS) as they pass each other **e)** Position of Patch Electrodes on Thigh for Electrical Stimulation

CHAPTER 4 : METHODS : QUALITY OF LIFE QUESTIONNAIRES

4.1 Introduction

Quality of life is a critical component of good patient care (Ahmedzai, 1990; Hjermstad et al., 1995). It is clear that any study of symptoms in patients with cancer would be incomplete without a consideration of how those symptoms affected quality of life. Many tools exist which assess different dimensions of quality of life. The following tools were chosen for the present work because they were valid and easy to complete.

4.1.1 Karnofsky Performance Status

In 1948, Karnofsky and colleagues developed a scale to quantify the functional ability of patients with advanced cancer. This is an 11 point numerical scale (0-100) which has become known as the Karnofsky Performance Status (KPS). This observational instrument was introduced as a measurement to assess the degree of patient independence and to establish the level of medical and nursing care required. This scale is among the most widely used scales for measuring functional ability in cancer patients (Yates, Chalmer and McKegney, 1980; Mor et al., 1984; Conill, Verger and Salamero, 1990).

The KPS has been criticised because, as with all observational scales, it is subjective and therefore the potential exists for inter and intra-observer variability (Clark and Fallowfield, 1986). However, Mor and colleagues (1984), in a national hospice study, described a highly significant rate of agreement between different observers and concluded that the KPS was a valuable tool for assessment of functional ability.

It has been suggested that a major disadvantage of the KPS is that, since it is normally scored by a physician, it does not reflect the patient's own experience (Padilla and Grant, 1985; Clark and Fallowfield, 1986). However, Conill and colleagues (1990) reported significant correlations between physician and patient scores, as well as between scores by different physicians. They suggested that these results demonstrated that physicians measure performance status adequately using the KPS.

Yates and colleagues (1980) compared the KPS to several independent measures of physical functioning and reported strong correlations. Another study reported a strong relationship between the KPS and the Katz activities of daily living index (Katz et al., 1963; Mor et al., 1984). These studies suggested that the KPS demonstrates construct validity, i.e., it measures what it claims to measure.

The KPS has also been shown to be a strong predictor of survival (Mor et al., 1984). Stanley (1980) reported the initial KPS score to be one of the three most important prognostic features affecting survival in inoperable lung cancer. A falling KPS score has also been reported to be a poor prognostic factor (Yates et al., 1980).

The KPS is simple to measure (Mor et al., 1984), is commonly used in cancer studies and seems a useful tool in measuring functional ability. However, it has its limitations in assessing quality of life as it is unidimensional and does not assess psychosocial factors.

4.1.2 Method For Assessing The Karnofsky Performance Status

The Karnofsky Performance Status Scale is an 11-point rating scale, which ranges from 100 (normal functioning) downwards in decrements of 10 to 0 (dead) (see appendix 1). It is completed by the observing clinician. To eliminate any possible problems of inter-observer reliability, all of the assessments in this work were performed by the same person (the author). When the performance status did not entirely fit one of the 11 points then a score half-way between two points, e.g., between 60 and 70 = 65, was made.

4.2 The EORTC QLQ-C30 Quality of Life Questionnaire

The European Organisation for Research and Treatment of Cancer (EORTC) was involved in the development of the EORTC QLQ-C30 quality of life questionnaire, which was originally designed to assess the quality of life of cancer patients participating in clinical trials (Aaronson et al., 1993). This is a 30 item self-report questionnaire which assesses different aspects of a patient's quality of life. It includes several subscales on patient function: physical function, role function, emotional function, cognitive function and social function. There is also a global health/quality of life scale. The questionnaire also includes several symptom measures with questions about fatigue, pain, nausea and vomiting, dyspnoea, sleep, appetite and bowel function as well as a question regarding financial problems. The EORTC QLQ-C30 core questionnaire was developed following the international field study on the initial 36 item questionnaire (Aaronson et al., 1993; Cella, 1995). The questionnaire has become widely accepted and is available in many different languages (Cella, 1995).

The original validity and reliability testing was performed in a multinational study of 346 cancer patients. The EORTC QLQ-C30 questionnaire was shown to be reliable in assessing many dimensions of quality of life. Although correlations between all the component subscales were statistically significant, the correlations were moderate, providing evidence that the scales were assessing distinct components of quality of life (Aaronson et al., 1993).

A test-retest reliability study was performed by Hjermstad and colleagues (1995). The scores obtained using the questionnaire were compared with scores obtained from

completion of the same questionnaire 4 days later. Correlations between scores on both days were found to be high.

The use of the EORTC QLQ-C30 is now widely established in cancer patients and provides information about diverse aspects of a patient's quality of life. It has also been used in the healthy population and has been reported to provide a valid measure of health-related quality of life in this group (Hjermstad et al., 1998). It is simple to complete, the average completion time being around 11 minutes (Aaronson et al., 1993). It is generally completed by the patient, but can also be completed by interview.

4.2.1 Completion of the EORTC QLQ-C30 Version 2.0

At the time of starting this work the EORTC QLQ-C30 version 2.0 was the current version of the questionnaire.

The QLQ-C30 version 2.0 (see appendix 1) is composed of both multi-item scales and single item measures. These include five functional scales (physical, role, cognitive, emotional and social functioning), three symptom scales (fatigue, pain and nausea/vomiting), a global health status/quality of life scale, and six single items (dyspnoea, sleep, appetite, constipation, diarrhoea and financial). All questions are worded in terms of a statement and ask the patient to assess how true that statement has been over the preceding 7 days.

Patients were asked to complete the questionnaire by themselves, or in an interview format if they were unable to self-complete the questionnaire. In the latter case the

investigator read aloud the questions and possible responses and recorded the patient's answers without in any way trying to influence the patient's answer.

The first five questions (the physical functioning scale) involve a simple choice between Yes and No. The subsequent 23 questions involve selection of the appropriate value on a numerical scale ranged between 1 and 4 (1 = not at all, 2 = a little, 3 = quite a bit, 4 = very much). The last 2 questions (the global health/quality of life scale) are numerical scales ranged between 1 and 7 (from 1 = very poor to 7 = excellent).

Questionnaire scoring is carried out according to the scoring algorithms produced by EORTC (see appendix 1). All of the scales and single item measures range in score from 0-100. A high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/quality of life scale represents a high quality of life, whereas a high score for a symptom scale/item represents a high level of symptomatology/problems.

If items are missing from multi-item scales then, provided at least 50% of the items within the scales are completed, it is assumed that the missing values have values equal to the average of those items which are present for that respondent (EORTC QLQ-C30 Scoring Manual).

The EORTC questionnaire is under copyright and permission, in writing, for use in this work was obtained via Christiane van Pottelsburghe of the EORTC Quality of Life Group, avenue E. Mounier 83 Bte 11, 1200 Brussels, Belgium.

4.3 The Functional Assessment of Cancer Therapy Fatigue Subscale

The Functional Assessment of Cancer Therapy (FACT) series of questionnaires was also developed with the view that quality of life was a subjective (patient-rated) and multi-dimensional concept (Cella et al., 1993). The FACT collaborators developed a 28-item core (general) questionnaire (FACT-G) and several cancer site, symptom and treatment specific modules which could be added to the general questionnaire as appropriate. The FACT-G scale consists of physical, functional, social, emotional and "relationship with the doctor" subscales as well as a total score. The authors reported the questionnaire to be valid compared with other established measures of quality of life and that the FACT-G was reliable on re-testing after 3-7 days. Correlation co-efficients for validity and reliability were all found to be high.

The same researchers subsequently developed a symptom module to try and accurately assess quality of life in cancer patients suffering from fatigue and other anaemia-related symptoms (Yellen et al., 1997). The FACT-F consists of the FACT-G and a 13 item fatigue subscale (FACT-Ftg). The FACT-F was reported to accurately predict patient-rated performance status and to stratify patients according to low or high haemoglobin level. It was also reported that the 13 item fatigue subscale also showed excellent internal consistency (i.e., all the questions measured part of the same phenomenon), test-retest reliability and predicted haemoglobin level and performance status. There were positive correlations with other measures of fatigue. The authors suggested that the fatigue subscale should prove useful as an independent, brief assessment of fatigue. It is short, takes only a few minutes to complete and like all FACT scales can also be completed by interview (Cella et al., 1993).

4.3.1 Completion of the FACT-Ftg Scale Version 3

The Functional Assessment of Cancer Therapy Fatigue Subscale (FACT-Ftg) version 3 was used in the present work (see appendix 1). All thirteen questions are rated on a numerical scale of 0-4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit and 4 = very much) with a total range of possible scores of 0-52. Questions 1-6 and 9-13 are scored by subtracting each item response from 4. Questions 7 and 8 are scored by adding the item response to 0.

High total scores indicate a low level of fatigue and low scores a high level of fatigue. Where some questions are left unanswered - provided that more than 50% of the questions have been completed - the total score can be extrapolated by multiplying the sum of the subscale by the number of items in the subscale (i.e., 13) and then dividing by the number of items actually completed, i.e.:

Final score = [sum of item scores] x 13 ÷ [number of items answered]

Permission for the use of the scale was obtained, in writing, from Kimberley Webster, M.A., Director of Communications, Center on Outcomes, Research and Education (CORE), Evanston Northwestern Healthcare, 1000 Central Street, Suite 101, Evanston, Illinois, 60201, USA.

4.4 Linear Analogue Self-Assessment Scales

Visual analogue scales, or linear analogue self-assessment (LASA) scales, use a 100 millimetre line with descriptors at each end and the length of which is taken to represent the continuum of a physical or emotional experience such as pain, anxiety or weakness (Clark and Fallowfield, 1986). Respondents are asked to mark the line at a point which they feel best represents how they are currently feeling. The score is measured in centimetres or millimetres from the 0 point on the far left (Cella, 1995).

LASA scales were originally used in cancer patients by Priestman and Baum (1976) to study quality of life in patients with advanced breast cancer receiving chemotherapy. They used ten scales, including questions on symptoms, mood and activity levels. They reported relationships between LASA scores and treatment response and treatment toxicity.

Coates and colleagues (1983) reported an association between performance status and LASA scores for general well-being, dyspnoea and physical activity in ovarian carcinoma patients receiving anti-cancer therapy. More recently, Gleeson and Spencer (1995) found an improvement in LASA scores of weakness, dyspnoea and general well-being following transfusion in anaemic cancer patients.

LASA scales are simple and readily reproducible (Clark and Fallowfield, 1986). They can provide a wide range of scores and are thought to be very sensitive and responsive to change over time (Girling, Hopwood and Ahmedzai, 1994; Cella, 1995). However, there has been some criticism of their use, in that it can be difficult to know what is the

minimal clinically significant - as opposed to statistically significant - difference in scoring (Cella, 1995). Some patients find it difficult to grasp the concept of LASA scales, though they have been used successfully in 5 year olds (Clark and Fallowfield, 1986).

4.4.1 Using Linear Analogue Self-Assessment Scales

Linear analogue self-assessment scales were used in this work because of their simplicity and because previous research has employed them to assess weakness and fatigue (Robustelli Della Cuna et al., 1989; Morant et al., 1993, Gleeson and Spencer, 1995).

Two scales were used in this work, designed by the author. One measured the patient's own perception of their level of weakness and has at its two extremes: "I don't feel weak at all" and "I couldn't feel any weaker" (see Figure 4.1). The other measured the patient's perception of their level of strength and its two extremes were "I feel I have no strength" and "I feel my strength is normal" (see Figure 4.2). Patients were instructed to "Please mark with a vertical line which point on this line best represents how weak/strong you feel at this moment". Patients were asked to imagine that the line was a scale of zero to ten, with zero at the left hand end and ten at the right hand end.

Each scale was scored by measuring the line with a ruler from the left hand end and measured to the nearest 1.0 mm.

4.5 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression (HAD) scale is a self-report questionnaire originally designed for use with medical patients (Zigmond and Snaith, 1983). It is a 14 item scale made up of two 7 item subscales measuring anxiety and depression. Zigmond and Snaith (1983) conducted their initial studies on 100 patients with a wide variety of illnesses in a medical outpatient clinic. The patients were asked to complete the HAD scale while waiting to be seen by a clinician and were subsequently interviewed by a researcher, who independently assessed their levels of anxiety and depression. The authors found that the scale had satisfactory internal consistency and validity, determined by a comparison with a rating from the psychiatric assessment. The authors reported the HAD scale to be reliable in detecting states of anxiety and depression and found a very low incidence of false results. They also suggested that the scores for the subscales could detect the severity of the emotional disorder (Zigmond and Snaith, 1983).

The HAD scale has been used in studies of cancer patients. Hopwood, Howell and Maguire (1991) studied a group of 81 patients with advanced breast cancer. They compared the HAD results with independent interviews by a psychiatrist. They concluded that the HAD scale performed well in detecting psychological problems, although more so with anxiety than with depression.

Ibbotson and colleagues (1994) compared the HAD scale with a psychiatric interview in 284 cancer patients. They reported that the HAD scale performed well in detecting

anxiety and depression in patients with stable disease and on anti-cancer treatment, compared to other questionnaires, though performed less well in progressive disease.

There has been some debate as to whether the HAD scale should be used as a single 14 item scale to detect psychological distress or as two distinct scales assessing both anxiety and depression. The study by Moorey and colleagues suggested that although anxiety and depression often co-exist, it is possible to distinguish between the two, at least early on in the illness (Moorey et al., 1991).

Although the usefulness of the HAD scale in patients with advanced cancer has been questioned (Moorey et al., 1991; Ibbotson et al., 1994), there are no other scales which have been successfully used on a regular basis in this patient group. The main advantage of the HAD scale is that it is quick to administer, taking on average 2 minutes to complete, is easily understood and easily scored (Clark and Fallowfield, 1986).

4.5.1 Completing The Hospital Anxiety and Depression Scale

Each of the 14 items of the HAD scale has four possible answers and patients are asked to tick the answer which comes closest to how they have been feeling in the previous week (see appendix 1). If the patient was unable to complete the questionnaire themselves, then the questions were read out to them by the investigator. Each question is scored from 0-3, therefore each scale is scored 0-21 (see appendix 1). Any score for either scale of 0-7 is regarded as "normal", 8-10 is a borderline case and 11-21 a probable clinical case of anxiety or depression.

4.6 Administering The Questionnaires

The questionnaires described above were administered at the beginning of this work, to avoid any influence of the other tests on the patient's responses to the questions. The weakness linear analogue scale was administered first and the strength linear analogue scale last to avoid patients scoring the latter with reference to the former. As there was some overlap between the fatigue scale of the EORTC QLQ-C30 questionnaire and the FACT-Ftg scale, the EORTC questionnaire was administered next after the weakness scale and taken from the patient before they were given the FACT-Ftg questionnaire. The HAD scale was then administered. No prompting was given to the patients other than an explanation of what they were expected to do.

Please mark with a vertical line which point on this line best represents how weak you feel at this moment:

I don't feel weak at all ——————————————————— I couldn't feel any weaker

Figure 4.1 Linear Analogue Self-Assessment Scale (Weakness)

Please mark with a vertical line which point on this line best represents how strong you feel at this moment:

I feel I have no strength ——————————————— I feel my strength is normal

Fig 4.2 Linear Analogue Self-Assessment Scale (Strength)

CHAPTER 5: CHARACTERISTICS OF A HOSPICE POPULATION

5.1 Introduction

Patients with advanced cancer have a variety of medical and non-medical problems. They are a group with poor prognosis, who have varied symptoms and are treated with an array of drugs and potentially disease-altering therapies. Weakness and fatigue are common symptoms in advanced cancer (Donnelly and Walsh, 1995) and many patients have difficulty in carrying out the activities of daily living (Rhodes et al., 1988). Many have lost weight (Watson and Sammon, 1980). To establish a baseline prior to studying some of these issues prospectively, a retrospective audit of patients in a typical palliative care unit was carried out.

Strathcarron Hospice is an independent hospice serving a large area in central Scotland, including Stirlingshire, Clackmannanshire and North Lanarkshire. It has eighteen in-patient beds and has a busy day unit (20 spaces/day; 3333 patient attendances in 1995/1996). The majority of patients are cared for at home by general practitioners with the input of hospice medical staff and Specialist Palliative Care Home Care nurses. The majority of its patients have advanced cancer, with a small number having advanced neurological conditions, such as motor neurone disease and multiple sclerosis.

5.2 Material and Methods

All cancer patients under the care of the hospice - in-patients, day-patients and home care patients - who died in a six month period (1st June 1996-30th November 1996) were included in this retrospective audit. All the details were recorded from the casesheets.

Factors recorded were age, sex, diagnosis, site of metastases, length of involvement with the palliative care services (including inpatient care, day care, home care), place of death, drugs prescribed and evidence of anorexia, weight loss, weakness, fatigue or tiredness during the illness.

Statistical analysis was carried out where appropriate using the Mann Whitney U Test and Fishers Exact Test (SPSS Inc., Chicago, Illinois, USA).

5.3 Results

Two hundred and twenty nine patients with cancer died during the 6 month period (Table 5.1). There were similar numbers of men and women. There was a wide age range (35-94 years) in the patients involved with the palliative care services, although the majority of patients were over the age of 65. There was no significant difference in age between the males and females.

The largest group of diagnoses was of gastrointestinal cancers comprising colorectal, oesophageal, pancreatic, gastric, caecal, cholangiocarcinoma, small bowel and anal cancers, in order of frequency. The most common single organ affected was lung, the 49 patients including non-small cell and small cell cancers, although for half of the lung cancer patients no histological diagnosis was documented in the casenotes and therefore the diagnosis was accepted on clinical grounds. The urinary tract cancers included both renal and bladder cancers and the gynaecological group contained ovarian, cervical and vulval cancers. The haematological malignancies included lymphoma, acute leukaemia and myeloma. The sites of the head and neck cancers included larynx, palate, tonsil and pharynx. The number of male and female patients for each cancer grouping was similar. The median age within the different cancer types was similar with the largest three groups - gastrointestinal, lung and breast - having median ages of 69, 70 and 71 respectively. The youngest group was the haematological group (65) and the oldest the prostate group (73) ($p < 0.05$), although both of these groups were small.

Many of the patients had progressive metastatic disease. Bone (n=50), liver (n=42), brain (n=21) and lung (n=18) were the commonest sites of metastatic spread. Fifty four

per cent of all the patients had the presence of weight loss documented in the notes (Table 5.2), although there were no actual weights documented in any of the patients. Eighteen per cent of patients had documented anorexia without weight loss and 35% of patients had both symptoms of anorexia and weight loss. Sixteen per cent of patients had no evidence of weight loss during their illness. The documentation within some of the notes was incomplete and, therefore, the presence of weight loss in some patients could not be confirmed or excluded.

Fifty one patients had documented generalised or muscle weakness (22% of total) and 24 had documented tiredness, exhaustion, lethargy or fatigue (10%) (see appendix 2). Twenty patients were noted to be frail (9%) and 82 (36%) had documented difficulties with their mobility, such as difficulty in toiletting and rising from a chair.

Patients were involved with the palliative care service for varying lengths of time from a single day to nearly 3 years, although the median length of involvement was just over 5 weeks. The majority of patients died in the hospice or in hospital (71%), although 25% died in their own home (Table 5.3).

This patient group were taking a large number of medications. The prevalence of usage, in this patient group, of drugs commonly used in palliative care is shown in Table 5.4. The commonest group of drugs used was the strong opioids (64% of patients), morphine sulphate being the commonest drug prescribed. Other commonly prescribed drugs were corticosteroids (54%), diuretics (31%), non-steroidal anti-inflammatory drugs (NSAIDs) (29%), benzodiazepines (22%) and antidepressants (21%).

5.4 Discussion

The present retrospective study describes a cross-section of cancer patients involved with a palliative care service and is representative of all the main cancer types registered in Scotland (Scottish Cancer Co-ordinating and Advisory Committee, 1996). The three main cancer types were gastrointestinal, lung and breast in order of frequency. Donnelly and Walsh (1995) found a similar picture in their large survey of patients involved with palliative care services in Cleveland, USA, although in that study lung cancer was commoner than gastrointestinal cancer. The median age in the Strathcarron study was similar to that in the study by Edmonds and colleagues (1998), which also described a heterogeneous group of cancer patients. Donnelly and Walsh (1995) had a younger median age of 65 years, but their patient group included patients with childhood malignancies (youngest patient aged 12).

It is clear that lung and gastrointestinal malignancies are the commonest malignancies cared for at Strathcarron Hospice. Lung cancers comprised the largest single group of cancers registered in Scotland between 1990 and 1994 (Scottish Cancer Co-ordinating and Advisory Committee, 1996), although if all the different gastrointestinal cancers registered are taken together they exceed the lung cancers in number. When cancer registrations are broken down into regional statistics, the two main areas covered by Strathcarron Hospice - Forth Valley and Lanarkshire - show very similar distributions, except that in Lanarkshire lung cancer is commoner than all gastrointestinal cancer. Breast cancer was the fourth highest group in cancer registrations and the third highest at Strathcarron. The third highest group in the registration statistics - skin neoplasms,

excluding melanoma - are cancers which are mainly curable and, therefore, are not usually cared for in hospice units.

The literature suggests that 50-70% of cancer patients wish to die at home (Carroll, 1998; Karlsen and Addington-Hall, 1998). However, from this study, only a quarter died at home and the majority in hospital or hospice. Karlsen and Addington-Hall (1998) reported that in an inner London area only 21% of patients died at home and in a review of all cancer registrations in England between 1985 and 1994, Higginson, Astin and Dolan (1998) established that 27% of patients died at home, with only minor regional variation. A similar picture has also been reported in Belgium (Schrijvers et al., 1998). Palliative care services should take into account the wishes of patients about place of death and Carroll (1998) reported, in Kincardineshire, that when this is done the percentage of patients who die in their place of preference is increased significantly. However, it is not always practicable to ensure this as patients may require admission to an in-patient unit for symptom management or intensive nursing care that would be impossible at home (Carroll, 1998).

Weight loss and anorexia are clearly important issues for cancer patients and previous work has shown that weight loss adversely affects quality of life and survival (DeWys et al., 1980; Ovesen, Hannibal and Mortensen, 1993; O'Gorman et al., 1999). Half of the patients in the present audit had definite weight loss and 18% had anorexia without documentation of whether weight had been lost. It is thought that around two-thirds of cancer patients develop cachexia (Kern and Norton, 1988). Weight loss is generally commonest in lung and gastrointestinal cancers (Calman, 1982). In this audit weight loss was documented in 54% of patients, although in 12% of patients there was

insufficient information to determine whether or not the patients had lost weight. In the present audit 65% of the lung cancer patients and 61% of the gastrointestinal cancer patients had definite weight loss and were the commonest cancer sites for weight loss, except for the haematological group (66%). However, this latter group was small (n=9).

Weakness, fatigue and tiredness also feature as symptoms documented in this cancer group, although are not documented as frequently as weight loss. The percentage of patients documented with these symptoms is smaller than in prospective studies (Donnelly and Walsh, 1995). However, this study was retrospective and, therefore, is dependent on full documentation. Some subjective symptoms are not always documented and an accurate assessment of the prevalence of weakness and fatigue would require a prospective study. It is possible that weakness and fatigue are documented less often than other symptoms such as pain or dyspnoea, because it is often assumed that there is little or nothing that can be done to improve these symptoms or that they are an inevitable part of the illness (Gordon, 1986; Vogelzang et al., 1997). Many of these patients also had a documented reduction in mobility and function. The role of weight loss in the production of weakness, fatigue and reduced function is not clear and, although the literature suggests that there is a connection between cachexia and weakness (Lichter, 1990), this relationship has not been formally studied.

Polypharmacy is often an issue in palliative care patients, and this sample population is no exception. The majority of patients were taking strong or weak opioids, mainly for analgesia, although opioids are sometimes used for palliation of breathlessness (Ahmedzai, 1998). Corticosteroids feature prominently and are frequently used for the palliation of anorexia, weakness and fatigue (Robustelli Della Cuna et al., 1989;

MacDonald et al., 1994). They do have the side effect of muscle weakness and the presence of proximal myopathy can seriously limit patients' mobility and function (Batchelor et al., 1997). Non-steroidal anti-inflammatory drugs (NSAIDs) are also frequently used as analgesics in cancer patients. NSAIDs are thought to reduce pain partly through effects on inflammation. They are thus thought to be useful in musculo-skeletal and bone pain and may have an opioid sparing effect (Pace, 1995; Rawlins, 1998; Jenkins and Bruera, 1999). As discussed in section 1.3.3, NSAIDs have also been reported to have an effect in moderating the acute phase response which is present in many cancer patients with cachexia (Preston et al., 1995; McMillan et al., 1995). As patients with cachexia are often reported to be weak and fatigued, it is possible that these latter symptoms may be improved by effects on the acute phase response and there may be a role for NSAIDs here. Other drugs which may contribute to the aetiology of weakness include benzodiazepines, diuretics and antidepressants (Lichter, 1990), which also feature prominently in this group of patients. The prevalence of antidepressants - although some are used in treatment of neuropathic pain - and antipsychotics indicate that there are often psychiatric or mood disturbances present in this patient group.

In summary, in the present audit, this hospice sample population was representative of other palliative care populations previously studied and also of all the common cancer types. Weight loss was a common symptom in this patient group, particularly in patients with lung and gastrointestinal malignancies. Weakness, tiredness and fatigue were also common symptoms in this group, although probably incompletely documented. Polypharmacy was common in this patient group, with opioids, corticosteroids, diuretics and non-steroidal anti-inflammatories the commonest drugs prescribed.

Table 5.1 Characteristics of Strathcarron Hospice Patients Who Died Between June 1st and November 30th 1996

	Male (n=117)	Female (n=112)	p-value
Age at hospice involvement (years)*	69 (36-91)	69 (35-94)	NS
Age at death (years)*	69 (36-91)	69 (35-94)	NS
Length of hospice involvement (days)*	41.5 (1-1017)	32 (1-693)	NS
Cancer Diagnosis			
Gastrointestinal	27	30	NS
Lung	30	19	NS
Unknown Primary	15	11	NS
Breast	-	25	-
Prostate	13	-	-
Urinary Tract	6	4	NS
Haematological	5	4	NS
Head & Neck	7	2	NS
Female GU	-	7	-
Primary Cerebral	3	3	NS
Melanoma	1	2	NS
Others	10	5	NS

NS = Not Significant

* Data presented as median and range

Table 5.2 Presence of Weight Loss or Anorexia in Strathcarron Hospice Patients

	Number	Percentage of Total (%)
Weight loss	124	54
No weight loss	37	16
Not known	27	12
Anorexia alone documented	41	18
Total	229	100

Table 5.3 Place of Death of Strathcarron Hospice Patients

	Number of deaths	Percentage of Total (%)
Hospice	94	41
Hospital	68	30
Patient's Home	58	25
Nursing Home	4	2
Relative's Home	1	<1
Not Known	4	2
Total	229	100

Table 5.4 Drugs Prescribed in Strathcarron Hospice Patients

	Number of patients	Percentage of Total (%)
Strong Opioids	146	64
Corticosteroids	123	54
Diuretics	70	31
Non-steroidal anti-inflammatory drugs	67	29
Benzodiazepines	50	22
Antidepressants	49	21
Weak opioids	33	14
Antipsychotics	25	11
Anticonvulsants	17	7
Disease modifying drugs	13	6
Megestrol acetate	12	5

CHAPTER 6: A STUDY OF THE IMPORTANCE OF WEIGHT LOSS, ALTERED BODY COMPOSITION, INFLAMMATION AND BLOOD PARAMETERS ON THE EXPERIENCE OF WEAKNESS AND FATIGUE IN PATIENTS WITH ADVANCED CANCER

6.1 Introduction

Weakness and fatigue are the commonest symptoms in patients with advanced cancer (Lichter, 1990; Glaus et al., 1996; Vogelzang et al., 1997; Pater et al., 1997). They are, however, poorly understood and are often regarded as an inevitable consequence of advancing disease (Lichter, 1990).

The relationship between weakness and fatigue is unclear and the two terms are often used interchangeably. They may be two components of a larger symptom complex, often called asthenia (Bruera and MacDonald, 1988; Morant, 1996). Morant (1993) suggested that it might be possible to distinguish between weakness and fatigue by hypothesising that weakness constituted difficulty in initiating activity and that fatigue related to difficulty in continuing activity once started. In a later study, Morant (1996) reported a significant correlation between linear analogue scale measures of weakness and of fatigue, suggesting that the two symptoms often co-exist. Glaus and colleagues (1996) suggested that weakness was a pathological symptom, while fatigue was found to some degree in the healthy population.

Many cancer patients lose weight and weight loss is known to be a poor prognostic factor (DeWys et al., 1980; Kern and Norton, 1988). Cancer cachexia has often been

suggested as an aetiological factor for weakness and fatigue (Theologides, 1979; MacDonald et al., 1995; Billingsley and Alexander, 1996). The weight loss consists of loss of both fat and fat free mass, of which muscle is a large component (McMillan et al., 1994a). Measurement of total body water gives an estimate of fat free mass (Heymsfield et al., 1994; Burman and Chamberlain, 1996). Twenty four hour urinary creatinine excretion is often used as a measure of muscle bulk (Heymsfield et al., 1983; Burman and Chamberlain, 1996) and has previously been found to correlate with fat free mass (Forbes and Bruining, 1976). Serum creatine kinase concentrations also give some indication of muscle mass (Giltay et al., 1999).

Raised C-reactive protein concentrations have previously been reported in weight-losing, compared with weight-stable cancer patients (Scott et al., 1996), suggesting that inflammation has a role in the aetiology of cancer cachexia. C-reactive protein concentrations may also relate to the severity of weakness and fatigue (Morant, 1996). Low albumin has been associated with raised C-reactive protein concentrations (O'Gorman et al., 1999) and may also relate to the level of weakness and fatigue (Morant, 1996). Low serum zinc and raised serum copper levels have also been reported to be associated with C-reactive protein concentrations in cancer patients (Sattar et al., 1997), although it is not known if these are related to the experience of weakness and fatigue.

Anaemia has been reported to be an aetiological factor for weakness and fatigue, although contrasting views exist as to whether or not the level of haemoglobin relates to the level of weakness or fatigue (Bruera et al., 1989; Gleeson and Spencer, 1995; Morant, 1996; Yellen et al., 1997). Low blood sodium, potassium and magnesium

concentrations, raised blood calcium concentrations and renal failure have all been reported as causes of weakness and fatigue (Regnard and Mannix, 1992; Barnish, 1994; Morant, 1996). It has been reported that Vitamin D concentrations are often low in medically ill patients (Thomas et al., 1998), but this has not previously been studied in patients with advanced cancer. Vitamin D deficiency may lead to proximal muscle weakness (Forbes and Jackson, 1993).

The aim of the present study was to investigate the importance of weight loss, altered body composition, the inflammatory response, haematological and biochemical parameters in the experience of weakness and fatigue in patients with advanced cancer.

6.2 Material and Methods

6.2.1 Patients

A cross-section of patients with advanced cancer was recruited from several palliative care centres - Strathcarron Hospice (Denny), Stobhill Hospital NHS Trust (Glasgow) and Hunter's Hill Marie Curie Centre (Glasgow). Patients were identified as suitable for the study by medical or nursing staff in the wards at each centre, the Respiratory/Oncology outpatient clinic, the hospice day centres or by hospice home care sisters. The investigator visited each of the centres on a regular basis and approached those patients identified as eligible for inclusion in the study, either at the centre or at the patient's own home.

Patients were included in the study if they had a firm clinical or histological diagnosis of cancer which was no longer amenable to curative treatment, if they were aged 18 years or more and if they were able to give full informed consent to the study. Patients were excluded from the study if they were under 18 years of age, if they had received surgery, chemotherapy or radiotherapy within the previous month, had an active connective tissue disease, a pre-existing neuromuscular disorder causing generalised muscle weakness, had uncontrolled pain, symptomatic angina, severe dyspnoea (breathless at rest), or were otherwise too ill to participate in the study.

Details of the patient's illness, including evidence of metastatic disease, were obtained from their casenotes and from a careful history. Details of the patient's drug history were recorded and they were questioned about their healthy weight and degree of weight loss. Previous weights documented in the casenotes were noted. Patients were

divided into weight-stable and weight-losing groups. Weight loss was defined as loss of ≥ 5% of body weight in the previous 3 months. If patients had lost weight earlier in their illness, but had remained weight-stable in the preceding 3 months, they were regarded as weight-stable for the purposes of the study. Patients were also asked about their pre-illness, and current, activity levels. Activity levels were rated on a simple 4 point scale devised by the investigator (0 = Inactive; mainly bed or chair bound; 1 = Sedentary lifestyle, some walking; 2 = Moderately active, walks a lot, light sporting activity; 3 = Very active, training or sports).

A group of healthy volunteers (n=15) was recruited from Strathcarron Hospice volunteers and also through personal contacts at the University of Glasgow.

The study was approved by the local ethics committees in Forth Valley (covering Strathcarron Hospice), Stobhill Hospital (which covers Hunter's Hill Marie Curie Centre) and in Lanarkshire (as some Strathcarron Hospice patients were from Lanarkshire). All patients and healthy subjects were aware of the purpose of the study and gave written, informed consent.

6.2.2 Questionnaires

Patient-rated levels of weakness and strength were obtained using two linear analogue scales (figures 4.1, 4.2) as described in section 4.4. The FACT-Ftg Version 3 scale (see appendix 1) was used as a validated measure of fatigue as described in section 4.3. The EORTC QLQ-C30 questionnaire version 2.0 (see appendix 1) was used as a general quality of life questionnaire as previously described in section 4.2; this questionnaire also includes a 3-item fatigue subscale ("Did you need to rest?", "Have you felt weak?",

"Were you tired?"). The Karnofsky Performance Status was used as an observer-rated measure of functional ability as described in section 4.1.

Prevalence estimates for weakness and fatigue were calculated, by using a cut-off point of the 95% centile of the healthy scores. This means that 95% of the healthy scores were regarded as normal and any results poorer than these in the cancer patients were regarded as pathological. Thus, a prevalence for pathological weakness and fatigue was calculated. This technique has recently been used in a study by Stone and co-workers (1999).

6.2.3 Body Composition

Height and weight were measured and body mass index calculated as described in section 2.2.1. Current body mass index was then divided by 23 and multiplied by 100 to express it as a percentage of healthy body mass index. Triceps, biceps and thigh skinfold thicknesses and mid-arm and mid-thigh circumference were measured as described in section 2.2.2.

Arm muscle area (in cm^2) was calculated using the equation:

$$\frac{[\text{Mid-arm circumference} - \pi \times \text{Triceps skinfold thickness}]^2}{4\pi}$$

Mid-thigh muscle area (in cm^2) was calculated using the equation:

$$\frac{[\text{Mid-thigh circumference} - \pi \times \text{Thigh skinfold thickness}]^2}{4\pi}$$

(Heymsfield et al, 1994)

Bioelectrical impedance analysis was carried out using the technique described in section 2.2.3. Twenty four hour urinary creatinine was measured using the technique described in section 2.2.4. A dietary history for the previous 48 hours was obtained, as the value obtained for creatinine excretion can be affected by red meat consumption.

6.2.4 Blood Testing

Haemoglobin, white cell count, sodium, potassium, urea, creatinine, albumin, creatine kinase, calcium, magnesium, zinc, copper, vitamin D and C-reactive protein concentrations were measured using the methods described in section 2.3.

6.2.5 Statistics

Data is presented as medians, with ranges. Comparisons were carried out, where appropriate, using Fisher's Exact test and the Mann Whitney U test, and correlations were calculated using the Spearman Rank Correlation (SPSS Inc., Chicago, Illinois, USA). Correlations were only carried out for the cancer group.

6.3 Results

One hundred and ten patients were approached about the study and given a full explanation of its purpose. However, only 68 patients actually participated in the study. Of the 42 patients lost to study, 16 patients subsequently declined to participate in the study, 10 became too unwell before the first measurement could be carried out and 9 died. Three patients were subsequently felt to be inappropriate for entry into the study, due to confusion in one patient and failure to understand the study in the other two. Four patients were lost to study for other reasons.

Sixty eight cancer patients participated in the study. There was no significant difference in the proportion of men and women between this sample and the hospice population described in chapter 5. However, there was a significant difference in the ages of the two samples ($p < 0.001$), the study sample being younger than the Strathcarron Hospice population. There were significantly more lung cancer patients ($p < 0.001$) in this sample. There were no significant differences between the two samples for any of the other malignancies.

The majority of patients had either lung or gastrointestinal malignancies (Table 6.1). Of the 38 patients with lung cancer, 28 had non-small cell lung cancer, 6 had small cell lung cancer and 4 had no histology. Of the 13 patients with gastrointestinal malignancy, 8 had colorectal cancer, 2 had pancreatic cancer, 2 had oesophageal cancer and one had gastric cancer. The patients with hormone dependent tumours (n=7) included 4 patients with breast cancer, 2 with ovarian cancer and one with prostate cancer.

Thirty two patients had metastatic disease, some at multiple sites (results not shown, see appendix 3). The commonest sites were bone (n=12), liver (n=8), lung (n=6), lymph node (n=5) and brain (n=4). There was no significant difference in the prevalence of these sites of distant spread compared to the hospice population described in chapter 5. Other patients had peritoneal (n=3), renal (n=1) and bladder (n=1) metastatic disease.

The co-existing medical conditions in the patient groups included cardiac and vascular disease, chronic chest disease and diabetes. One patient had a co-existing superficial papillary bladder tumour, which was not felt to be linked significantly to his clinical condition. Six of the 15 healthy subjects reported high blood pressure, which was controlled on medication, compared to only 3 of the patient group ($p < 0.01$). There were no significant differences between the healthy and cancer groups for the prevalence of other medical conditions.

Fifteen healthy volunteers also participated in the study. The cancer and healthy groups were similar in terms of gender, age, healthy weight and healthy body mass index (Table 6.1). The cancer group were significantly lighter at study entry ($p < 0.01$) and, compared to the control group, the Karnofsky Performance Status was significantly lower ($p < 0.001$).

Total body water ($p < 0.01$), intracellular fluid volume ($p < 0.05$), the intracellular to extracellular fluid ratio ($p < 0.05$), limb circumferences ($p < 0.001$), limb muscle areas ($p < 0.01$) and 24 hour urinary creatinine excretion ($p < 0.05$) were all significantly reduced in the cancer patients (Table 6.2), indicating that the cancer group had lost lean body tissue. There were highly significant correlations between mid-arm circumference

and arm muscle area ($r = 0.91$, $p < 0.001$) and mid-thigh circumference and thigh muscle area ($r = 0.96$, $p < 0.001$). There was also a significant correlation between 24 hour urinary creatinine excretion and total body water ($r = 0.75$, $p < 0.001$). There were similar numbers of healthy subjects and cancer patients who had eaten red meat in the previous 48 hours. The cancer group had also lost body fat, as indicated by significantly lower skinfold thicknesses at all sites ($p < 0.05$). Nine patients had evidence of peripheral oedema or lymphoedema.

The majority of patients were moderately active prior to their cancer diagnosis, with most having an activity level of 2 (Table 6.3). However, the patients' activity level at study entry was much reduced, with the majority of patients in activity level 1. Most of the volunteers were moderately to very active, with a similar picture to the patient group prior to their illness.

The cancer patients scored significantly higher on the weakness scale than the healthy subjects ($p < 0.001$, Table 6.4), and significantly lower on the strength scale ($p < 0.001$). They scored significantly lower on the FACT-Ftg scale ($p < 0.001$) and higher on the EORTC Fatigue scale ($p < 0.001$), indicating higher levels of fatigue. The weakness scale was correlated with both the FACT-Ftg scale ($r = -0.50$, $p < 0.001$) and the EORTC Fatigue scale ($r = 0.47$, $p < 0.001$). The FACT-Ftg and EORTC Fatigue scales were strongly correlated ($r = -0.81$, $p < 0.001$). There were correlations between the weakness scale and the individual questions within the EORTC Fatigue scale and the FACT-Ftg scale except for questions 7, 8 and 10 of the FACT-Ftg scale ("I have energy", "I am able to do my usual activities" and "I am too tired to eat"). The

relationship between subjective weakness and subjective strength linear analogue scales was weak ($r = -0.29$, $p < 0.05$).

A cut-off point of the 95% centile of the healthy scores was taken for estimation of prevalence of weakness and fatigue as discussed in section 6.2.2. The prevalence for weakness in the cancer group in the present study was calculated as 64%. The prevalence for fatigue on the FACT-Ftg scale was calculated as 94%, and on the EORTC Fatigue scale as 72%.

There was no relationship between patient age or gender and the weakness score, nor with either of the fatigue scales. There were too few patients in most of the cancer diagnostic groupings to compare weakness and fatigue scores. However, there were no differences in these scores when the lung cancer group was compared with the gastrointestinal cancer group, nor between the lung cancer patients and the other patient groups combined. The weakness score was related to mid-thigh circumference ($r = -0.25$, $p < 0.05$), but not to mid-thigh muscle area. The FACT-Ftg scale was related to triceps skinfold thickness ($r = 0.24$, $p = 0.05$), mid-arm circumference ($r = 0.28$, $p < 0.05$) and mid-thigh circumference ($r = 0.28$, $p < 0.05$) and mid-thigh muscle area ($r = 0.29$, $p < 0.05$).

Many patients were taking drugs implicated in the aetiology of weakness and fatigue (data not shown, see appendix 3), including strong opioids (n=38), benzodiazepines (n=26), antidepressants (n=17) and diuretics (n=15). Twenty two patients were taking corticosteroids and 7 were taking megestrol acetate. Twenty two patients were also taking non-steroidal anti-inflammatory drugs. Those patients taking benzodiazepine

drugs had higher scores on both the FACT-Ftg scale ($p < 0.05$) and the EORTC Fatigue scale ($p < 0.01$). This was not true for opioids, antidepressants, non-steroidal anti-inflammatory drugs or steroids. There was no relationship between weakness or fatigue scores and either opioid dose or steroid dose.

Haemoglobin concentrations were significantly lower in the cancer group compared with the healthy group ($p < 0.001$; Table 6.5) and haemoglobin was correlated with the FACT-Ftg score ($r = 0.29$, $p < 0.05$). There was a trend towards lower FACT-Ftg scores, i.e., more fatigue, in those patients with haemoglobin concentrations less than 12.0 g/dl compared with those with concentrations of 12.0 g/dl or more ($p < 0.10$). White cell count was significantly higher in the cancer group ($p < 0.001$) and was correlated with the FACT-Ftg scale ($r = -0.26$, $p < 0.05$) and the EORTC Fatigue scale ($r = 0.33$, $p < 0.01$).

Sodium ($p < 0.01$), albumin ($p < 0.001$), creatine kinase ($p < 0.001$), zinc ($p < 0.001$) and vitamin D ($p < 0.01$) concentrations were all significantly lower in the cancer patients (Table 6.5). Albumin concentrations were correlated with both the FACT-Ftg scale ($r = 0.33$, $p < 0.01$) and the EORTC Fatigue scale ($r = -0.34$, $p < 0.01$). Calcium ($p < 0.05$), copper ($p < 0.01$) and C-reactive protein ($p < 0.001$) concentrations were significantly higher in the cancer group. Calcium concentrations were correlated with the weakness scale ($r = 0.38$, $p < 0.01$) and the EORTC Fatigue scale ($r = 0.26$, $p < 0.05$). C-reactive protein concentrations were correlated with the weakness scale, the FACT-Ftg scale, the EORTC Fatigue scale, white cell count and albumin, zinc, copper and vitamin D concentrations (Table 6.6). There were no relationships between any of the other blood parameters and the weakness and fatigue scores.

Dividing the cancer patients into weight-stable and weight-losing groups, the sex and age distributions were similar (Table 6.7). There were no significant differences in the numbers of patients of each cancer type between the two groups, except that all the patients in the "others" group were weight-stable ($p < 0.05$). There were similar numbers of patients with metastatic disease in each group. The healthy weight and body mass index were similar in both groups. However, the weight-losing group had lower Karnofsky Performance Status ($p < 0.01$).

In terms of body composition, there was no significant difference between the weight-losing and weight-stable patients in triceps, biceps and thigh skinfold thickness, nor in mid-arm circumference, nor any of the bioelectrical impedance parameters (Table 6.8). The mid-thigh circumference and thigh muscle area were, however, significantly lower ($p < 0.05$) in the weight-losers, as was the 24 hour urinary creatinine excretion ($p < 0.01$). Five weight-losing and 4 weight-stable patients had evidence of peripheral oedema or lymphoedema.

The number of patients with metastatic disease and with different pre-existing medical conditions were similar in both groups. Activity levels were also similar both pre-diagnosis and at study entry in both groups (data not shown, see appendix 3). More patients in the weight-losing group were taking strong opioid drugs than in the weight-stable group (72% v 42%; $p < 0.05$), although the median equivalent morphine dose for each group was similar (see appendix 3). There was no significant difference between the two groups for any other medication.

The weight-losing group scored higher on the weakness scale ($p < 0.01$) and rated as more fatigued on the FACT-Ftg scale ($p < 0.05$, Table 6.9). Degree of weight loss was related to both the weakness score ($r = 0.25$, $p < 0.05$) and the FACT-Ftg score ($r = -0.36$, $p < 0.01$).

There were significant differences between the two groups in scores for the individual questions in the two fatigue scales (see appendix 3). Weight-losers scored higher on the "Did you need to rest" EORTC scale question ($p < 0.05$) and on the FACT-Ftg scale they reported more difficulty in starting activity (question 5, $p < 0.05$), lower energy levels (question 7, $p < 0.01$), needing more help in doing their usual activities (question 11, $p < 0.001$), increased frustration at their limitations (question 12, $p < 0.05$) and limitation of their social activities (question 13, $p < 0.05$).

The weight-losing group had lower sodium ($p < 0.05$), creatine kinase ($p < 0.05$) and albumin ($p < 0.01$) concentrations than the weight-stable group (Table 6.10). White cell count ($p < 0.001$) and C-reactive protein ($p < 0.01$) concentrations were significantly higher in the weight-losing group.

6.4 Discussion

The present study examined a group of patients with advanced cancer. The majority of these patients had lung or gastrointestinal cancer. The lung cancer group forms a greater proportion of this group than in Scottish cancer registration statistics (Scottish Cancer Co-ordinating and Advisory Committee, 1996). However, all of the patients recruited at Stobhill Hospital were recruited via the Respiratory Oncology services and had either lung cancer or mesothelioma. It was of note, however, that many of the patients recruited from Hunter's Hill Marie Curie Centre, a heterogeneous cancer population, also had lung cancer, which may be a reflection of the fact that Glasgow has a higher proportion of lung cancer patients than the national average.

Many of the patients approached for the study were unable to participate due to disease progression or death, which illustrates the frequent problem of attrition rates in studies involving palliative care patients (Loprinzi et al., 1990; Tchekmedyian et al., 1992; McMillan et al., 1999). The attrition rate prior to study entry in this study was 38%. For a variety of reasons not all patients were able to complete all the tests. Some questionnaires were left incomplete and some blood samples were haemolysed and inappropriate for certain analyses. The bioelectrical impedance analysis apparatus was occasionally unavailable. The 24 hour urine collection was not felt to be suitable for all patients, as this test involves significant patient co-operation to remember to use the container each time they need to pass urine. Therefore, those who were too frail or for whom the test would prove practically difficult did not collect a urine specimen.

The study group was younger than the hospice population described in chapter 5. The reason for this is unclear. However, it was of interest that those patients approached about the study who declined to participate were of a similar age distribution to the hospice population (median 67.5 years (49-78)). Given the nature of the present study it may be that it was not attractive to the older patients.

It is clear that the cancer patient group were more unwell than the healthy subject group, with reduction in both fat and fat free mass. It was also clear that muscle mass was reduced, as there was a reduction in limb circumferences and limb muscle area, as well as a reduction in 24 hour urinary creatinine excretion and serum creatine kinase. The cancer patients had significantly more weakness and fatigue. The cancer group also had lower haemoglobin, sodium, albumin, zinc and vitamin D concentrations compared with the healthy group, as well as higher white cell count, calcium, copper and C-reactive protein concentrations.

The literature describes fatigue as a symptom present in normal individuals (Barnish, 1994; Glaus et al., 1996), and suggests that weakness is a symptom that is pathological (Glaus et al., 1996). The weakness and fatigue scores in this study were generally low in the healthy group. The prevalences for weakness and fatigue in this study have to be interpreted in the light of the small control group. However, they are consistent with previous estimates in uncontrolled studies (Dunlop, 1989; Donnelly and Walsh, 1995). Previous studies of fatigue have largely considered the role of chemotherapy and radiotherapy in the aetiology of fatigue (Meyerowitz et al., 1979; Nail and King, 1987; Richardson, 1995). In this study, patients in the baseline group had received neither of these treatment modalities in the previous month, suggesting that weakness and fatigue

are also common symptoms in cancer patients not receiving anti-cancer treatment. These results are consistent with recent work by Stone and colleagues (1999), who reported a prevalence for fatigue of 75% in patients with advanced cancer not receiving chemotherapy or radiotherapy.

There were significant relationships between the weakness scale and the measures of fatigue (FACT and EORTC), and this is extended into individual questions within the fatigue scales: there were positive correlations between the weakness scale and all three components of the EORTC fatigue scale and with most of the questions of the FACT-Ftg scale. Although the weakness linear analogue scale measured weakness at a single point in time and the fatigue scales considered the patients' experience over the previous seven days, these results suggest that fatigue, tiredness and weakness tend to coexist in cancer patients and may be components of the same phenomenon.

The cancer patients had clearly lost fat and fat free mass compared with the healthy subjects. This is consistent with the published literature, which has reported that cancer patients who lose weight lose both adipose tissue and muscle (Nelson et al., 1994a; Toomey et al., 1995). Although total body water was reduced in the cancer patients, intracellular water was reduced more than extracellular water, suggesting that in the cancer patients there was either fluid retention into the extracellular space or that there were fluid shifts from the intracellular to the extracellular compartments. It was of note that some of the patients had clinically detectable oedema. Previous work has reported that ill patients retain fluid into the extracellular space (Hannan et al., 1995), with a consequent expansion of total body water. Overestimation of total body water in cachectic cancer patients, using bioelectrical impedance analysis, has also previously

been reported (Simons et al., 1995). It is possible that, in the present study, as well as those patients with oedema, there were also patients with clinically undetectable fluid retention, and that together these patients contributed to overestimation of extracellular fluid and, consequently, total body water and fat free mass. However, it was clear from the 24 hour urinary creatinine excretion and limb circumference measurements that loss of muscle mass had occurred.

Higher fatigue scores were recorded in those patients taking benzodiazepine drugs. Although benzodiazepines have been suggested as an aetiological factor for weakness and fatigue in cancer patients (Regnard and Mannix, 1992), this association does not appear to have previously been reported in a prospective study. These are commonly prescribed drugs in palliative care patients and it would be important for future studies to establish whether or not this is a coincidental finding.

As has been previously reported, there was a relationship demonstrated between haemoglobin and fatigue scores and the level of haemoglobin was lower in the cancer group. In the present study, there was a trend for FACT-Ftg scores to be lower in those with haemoglobin concentrations lower than 12.0 g/dl. This is consistent with previous work by Cella (1998), who reported a significant difference in FACT-Ftg scores between high and low haemoglobin scores in a larger study of patients with cancer and human immunodeficiency virus (HIV) infection.

Raised C-reactive protein concentrations and elevated white cell count, as well as low albumin concentrations, were present in the cancer patients. C-reactive protein and albumin were correlated, as previously reported (O'Gorman et al., 1999). These

parameters also seem related to the subjective experience of weakness and fatigue, consistent with previous work by Morant (1996). It is of interest that a previous study by Morant and colleagues (1993) found no relationship between C-reactive protein and weakness and fatigue scores. However, this latter study had a much smaller patient group (n = 31) compared with the 1996 study (n = 225) and this may well explain the difference between the two studies. The low zinc and raised copper concentrations were also related to the magnitude of the inflammatory response, as previously reported (Sattar et al., 1997), but not to the weakness and fatigue scores. Vitamin D concentrations were inversely related to the inflammatory response, as with other vitamins (Galloway, McMillan and Sattar, 2000). The inflammatory response may have a role in the production of weakness and fatigue, but low trace element and vitamin concentrations appear not to have a primary role in these symptoms. Further work on the temporal relationship of the inflammatory response and weakness/fatigue would be of considerable interest.

The lack of difference between the weight-stable and the weight-losing group, in terms of skinfold thicknesses and bioelectrical impedance measurements, suggests that the weight-stable group themselves are also quite ill, and certainly not normal, compared with the healthy group. It is also possible that the weight-losing group had retained more fluid - this group had lower albumin concentrations - and, thus, the accuracy of the bioelectrical impedance results may have been affected, with a consequent overestimation of lean body mass. The skinfold thickness measurements in the weight-losing patients were similar to those of the weight-stable patients, suggesting that both patient groups had lost fat compared with the healthy group. However, the weight-losers had clearly lost muscle compared with the weight-stable patients as mid-thigh

circumference, thigh muscle area and 24 hour urine creatinine were reduced. There are more errors inherent to measures of skinfold thickness than in measure of limb circumference (Burkinshaw et al., 1973) and this may, in part, have influenced the results.

Weakness and fatigue were more marked in the weight-losing group and weight loss, as well as the limb circumferences and triceps skinfold thickness, were associated with the severity of weakness/fatigue. It may be, therefore, that cancer cachexia plays a role in the production of weakness/fatigue.

The weight-losers needed significantly more help in doing their usual activities (FACT-Ftg question 11) and also had a significantly lower performance status, suggesting that the weight-losers had poorer functional ability. No difference was noted between the weight-stable and weight-losing cancer groups for the author's activity scale, suggesting that it was less sensitive to change than the FACT-Ftg questions or performance status. It is of interest that the weight-losers scored significantly worse in the "I have trouble starting things because I am tired" question (question 5) of the FACT-Ftg scale than the weight-stable patients, but not in the "I have trouble finishing things because I am tired" question (question 6). This may give credence to the suggestion that it is possible to differentiate between difficulty in initiating activity and difficulty in continuing activity (Morant et al., 1993). The terms "weakness" and "fatigue" may be used synonymously by cancer patients, but it may be possible to describe difficulty in activity as weakness and the subjective element as fatigue. The FACT-Ftg scale, by including questions on activity, may tap into both dimensions and may explain why the prevalence of fatigue would be higher on the FACT scale than the EORTC scale. However, it may be

academic as to whether or not it is possible to differentiate between weakness and fatigue in terms of definition. Ultimately, what matters most are the problems reported by the patient and how these problems affect their life.

Although there was more weakness and fatigue in the weight-losing group, the haemoglobin was not reduced compared to the weight-stable group. This would suggest that anaemia in itself may not be the most important factor in the aetiology of these symptoms, although weakness, fatigue and anaemia seem often to co-exist. C-reactive protein and white cell count were elevated and albumin was reduced in the weight-losing patients, consistent with the inflammatory response having a role in weight loss.

In summary, this study has found a relationship between patient-rated weakness and more comprehensive fatigue scales, suggesting that weakness, fatigue and tiredness are overlapping parts of the same phenomenon. The cancer patients had altered body composition and had lost both fat and muscle. Cancer cachexia and the inflammatory response appear to be important factors in the production of weakness and fatigue. Anaemia and benzodiazepine drugs also appear to be factors in the aetiology of weakness/fatigue. There appears to be a spectrum ranging from healthy individuals to weight-stable cancer patients, to weight-losing cancer patients, with loss of muscle, deranged biochemistry, increasing levels of weakness/fatigue and increasing difficulty in initiating and performing daily activities. However, for some aspects of body composition, such as body water, there was little difference between the weight-stable and weight-losing cancer groups. The relationships between these factors would, therefore, appear to be complex and merit further study.

Table 6.1 Healthy Subject and Cancer Patient Characteristics

	Healthy Subjects (n=15)	Cancer Patients (n=68)	p-value
Sex (M/F)	7/8	41/27	NS
Age	64 (46-74)	64 (38-83)	NS
Healthy Weight (kg)	68.0 (52.0-87.0)	63.5 (44.5-114.3)	NS
Current Weight (kg)	-	58.0 (35.0-95.0)	< 0.01
Healthy BMI (kgm^{-2})	24.6 (20.9-28.9)	24.3 (15.9-40.0)	NS
Current BMI (kgm^{-2})	-	21.4 (13.8-33.3)	< 0.01
%age of Healthy BMI	107 (91-126)	93 (60-145)	< 0.01
Karnofsky Performance Status	100 (90-100)	65 (25-100)	< 0.001

Cancer Types (M/F)	Male	Female	p-value
Lung	23	15	NS
Mesothelioma	4	0	NS
Gastrointestinal	5	8	NS
Hormone Dependent	1	6	NS
Others*	4	2	NS

* = 2 Non-Hodgkin's lymphoma, 1 patient with both non-small cell lung cancer & colonic carcinoma, 1 patient with both prostate and head & neck malignancies, 1 with cerebral astrocytoma and 1 with head & neck cancer

M/F = Male/Female BMI = Body Mass Index NS = Not Significant

Data is presented as median (range)

Table 6.2 Body Composition of Healthy Subjects and Cancer Patients

	Healthy Subjects (n=15)	Cancer Patients (n=58)	p-value
Total Body Water (l)	31.5 (23.8-41.5)	26.7 (17.3-41.0)	< 0.01
Volume ECF (l)	18.0 (13.2-23.6)	16.1 (10.6-24.1)	< 0.10
Volume ICF (l)	14.3 (10.6-18.9)	10.4 (6.8-20.9)	< 0.01
ICF/ECF Fluid Ratio	0.78 (0.64-1.00)	0.70 (0.40-1.25)	< 0.05
Triceps Skinfold Thickness (mm)	17.0 (6.5-32.0)	10.0 (2.5-34.5)	< 0.01
Biceps Skinfold Thickness (mm)	10.0 (3.5-29.5)	6.3 (2.0-20.5)	< 0.01
Thigh Skinfold Thickness (mm)	18.3 (8.5-56.5)	12.5 (3.0-39.5)	< 0.05
Mid-Arm Circumference (cm)	31.2 (25.6-33.5)	25.2 (16.5-37.1)	< 0.001
Arm Muscle Area (cm^2)	49.1 (36.9-65.5)	36.2 (19.3-76.7)	< 0.001
Mid-Thigh Circumference (cm)	51.3 (44.8-59.1)	44.6 (28.0-66.3)	< 0.001
Thigh Muscle Area (cm^2)	163.1 (96.2-209.5)	120.5 (58.3-294.4)	< 0.01
Twenty Four Hour Urinary Creatinine (mmol/l)	12.0 (7.0-19.2)	8.2 (1.4-20.4)[a]	< 0.05

[a] n = 27

ECF = Extracellular Fluid; ICF = Intracellular Fluid

Data is presented as median (range)

Table 6.3 Activity Levels In Healthy Subjects and in Cancer Patients Before Diagnosis and at Study Entry

	Healthy subjects (n=15)	Cancer patients pre-diagnosis (n=65)	Cancer patients at study entry (n=68)
Activity level			
0	-	-	8
0-1	-	-	3
1	-	5	46
1-2	3	5	7
2	8	42	4
2-3	2	7	-
3	2	6	-

Key:

0 = Inactive; mainly bed or chair bound

1 = Sedentary lifestyle, some walking

2 = Moderately active, walks a lot, light sporting activity

3 = Very active, training or sports

Table 6.4 Baseline Data for Linear Analogue Scales of Weakness and Strength, FACT-Ftg Scale and EORTC Fatigue Scale in Healthy Subjects and Cancer Patients

	Healthy Subjects (n=15)	Cancer Patients (n=66)	p-value
Linear Analogue Scales			
Weakness Scale (cm)	1.0 (0.1-3.3)	4.2 (0.4-8.3)	< 0.001
Strength Scale (cm)	9.2 (4.8-10.0)	4.4 (0.4-10)	< 0.001
FACT-Ftg Scale	49 (43-51)	28 (0-47)	< 0.001
EORTC-Fatigue Subscale	0 (0-33.3)	55.6 (0-100)	< 0.001

Data is presented as median (range)

Table 6.5 Baseline Data for Blood Tests in Healthy Subjects and Cancer Patients

	Healthy Subjects (n=15)	Cancer Patients (n=67)	p-value
Haemoglobin (g/l)	144 (123-161)	123 (91-177)	< 0.001
White Cell Count	6.5 (4.08-8.40)	9.3 (4.39-27.17)	< 0.001
Sodium (mmol/l)	139 (137-144)	137 (123-145)	< 0.01
Potassium (mmol/l)	4.3 (3.6-4.8)	4.4 (3.3-5.6)	NS
Urea (mmol/l)	5.5 (3.8-17.7)	6.2 (2.0-17.6)	NS
Creatinine (μmol/l)	90 (74-323)	83 (56-161)	NS
Albumin (g/l)	44 (41-47)	39 (23-46)	< 0.001
Creatine Kinase (IU/l)	105 (38-199)	35 (10-318)	< 0.001
Calcium (mmol/l)	2.31 (2.23-2.52)	2.37 (2.14-3.29)	< 0.05
Magnesium (mmol/l)	0.85 (0.69-1.03)	0.87 (0.58-1.02)	NS
Zinc (μmol/l)	12.4 (9.1-18.5)	10.0 (4.7-15.8)	< 0.001
Copper (μmol/l)	18.2 (11.4-27.5)	21.6 (10.8-37.5)	< 0.01
Vitamin D (nmol/l)	35 (21-82)	22 (< 6-128)	< 0.01
C-Reactive Protein (mg/l)	4 (1-30)	40 (1-214)	< 0.001

NS = Not Significant

Data is presented as median (range)

Table 6.6 Spearman Rank Correlations Between C-Reactive Protein and Other Parameters in Cancer Patients

	r-value	p-value
EORTC Fatigue scale	0.41	< 0.01
FACT-Ftg scale	-0.36	< 0.01
Weakness scale	0.29	< 0.05
Albumin	-0.63	< 0.001
Zinc	-0.40	< 0.01
Copper	0.40	< 0.01
White cell count	0.39	< 0.01
Vitamin D	-0.25	0.05

Table 6.7 Characteristics of Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=36)	Weight-Losing (n=32)	p-value
Sex (M/F)	22/14	19/13	NS
Age	64 (45-83)	64 (38-81)	NS
Healthy Weight (kg)	63.5 (44.5-95.3)	66.8 (45.3-114.3)	NS
Current Weight (kg)	64.0 (35.0-92.5)	54.0 (39.0-95.0)	< 0.10
Weight Loss from pre-illness weight (kg)	2.1 (-18.8 to 22.3)	12.8 (-3.3 to 36.3)	< 0.001
Healthy BMI (kgm^{-2})	23.6 (15.9-33.9)	25.0 (16.8-40.0)	NS
Current BMI (kgm^{-2})	22.8 (13.8-31.5)	19.9 (14.8-33.3)	< 0.05
% age Ideal BMI	99 (60-137)	86 (64-145)	< 0.05
Karnofsky Performance Status	75 (40-100)	60 (25-85)	< 0.01
<u>Cancer Types (M/F)</u>			
Lung	17 (11/6)	21 (12/9)	NS
Mesothelioma	2 (2/0)	2 (2/0)	NS
Gastrointestinal	5 (0/5)	8 (5/3)	NS
Hormone Dependent	6 (1/5)	1 (0/1)	NS
Others	6 (4/2)	-	< 0.05

M/F = Male/Female BMI = Body Mass Index NS = Not Significant

Data is presented as median (range)

Table 6.8 Baseline Anthropometrics for Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=31)	Weight-Losing (n=27)	p-value
Volume ECF (l)	17.2 (12.3-24.1)	14.9 (10.6-21.7)	NS
Total Body Water (l)	30.0 (20.9-41.0)	25.1 (17.3-37.5)	NS
Volume ICF (l)	11.1 (7.0-20.9)	10.0 (6.8-16.2)	NS
ICF/ECF Fluid Ratio	0.72 (0.40-1.25)	0.69 (0.56-0.97)	NS
Triceps Skinfold Thickness (mm)	10.0 (2.5-34.5)	10.0 (3.0-33.5)	NS
Biceps Skinfold Thickness (mm)	6.5 (2.0-20.5)	5.8 (2.0-20.5)	NS
Thigh Skinfold Thickness (mm)	12.5 (3.0-39.5)	12.5 (3.5-36.5)	NS
Mid-Arm Circumference (cm)	26.6 (16.5-37.1)	24.2 (17.1-37.0)	NS
Arm Muscle Area (cm^2)	38.9 (19.3-69.8)	34.1 (19.6-76.7)	NS
Mid-Thigh Circumference (cm)	45.4 (28.0-66.3)	41.8 (32.3-57.1)	< 0.05
Thigh Muscle Area (cm^2)	136.2 (58.3-294.4)	111.4 (76.2-212.6)	< 0.05
Twenty Four Hour Urinary Creatinine (mmol/l)	9.9 (6.2-20.4)[b]	6.1 (1.4-9.5)[a]	< 0.01

[a] n = 7; [b] n = 20

ECF = Extracellular Fluid; ICF = Intracellular Fluid NS = Not Significant

Data is presented as median (range)

Table 6.9 Baseline Data for Linear Analogue Scales of Weakness and Strength, FACT-Ftg Scale and EORTC Fatigue Scale in Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=35)	Weight-Losing (n=31)	p-value
Linear Analogue Scales			
Weakness Scale	3.0 (0.4-7.5)	5.1 (1.3-8.3)	< 0.01
Strength Scale	5.0 (0.2-10.0)	4.1 (0.2-9.6)	NS
FACT-Ftg Scale	30 (12-47)	24 (0-43)	< 0.05
EORTC-Fatigue Scale	55.6 (0-88.9)	61.1 (11.1-100)	< 0.10

NS = Not Significant

Data is presented as median (range)

Table 6.10 Blood Tests in Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=35)	Weight-Losing (n=32)	p-value
Haemoglobin (g/l)	124 (96-177)	122 (91-153)	NS
White Cell Count	7.4 (4.4-16.9)	10.7 (5.8-27.2)	< 0.001
Sodium (mmol/l)	138 (134-145)	136 (123-144)	< 0.05
Potassium (mmol/l)	4.4 (3.5-5.6)	4.4 (3.3-5.1)	NS
Urea (mmol/l)	5.8 (2.2-13.1)	6.5 (2.0-17.6)	NS
Creatinine (μmol/l)	79 (56-161)	91 (62-161)	NS
Albumin (g/l)	41 (31-46)	37 (23-44)	< 0.01
Creatine Kinase (IU/l)	46 (16-205)	30 (10-318)	< 0.05
Calcium (mmol/l)	2.35 (2.18-2.61)	2.41 (2.14-3.29)	NS
Magnesium (mmol/l)	0.85 (0.58-1.02)	0.88 (0.63-0.99)	NS
Zinc (μmol/l)	10.5 (5.3-15.8)	9.5 (4.7-12.4)	< 0.10
Copper (μmol/l)	21.3 (11.6-35.3)	22.1 (10.8-37.5)	NS
Vitamin D (nmol/l)	22 (<6-128)	21 (<6-68)	NS
C-Reactive Protein (mg/l)	14 (1-204)	67 (2-214)	< 0.01

NS = Not Significant

Data is presented as median (range)

CHAPTER 7: A STUDY OF THE RELATIONSHIPS BETWEEN WEAKNESS, FATIGUE, OBJECTIVE STRENGTH AND FUNCTION AND THEIR IMPACT ON QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER

7.1 Introduction

Weakness and fatigue are the commonest symptoms in patients with advanced cancer, and as previously discussed in chapter 6, patients probably use these terms synonymously to refer to the same problems. Many patients complain of reduced strength, but the literature describing the relationship between the subjective experience of weakness or fatigue and objective measures of strength in patients with advanced cancer is very limited. Stone and colleagues (1999) recently reported that there was no relationship between voluntary handgrip strength and fatigue as measured by the Fatigue Severity Scale, in patients with advanced cancer and poor performance status. However, Glaus and co-workers (1996) suggested that strength might be a key dimension of weakness to be isolated and studied. Lichter (1990) suggested that loss of muscle mass in cancer patients would lead to loss of muscle strength.

Many cancer patients report difficulty in performing daily activities and symptoms such as weakness, fatigue and tiredness often prevent them caring for themselves (Rhodes et al., 1988; Dunlop, 1989; Morant et al., 1993). Many quality of life questionnaires recognise that performance of ordinary daily activities are important and some, like the EORTC QLQ-C30 questionnaire (Aaronson et al., 1993), contain subscales which measure physical functioning. As previously noted in chapter 6, the FACT-Ftg questionnaire (Yellen et al., 1997) also includes some questions related to the

performance of activity. Cancer patients, and in particular those who have lost weight, have difficulty in initiating activity and need increased help in performance of activity. Karnofsky Performance Status (Karnofsky et al., 1948) is also commonly used in studies of patients with advanced cancer (O'Gorman et al., 1998; McMillan et al., 1999) as an observer-rated measure of functional ability.

The relationship between strength and functional ability has not been formally studied in cancer patients. Previous studies in the healthy elderly have found relationships between muscle strength and power and objective measures of function. One study in 70 year old men and women reported positive correlations between isokinetic and isometric quadriceps strength, walking speed and maximum step height attainable (Aniansson et al., 1980). Another study in octogenarian men and women in a residential care setting reported positive correlations between quadriceps power and speed of rising from a chair, stair climbing and walking (Bassey et al., 1992). Cress and co-workers (1995) demonstrated a positive relationship between self-perceived physical function - measured using a subscale of the Sickness Impact Profile questionnaire (Bergner et al., 1981) - and walking speed in a group of men and women over the age of 60, as well as an inverse correlation between physical function and time to stand up from a chair.

Research in palliative care has emphasised the importance of patient-rated quality of life (Ahmedzai, 1990; Hjermstad et al., 1995). Quality of life is multi-dimensional and includes physical, emotional, cognitive and spiritual elements (Richards and Ramirez, 1997). Although there are no specific quality of life instruments developed for use with palliative care patients, the importance of quality of life in this patient group has recently been demonstrated using the EORTC QLQ-C30 questionnaire (Aaronson et al.,

1993) in a group of patients with advanced gastrointestinal cancer (O'Gorman et al., 1998).

The aim of this study was to examine the relationships between objective tests of strength and function and measures of weakness and fatigue and patient-related quality of life in patients with advanced cancer.

7.2 Material and Methods

7.2.1 Patients

Sixty eight patients and healthy controls, as previously described in chapter 6.2.1, participated in this study. Tests and questionnaires used in this study were carried out at the same time as those tests previously described (chapter 6). Ethics committee approval and informed consent, as previously described in chapter 6.2.1., applied to this study.

7.2.2 Questionnaires

Different aspects of patient-rated quality of life, including self-perceived physical function, were measured using the EORTC QLQ-C30 general quality of life questionnaire version 2.0, as described in chapter 4.2. The Hospital Anxiety and Depression scale was administered as a measure of patient-rated anxiety and depression, as described in chapter 4.5.

7.2.3 Strength Measures

Baseline muscle strength was graded in proximal and distal limb muscles using the Medical Research Council (MRC) 0-5 scale (see appendix 1). Handgrip strength was measured in all patients, as previously described in chapter 3.2.1. Isokinetic and isometric quadriceps strength was measured in most of the patients with good performance status (performance status $\geq$ 70), as described in chapter 3.2.2. In the quadriceps testing, to try and establish whether patients had performed maximal efforts when asked to do so, electrical stimulation of the quadriceps was performed using the technique described in chapter 3.2.2.

7.2.4 Functional Tests

Chair stand time and triple chair rise time were measured, using the method described in chapter 3.3.1. Time for ascent and descent of four, 15 centimetre, stairs was measured as described in chapter 3.3.2. Walking distance for 2 minutes and 6 minutes was measured using the method outlined in chapter 3.3.3.

7.2.5 Statistics

Data is presented as medians, with ranges. Comparisons were carried out, where appropriate, using Fisher's Exact test and the Mann Whitney U test, and correlations were calculated using the Spearman Rank Correlation (SPSS Inc., Chicago, Illinois, USA). Correlations were only carried out on the cancer patient data. Multiple regression analyses were carried out as appropriate and are described in chapter 7.4.

7.3 Results

The characteristics of the healthy subjects and cancer patients have been previously described in Tables 6.1 and 6.2. There was no difference between the median values of MRC muscle strength for the healthy subjects and the cancer patients in any of the muscle groups (median value 5). However, handgrip strength was significantly lower in the cancer patient group. This was true for both dominant ($p < 0.01$) and non-dominant ($p < 0.05$) handgrip strength (Table 7.1). There was an excellent correlation between dominant and non-dominant handgrip strength ($r = 0.95$, $p < 0.001$) with the dominant handgrip strength significantly greater than that of the non-dominant ($p < 0.01$). Therefore, the dominant handgrip strength was used in subsequent analyses. Isometric torque was significantly lower in the cancer group ($p < 0.05$). There were good correlations between handgrip strength and both isokinetic ($r = 0.72$, $p < 0.001$) and isometric ($r = 0.73$, $p < 0.001$) torque measurements. Handgrip strength and age were related ($r = -0.50$, $p < 0.001$).

The cancer patients were significantly slower than the healthy subjects in both the single chair stand test and the triple chair rise ($p < 0.001$, Table 7.2), with 8 patients using the chair arms during the chair tests. The cancer group was also significantly slower in both ascending and descending the stairs than the healthy subject group ($p < 0.001$), with 21 cancer patients and 5 healthy subjects using the banisters. The cancer patients walked a significantly shorter distance in 2 minutes and 6 minutes, compared with the healthy subjects ($p < 0.001$). Seven patients who participated in the walking tests had to stop walking before 2 minutes had elapsed. The chair stand and triple chair rise test times were strongly correlated ($r = 0.81$, $p < 0.001$) and correlations between these two tests

and the other functional tests were virtually identical. The stair ascent and descent times were also strongly correlated ($r = 0.92$, $p < 0.001$) and correlations between both and the chair and walking tests were also virtually identical. Correlations between all the functional tests, except the 6 minute walk, were strong.

The cancer group had significantly poorer scores on all of the functional scales of the EORTC QLQ-C30 questionnaire, compared with the healthy group ($p < 0.01$, Table 7.4). They also scored significantly higher on all of the symptom scales ($p < 0.05$), except for the diarrhoea scale.

The cancer group scored significantly higher on both the anxiety and depression subscales of the Hospital Anxiety and Depression (HAD) scale compared with the healthy group ($p < 0.001$, Table 7.5). Eleven patients (17.5%) had anxiety scores of 11 or more, fitting the criteria for an anxiety disorder, with another 19 patients (30.2%) being borderline cases (scores 8-10). Fifteen patients (24.2%) scored 11 or more in the depression scale, fitting the criteria for clinical depression, with another 16 patients (25.8%) in the borderline category. None of the healthy group scored more than 10 in either the anxiety or depression subscales. The anxiety and depression scales were related ($r = 0.43$, $p < 0.001$).

On dividing the cancer patients into weight-stable (median weight loss 2.1 kg from pre-illness weight) and weight-losing patients (median weight loss of 12.8 kg from pre-illness weight), handgrip strength was significantly lower in the weight-losing group ($p < 0.05$, Table 7.6). There was no significant difference between the weight-stable and weight-losing groups for isokinetic torque (see appendix 3). There were too few subjects

in the isometric weight-losing group (n=5) and this parameter was not tested statistically. Handgrip strength and the degree of weight loss were related ($r = -0.28$, $p < 0.05$), but there were no relationships between weight loss and the other strength measures.

The weight-losing patients were significantly slower in both of the chair tests than the weight-stable patients ($p < 0.01$, Table 7.6). The weight-losing patients were also slower than the weight-stable patients on both stair ascent and stair descent ($p < 0.01$). There was no significant difference between weight-losing and weight-stable patients for the 2 minute walking test. There were too few patients who completed the 6 minute walk to make meaningful statistical comparisons.

Comparing the weight-losing and weight-stable groups for the scores recorded in the EORTC QLQ-C30 questionnaire (Table 7.7), the weight-losers scored significantly poorer in the physical functioning scale ($p < 0.01$), but there were no significant differences for any of the other functional scales. In the symptom scales, weight-losing patients rated themselves as having significantly more constipation and diarrhoea, nausea and vomiting, pain and poorer appetite ($p < 0.05$). The sleep scores of the weight-losers were poorer ($p = 0.05$). Weight-losing patients scored significantly higher on both the anxiety and depression subscales of the HAD scale ($p < 0.05$; Table 7.8).

Taking the cancer patients as a whole, there were no relationships established between the subjective weakness linear analogue scale and any of the measures of objective strength, nor between the subjective strength scale and the objective strength measures. There were, however, correlations between the FACT-Ftg scale and handgrip strength

($r = 0.30$, $p < 0.05$) and between the EORTC fatigue subscale and handgrip strength ($r = -0.27$, $p < 0.05$). There was no relationship found between the fatigue scales and either the isokinetic or isometric strength measures.

Vitamin D concentrations were related to maximum isometric torque ($r = 0.48$, $p < 0.05$), but there was no similar relationship with the other strength measures.

The electrical stimulation tests did not produce clear data and in particular the results from the isokinetic studies were unsatisfactory. There were no definite twitches produced in any of the isokinetic tests, although in some series of contractions dips in the force tracing were noted shortly after the angle of stimulation (Figure 7.1). Many patients were unable to produce smooth force tracings and many did not reach the peak force at 70°, nor reach the peak force at the same angle on consecutive contractions. In later patients, the angle of delivery of the electrical stimulus was altered to take account of the most consistent angle of peak force attained during the warm-up. However, even then, during the test, the peak force was not consistently reached at the same angle. As there were no obvious twitches seen on the force tracings, the maximum force attained was recorded as the maximum voluntary force, and torque calculated from this.

The isometric testing was more successful and did produce twitches in many - but not all - of the patient and healthy subject tracings (Figure 7.2). The twitches were produced most consistently in healthy subjects. As there were no discernible twitches in any of the maximum isometric forces achieved, this was recorded as the maximum voluntary force and torque calculated from this.

Isometric torque was correlated with the chair stand, and handgrip strength was related to both chair tests (Table 7.9), but otherwise there were no relationships established between objective strength and the functional tests. There was a correlation between Karnofsky Performance Status and the physical functioning scale of the EORTC QLQ-C30 questionnaire. There were correlations between performance status and all of the functional tests, and a similar pattern was seen with the physical functioning scale. Performance status and the physical functioning scale were both correlated with handgrip strength, the FACT-Ftg scale and the weakness scale. Both the FACT-Ftg scale and the weakness scale were correlated with the chair stand time and the FACT-Ftg scale with the triple chair rise and the 2 minute walk (Table 7.9).

There was a correlation between the EORTC QLQ-C30 global quality of life scale and the FACT-Ftg scale as well as inverse correlations with the weakness scale and the chair stand time (Table 7.10). There were relationships between many of the symptom scales of the EORTC QLQ-C30 questionnaire and the FACT-Ftg scale, the weakness scale and the chair tests, but not with any of the other functional tests.

The group of patients with depression scores of 11 or more had significantly higher weakness scores ($p < 0.01$), significantly more fatigue on the FACT-Ftg scale ($p < 0.001$) and significantly lower handgrip strength ($p < 0.001$) than those with scores in the normal range (0-7). There was significantly more fatigue (FACT-Ftg) ($p < 0.001$) in the group with anxiety scores of 11 or more compared to those with normal anxiety scores. There were also good inverse correlations between the depression subscale and Karnofsky Performance Status, the EORTC QLQ-C30 global quality of life scale and many of the symptom scales (Table 7.10). There were correlations between the

depression score and the FACT-Ftg score (see Figure 7.3), the weakness score, handgrip strength, both chair tests and the walking test. The relationships described for the FACT-Ftg score in Tables 7.9 and 7.10 were also generally true of the EORTC fatigue score.

7.4 Relationship of Weakness and Fatigue Scales and Handgrip Strength With Other Variables

In the present study, many of the variables examined were related to the weakness and fatigue scales and to handgrip strength. For example, among other variables, the weakness scale score was related to weight loss, pain and depression score, the FACT-Ftg score was related to weight loss, handgrip strength, haemoglobin, many of the symptom scores and depression score, and handgrip strength was related to age, body mass and muscle area (see Tables 7.11-7.14). To determine which were the most important of these variables, multiple regression analyses were carried out in a stepwise fashion.

As with previous fatigue research (Stone et al., 1999), performance status, the physical functioning scale, the role functioning scale and the quality of life scale were excluded from the regression analysis for the weakness scale and the two fatigue scales as these variables were most likely to be outcomes of weakness/fatigue rather than causes. They were also excluded from the handgrip strength regression for the same reason.

Only those predictors which were significantly correlated on univariate analysis were entered into the regression model. The 6 significant variables related to the weakness score on univariate analysis were entered into the regression model and are listed in Table 7.11. Depression was the strongest predictor of weakness, accounting for 25% of the variance, with pain accounting for a further 8%. When question 8 of the HAD scale ("I feel slowed down") was omitted, then these two factors remained the most

important, but were reversed, with pain accounting for 21% of the variance and depression a further 9%.

Those variables related to the FACT-Ftg scale on univariate analysis are listed in Table 7.12. Depression was the strongest predictor of the FACT-Ftg score, accounting for 45% of the variance, and social function and anxiety score a further 8% and 6% respectively. When question 8 of the HAD scale was removed it did not alter the analysis.

Those variables related to the EORTC fatigue score on univariate analysis are listed in Table 7.13. Depression was again the strongest predictor of the fatigue score, accounting for 32% of the variance, with dyspnoea and pain accounting for a further 14% and 6% respectively. When question 8 of the HAD scale was removed emotional functioning was the strongest predictor, accounting for 30% of the variance, with social functioning and the depression score accounting for a further 12% and 8% respectively.

Those variables related to handgrip strength on univariate analysis are listed in Table 7.14. The strongest predictor of strength was arm muscle area, accounting for 43% of the variance with patient age accounting for a further 11%.

7.5 Discussion

In this work, the cancer group had both increased subjective weakness/fatigue and reduced objective strength. The inverse relationship between the weakness scale scores and the strength scale scores (see chapter 6.3) suggests that they were measuring opposites, i.e., that patients regarded weakness as loss of strength. However, in this work, there was no direct relationship established between subjective weakness and any of the measures of objective physical strength, nor between subjective strength and objective strength. Correlations between both fatigue scales and handgrip strength were weak.

It has been suggested that reduction in physical strength is an important part of fatigue and that this component of fatigue might be considered as weakness (Glaus et al., 1996). In the present work, objective strength was reduced and subjective weakness/fatigue was increased in the patient group, compared with the healthy control group. However, it would appear that the relationship between subjective weakness/fatigue and objective strength is not strong. This would indicate that a distinction must be drawn between the patient's own experience and what can be objectively measured. As Portenoy (1998) suggests, we must not wait for objective evidence of muscle weakness, before we believe the patient's complaint of weakness. Indeed, some patients in the present work had high weakness/fatigue scores and yet had normal strength measurements, compared with the healthy group. The implication of these findings may be that attempts to improve physical strength *per se* may not actually improve the patient's symptoms of weakness.

The significant relationships between the different strength measures suggest that, in this group of patients, when strength is lost compared to baseline, it is lost in different muscle groups at the same time. MRC muscle strength, although at times giving a rough impression of muscle strength, appears less sensitive in picking up change than handgrip strength or quadriceps strength. Dominant handgrip strength was measured in all patients, unlike the isokinetic and isometric dynamometry which would not have been tolerated by all patients.

During the course of the study it became clear that there were conflicting opinions as to whether dominant or non-dominant handgrip strength should be used. It is argued that dominant handgrip strength may allow those with manual occupations to have an advantage by virtue of a training effect in that hand (Buchner et al., 1993; Burman and Chamberlain, 1996). However, this is far from clear and McMurdo and Burnett (1992) used dominant handgrip strength in their study of elderly patients. Later assessments in the present study included a measure of non-dominant handgrip strength. The strength of the correlation between dominant and non-dominant strength and the fact that the dominant value was consistently and statistically significantly higher than the non-dominant value across the patient group, is strong evidence that dominant handgrip strength is a perfectly acceptable test in cancer patients. It also allowed comparison with dominant isokinetic/isometric quadriceps strength.

The failure of the electrical stimulation component of the study to give information about the voluntary and non-voluntary components of quadriceps muscle strength is disappointing. The stimulation technique did produce twitches during isometric testing in the majority of the healthy group, but not as consistently in the patient group. This

may be because of lower tolerance of the patients to the stimulus delivered and, therefore, the current could not be increased to a level both comfortable to the patient and high enough to produce visible twitches on the force tracing. In those patients and volunteers for which the technique did produce twitches on sub-maximal muscle contractions, the voluntary maximum force tracings produced showed no twitches, suggesting that these subjects were fully activating their muscles.

In some patients during isokinetic testing, there were consistent dips in the force tracing after the angle of stimulation (Figure 7.1). It is likely that the dips indicate that stimulation has occurred, the dip caused by a combination of factors, including the surprise of the stimulus and the refractory period of multiple motor units synchronised during the stimulus. The refractory period is the period after electrical stimulation, when the muscle fibres are insensitive to further stimulation and lasts about 1 to 3 milliseconds (Ganong, 1981a). Negative feedback from inhibitory neurones which synapse on to the original motor neurone and other motor neurones, briefly stopping the neuronal electrical discharge, may have been another factor (Ganong, 1981b).

Due to the type of patient, the time constraints of the study and the number of other tests carried out at the same time, it was impractical to arrange for a pre-test familiarisation session on the machine. However, a recent study in healthy students, using similar methods to those adopted in this study, has reported that it is possible to achieve consistent angle of peak force and twitches in motivated subjects who are familiar with the technique (Coogans and Deighan, 1998). It may be that this technique is worthy of further study in this patient group, although some of the difficulties encountered in this

study will need to be considered. It is clearly important that any future work considers patient acceptability.

The cancer group performed significantly less well in all the functional tests than the healthy subject group, despite the cancer patients completing the stair and walking tests being significantly younger than the healthy group. Given that strength and function are both known to decline with age (Aniansson et al., 1980; Kallman et al., 1990) and, all other things being equal, one might expect the younger group to perform better than the older group. The fact that the younger, cancer, group performed less well emphasises how poorly the cancer patients did in these tests. The cancer group as a whole performed less well in the walking tests and may have been limited in part by their increased symptom burden, compared with the healthy group.

The use of timed tests has been questioned (Gillies et al., 1999), as one might argue that what is important is safe completion of a task, not how quickly the patient performs it. However, the more time that individual tasks take, the greater the proportion of the day that will be taken up by doing those tasks. Consequently, more effort will be expended on activity and the patient will become more tired.

Cancer patients have difficulty in performing daily activities (Rhodes et al., 1988). Cress and co-workers (1995), in research carried out in the elderly population, have previously reported a relationship between self-perceived physical function and actual performance in chair stand and walking tests. In the present study, chair stand time, triple chair rise, stair descent and 2 minute walking distance were all found to correlate significantly with a patient-assessed functioning score (the EORTC physical functioning

scale), suggesting that cancer patients are also able to assess their own level of functioning accurately. This is an observation that has not previously been reported in a cancer population.

Observer rating of patients' physical function using the Karnofsky Performance Status also correlated well with patients' own assessment of their level of function. Of the 3 measures of weakness and fatigue used in this work, the FACT-Ftg scale correlated best with both subjective assessment of function and with actual performance of activity. This may well be because the FACT-Ftg scale is a 13 item scale which not only measures subjective feelings of tiredness, weakness and fatigue, but also includes questions on performance of activity, whereas the shorter 3 item EORTC fatigue scale and the weakness linear analogue scale are primarily measuring subjective symptoms. In the present work, the relationship found here between fatigue and patient-rated function in cancer patients is consistent with previous work which reported a relationship between fatigue and physical function (Irvine et al., 1994).

There were significant relationships between handgrip strength and the chair tests, and between isometric torque and chair stand time. However, there were no other significant relationships established between the functional tests and any of the strength measures. These results are less striking than some of the results reported from research in the elderly, which have reported significant relationships between muscle strength and power and chair rising, stair climbing and walking speed (Aniansson et al., 1980; Bassey et al., 1990; Bassey et al., 1992). However, it has been observed that although strength may decline in a linear fashion, function declines quantally, i.e., loss of strength may not become apparent until the person crosses the threshold of being just able to

perform an activity to not being able to do it (Young, 1986; Loy et al., 1994). Skelton and colleagues (1995) reported that strength training in the elderly produced only a limited improvement in function. A more recent study has suggested that it is possible to improve daily functioning in the elderly by simply practising important daily activities like getting out of a chair or stair climbing (Gillies et al., 1999). If this can be extrapolated to cancer patients, it may be that strength training in cancer patients may be less useful than training patients to perform specific important functional activities.

The cancer patient group scored more poorly on almost all of the individual scales of the EORTC quality of life questionnaire, indicating a self-assessed poor level of functioning and high symptom burden. The weakness and fatigue scales all correlated with the global quality of life measure on the EORTC questionnaire, suggesting that these symptoms do indeed impact on patients' overall quality of life. Many of the symptom scales were also related to the weakness and fatigue scores, suggesting either that weakness and fatigue are symptoms that tend to co-exist with other symptoms in this patient group, or that these symptoms are important in the aetiology of weakness and fatigue, or that both are correct. In the multiple regression analyses for the weakness and EORTC fatigue scales, pain and dyspnoea explained some of the variance in the scores and would appear to be important symptoms related to fatigue. This is consistent with previous work by Stone and colleagues (1999).

There was a greater level of psychological distress in the cancer group compared to the healthy group. Around a quarter of the patients scored within the range for diagnosis of clinical depression, which is comparable to other studies in this population (Vachon, 1998; Lloyd-Williams, Friedman and Rudd, 1999). Other studies have found lower

levels of depression, although similar levels of anxiety (Maher et al., 1996). It is of interest that patients completing the HAD scale often scored the "I feel slowed down" question (question 8) with the highest or second highest score. The questionnaire was originally designed to be free of somatic symptoms (Zigmond and Snaith, 1983) and this question was designed to pick up slowing of the affect. However, in this patient group, many patients are physically slowed down because of their illness and may well have rated this question accordingly. Thus, depression scale scores may be artificially elevated in this study. However, the depression scores were more strongly related to the other parameters than the anxiety scores in this study. Those with presumed clinical depression (scores greater than 10) scored more highly on the weakness and fatigue scales and had lower handgrip strength. Even when question 8 was excluded from the depression score, depression was still, by far, the strongest predictor of fatigue on the FACT-Ftg scale on multivariate analysis. Depression score was also related to performance status, the functional tests, the EORTC global quality of life scale and many of the symptom scales. It is difficult to determine from this study as to whether depression leads to poorer quality of life, strength and function or whether poorer strength and function leads to poorer quality of life and psychological distress. However, it is clear that depression is a very important correlate of fatigue. Longitudinal data may help to disentangle these relationships.

With reference to the cancer patients, the weight-losing group had lower handgrip strength and performed less well in both the chair and stair tests, but not the walking test. As previously reported in chapter 6, mid-thigh circumference was reduced in the weight-losing group (Table 6.8). Therefore, the poorer performance in the chair and stair tests in the weight-losers may, in part, have been due to loss of muscle bulk in the thigh

muscles, as the quadriceps is important in the activities of rising from a chair and climbing stairs (St. Pierre et al., 1992). Although there was no similar reduction in mid-arm circumference that might explain the reduced handgrip strength in weight-losers, arm muscle area was clearly the strongest predictor of handgrip strength on multivariate analysis. This would suggest that arm muscle mass is an important factor in determining handgrip strength in patients with advanced cancer. This is consistent with previous work in the elderly population (Larsson et al., 1979; Frontera et al., 1991). Muscle strength is known to decline with age (Kallman et al., 1990) and increasing age was also an important factor in reduced handgrip strength in this patient group.

It is also known that in cancer patients type 2 muscle fibres are lost preferentially and these are the fibres involved in activities such as standing up from a chair and using the stairs (Warmolts et al., 1975; Gomm et al., 1990). As the quadriceps is involved in these activities, but plays less of a role in walking (Moore, 1985), this may explain the similar walking distances in the two cancer groups in the face of clear differences for the other functional tests.

Both weight-stable and weight-losing patients had poor levels of functioning, as rated by the EORTC questionnaire. Although the median values in all the functional scales were lower in the weight-losing group, only the physical functioning scale was scored significantly more poorly. It is possible that the patients regarded ability to perform physical tasks as more important than other aspects of function. However, the physical functioning scale is the only one of the functional scales rated as a Yes/No alternative with the other functional scales graded 1-4, which may have influenced the results. The weight-losers had an increased symptom burden, compared to the weight-stable patients,

with more bowel dysfunction, nausea and vomiting, pain and anorexia and poorer sleep. Weight-losers also had significantly more psychological distress than the weight-stable patients.

Although the weight-stable and weight-losing cancer groups were both poorer at the functional tests, compared with the healthy subjects, and also had scored more poorly on the global quality of life scale, the relationship between these variables does not seem linear. This, in conjunction with the poor EORTC function scale scores in both cancer groups, adds weight to the concept that quality of life is a multi-dimensional phenomenon and is not purely related to physical ability.

In summary, this study has shown that cancer patients have reduced physical strength, poorer performance in activities of daily living and also poorer self-perceived physical function. Loss of weight, and muscle in particular, seems important in the aetiology of reduced strength in this patient group. Loss of muscle bulk and loss of type 2 muscle fibres may be important factors in determining loss of function. There was no clear relationship established between objective physical strength and objective function, suggesting that perhaps to focus on training patients in specific functional tasks may be a better approach to rehabilitation than generalised strength training. Similarly to the findings for weakness and fatigue in chapter 6, there is a spectrum ranging from normal muscle strength, good function, good quality of life and low levels of psychological distress in the healthy population, through to weight-stable cancer patients with modest derangements, and then to poor levels of strength and function, increased symptom burden and high levels of psychological distress in the weight-losing cancer patients.

The FACT-Ftg scale appears good at not only measuring fatigue, but also at describing abilities to perform activities of daily living. It was also clear from the study that handgrip strength and the chair tests were straightforward tests tolerated by most of the cancer patients and with the advantage of being portable. They were also sensitive to differences across the study groupings. The relationships between high levels of weakness and fatigue, high levels of symptom and psychological distress and poor performance in functional tests remain unclear, and although they tend to co-exist, the relationships may not be causal. However, depression seems to be the most important single factor related to fatigue. Longitudinal assessments may shed more light on these issues. In order to develop interventional strategies to improve function, further study of the relationships between strength and function is merited.

Table 7.1 Baseline Data for Handgrip Strength, Isokinetic Quadriceps Torque and Isometric Quadriceps Torque in Healthy Subjects and Cancer Patients

	Healthy Subjects (n=15)	Cancer Patients (n=23)	p-value
Dominant Handgrip Strength (kgW)	28.5 (20.0-49.0)	21.0 (6.5-51.0)[a]	< 0.01
Non-Dominant Handgrip Strength (kgW)	28.0 (18.0-50.5)	20.5 (2.0-46.0)	< 0.05
Maximum Isokinetic Torque (Nm)	181.4 (71.9-302.4)	125.1 (62.1-223.5)	< 0.10
Maximum Isometric Torque (Nm)	185.4 (73.8-268.2)	118.9 (60.1-270.3)	< 0.05

[a] n = 68

Data presented as median and range

Table 7.2 Chair, Stair and Walking Tests in Healthy Subjects and Cancer Patients

	Healthy Subjects (n=15)	Cancer Patients (n=21)	p-value
Chair Rise (s)	0.97 (0.81-1.60)	1.43 (0.70-6.06)[c]	< 0.001
Triple Chair Rise (s)	5.00 (3.02-10.71)	7.76 (4.38-33.30)[c]	< 0.001
Stair Ascent (s)	2.09 (1.44-2.59)	3.06 (1.75-9.28)[b]	< 0.001
Stair Descent (s)	1.66 (1.20-2.40)	2.80 (1.46-9.89)[b]	< 0.001
Two Minute Walk (m)	185 (122-214)	130 (30-194)[a]	< 0.001
Six Minute Walk (m)	566 (361-614)	395 (279-604)	< 0.001

[a] n =39; [b] n =44; [c] n =57

Data presented as median and range

Table 7.3 Spearman Rank Correlations Between the Functional Tests in Cancer Patients

	Chair Stand	Stair Ascent	2 minute walk	6 minute walk
Chair Stand	-	0.68**	-0.37*	0.12
Stair Ascent	0.68**	-	-0.72**	-0.35
2 minute walk	-0.37*	-0.72**	-	0.94**
6 minute walk	0.12	-0.35	0.94**	-

Values listed are r-values

* $p < 0.05$
** $p < 0.001$

All other correlations were not significant

Table 7.4 EORTC QLQ-C30 Quality of Life Scores in Healthy Subjects and Cancer Patients

	Healthy Subjects (n=15)	Cancer Patients (n=65)	p-value
Functional Scales:			
Physical	100 (60-100)	40 (0-100)	< 0.001
Role	100 (66.67-100)	50 (0-100)	< 0.001
Emotional	100 (66.67-100)	70.8 (0-100)	< 0.001
Cognitive	83.3 (66.7-100)	75 (16.7-100)	< 0.01
Social	100 (66.7-100)	66.7 (0-100)	< 0.001
Quality of Life	83.3 (66.7-100)	50 (0-100)	< 0.001
Symptom Scales			
Fatigue	0 (0-33.3)	55.6 (0-100)	< 0.001
Nausea & Vomiting	0 (0-16.7)	16.7 (0-100)	< 0.01
Pain	0 (0-50)	33.3 (0-100)	< 0.01
Dyspnoea	0 (0-33.3)	33.3 (0-100)	< 0.001
Sleep	0 (0-33.3)	33.3 (0-100)	< 0.05
Appetite	0	33.3 (0-100)	< 0.001
Constipation	0 (0-33.3)	33.3 (0-100)	< 0.01
Diarrhoea	0 (0-33.3)	0 (0-100)	NS
Financial	0	0 (0-100)	< 0.001

NS = Not Significant

Data presented as median and range

Table 7.5 Hospital and Anxiety and Depression Scale in Healthy Subjects and Cancer Patients

	Healthy Subjects (n = 15)	Cancer Patients (n=63)	p-value
Anxiety Subscale	2 (0-10)	7 (0-17)	< 0.001
Depression Subscale	1 (0-5)	8 (1-18)	< 0.001

Data presented as median and range

Table 7.6 Baseline Handgrip Strength, Chair, Stair and Walking Tests in Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=24)	Weight-Losing (n=14)	p-value
Handgrip Strength (kgW)	23.3 (10.0-44.0)[d]	19.3 (6.5-51.0)[c]	< 0.05
Chair Rise (s)	1.33 (0.7-4.9)[c]	1.61 (0.8-6.06)[b]	< 0.01
Triple Chair Rise (s)	7.19 (4.38-33.30)[c]	9.07 (4.76-23.85)[b]	< 0.01
Stair Ascent (s)	2.76 (1.75-8.75)	3.56 (2.06-9.28)[a]	< 0.01
Stair Descent (s)	2.31 (1.46-7.94)	3.03 (1.70-9.89)[a]	< 0.01
Two Minute Walk (m)	130 (30-160)	127 (70-194)	NS

[a] n = 20; [b] n = 25; [c] n = 32; [d] n = 36

NS = Not Significant

Data presented as median and range

Table 7.7 EORTC QLQ-C30 Quality of Life Scores in Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=35)	Weight-Losing (n=30)	p-value
Functional Scales			
Physical	60 (0-100)	40 (0-80)	< 0.01
Role	50 (0-100)	33.3 (0-100)	NS
Emotional	75 (25-100)	66.7 (0-100)	NS
Cognitive	83.3 (16.7-100)	66.7 (16.7-100)	NS
Social	66.7 (16.7-100)	50 (0-100)	NS
Quality of Life	58.3 (0-100)	50 (0-100)	NS
Symptom Scales			
Fatigue	55.6 (0-88.9)	61.1 (11.1-100)	< 0.10
Nausea & Vomiting	0 (0-66.7)	16.7 (0-100)	< 0.05
Pain	16.7 (0-100)	33.3 (0-100)	< 0.05
Dyspnoea	33.3 (0-100)	33.3 (0-100)	NS
Sleep	0 (0-100)	33.3 (0-100)	0.05
Appetite	0 (0-100)	33.3 (0-100)	< 0.05
Constipation	0 (0-100)	33.3 (0-100)	< 0.01
Diarrhoea	0 (0-66.7)	0 (0-100)	< 0.01
Financial	0 (0-100)	0 (0-33.3)	NS

NS = Not Significant

Data presented as median and range

Table 7.8 Baseline Data for Hospital Anxiety and Depression Scale in Weight-Stable and Weight-Losing Cancer Patients

	Weight-Stable (n=33)	Weight-Losing (n=30)	p-value
Anxiety Subscale	6 (0-13)	8 (0-17)	< 0.05
Depression Subscale	6 (1-13)	9 (2-18)	< 0.05

Data presented as median and range

Table 7.9 Spearman Rank Correlations between Weakness and FACT-Ftg Scales, Strength Tests, Performance Status and Function in Cancer Patients

	Physical Functioning Scale	KPS	Chair Stand	Triple Chair Rise	Stair Ascent	Stair Descent	2 Minute Walk
Physical Functioning Scale	-	0.69***	-0.51***	-0.46***	-0.29	-0.37*	0.38*
KPS	0.69***	-	-0.63***	-0.47***	-0.50**	-0.53**	0.44**
Weakness Scale	- 0.34**	-0.35**	0.41***	0.20	0.10	0.21	-0.12
FACT-Ftg Scale	0.65***	0.61***	-0.48***	-0.33*	-0.12	-0.17	0.39*
Handgrip Strength	0.25*	0.51***	-0.29*	-0.32*	-0.25	-0.29	0.14
Isometric Torque	0	-0.15	-0.49*	-0.42	0.30	0.30	0

Values listed are r-values

KPS = Karnofsky Performance Status

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

All other correlations were not significant

Table 7. 10 Spearman Rank Correlations Between Weakness and FACT-Ftg Scales, Handgrip Strength, Function, EORTC QLQ-C30 and the HAD Scale in Cancer Patients

	Weakness Scale	FACT-Ftg Scale	Handgrip Strength	Chair Stand	Triple Chair Rise	2 minute walk	Depression
KPS	-0.35**	0.61***	0.51***	-0.63***	-0.47***	0.44**	-0.67***
Global Quality of Life	-0.39**	0.51***	0.11	-0.30*	-0.22	0	-0.51***
Pain	0.39**	-0.40**	0	0.32*	0.35**	-0.23	0.33**
Dyspnoea	0.19	-0.41**	-0.11	0.21	0.20	-0.38*	0.34**
Sleep	0.29*	-0.34**	-0.34	0.15	0	-0.31	0.48***
Appetite	0.15	-0.36**	-0.20	0.35**	0.31*	-0.17	0.35**
Anxiety	0.22	-0.52***	-0.14	0.20	0.18	-0.15	0.43***
Depression	0.44***	-0.69***	-0.49***	0.48***	0.33*	-0.51***	-

KPS = Karnofsky Performance Status

Values listed are r-values

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

All other correlations were not significant

Table 7.11 Relationships With Weakness Scale on Univariate and Multivariate Analysis in Cancer Patients

	Univariate (p-value)	Multivariate (p-value)
Weight Loss	< 0.05	0.11
Mid-Thigh Circumference	< 0.05	0.25
Emotional Functioning	< 0.05	0.58
Nausea & Vomiting	< 0.05	0.71
Pain	< 0.01	0.18
Depression	< 0.001	< 0.05

Table 7.12 Relationships With FACT-Ftg Scale on Univariate and Multivariate Analysis in Cancer Patients

	Univariate (p-value)	Multivariate (p-value)
Weight Loss	< 0.01	0.13
Triceps Skinfold Thickness	0.05	0.38
Mid-Arm Circumference	< 0.05	0.76
Handgrip Strength	< 0.05	0.38
Haemoglobin	< 0.05	0.96
White Cell Count	< 0.05	0.56
Albumin	< 0.01	0.65
Emotional Functioning	< 0.001	0.80
Cognitive Functioning	< 0.01	0.83
Social Functioning	< 0.01	0.18
Pain	< 0.01	0.36
Dyspnoea	< 0.01	0.81
Appetite	< 0.01	0.92
Constipation	< 0.01	0.35
Anxiety	< 0.001	0.26
Depression	< 0.001	< 0.001

Table 7.13 Relationships With EORTC Fatigue Scale on Univariate and Multivariate Analysis in Cancer Patients

	Univariate (p-value)	Multivariate (p-value)
Handgrip Strength	< 0.05	0.72
White Cell Count	< 0.01	0.31
Albumin	< 0.01	0.83
Calcium	< 0.05	0.35
C-Reactive Protein	< 0.01	0.63
Emotional Functioning	< 0.001	0.14
Cognitive Functioning	< 0.01	0.41
Social Functioning	< 0.001	0.29
Pain	< 0.01	0.27
Dyspnoea	< 0.001	0.14
Constipation	< 0.05	0.69
Anxiety	< 0.01	0.52
Depression	< 0.001	0.12

Table 7.14 Relationships With Handgrip Strength on Univariate and Multivariate Analysis in Cancer Patients

	Univariate	Multivariate
Age	< 0.001	< 0.01
Current Body Mass Index	< 0.001	0.51
Mid-Arm Circumference	< 0.001	0.50
Arm Muscle Area	< 0.001	< 0.05
Mid-Thigh Circumference	< 0.001	0.12
Thigh Muscle Area	< 0.001	0.20
FACT-Ftg	< 0.05	0.44
EORTC Fatigue	< 0.05	0.61
Constipation	< 0.01	0.17
Depression	< 0.001	0.20
Albumin	< 0.01	0.36

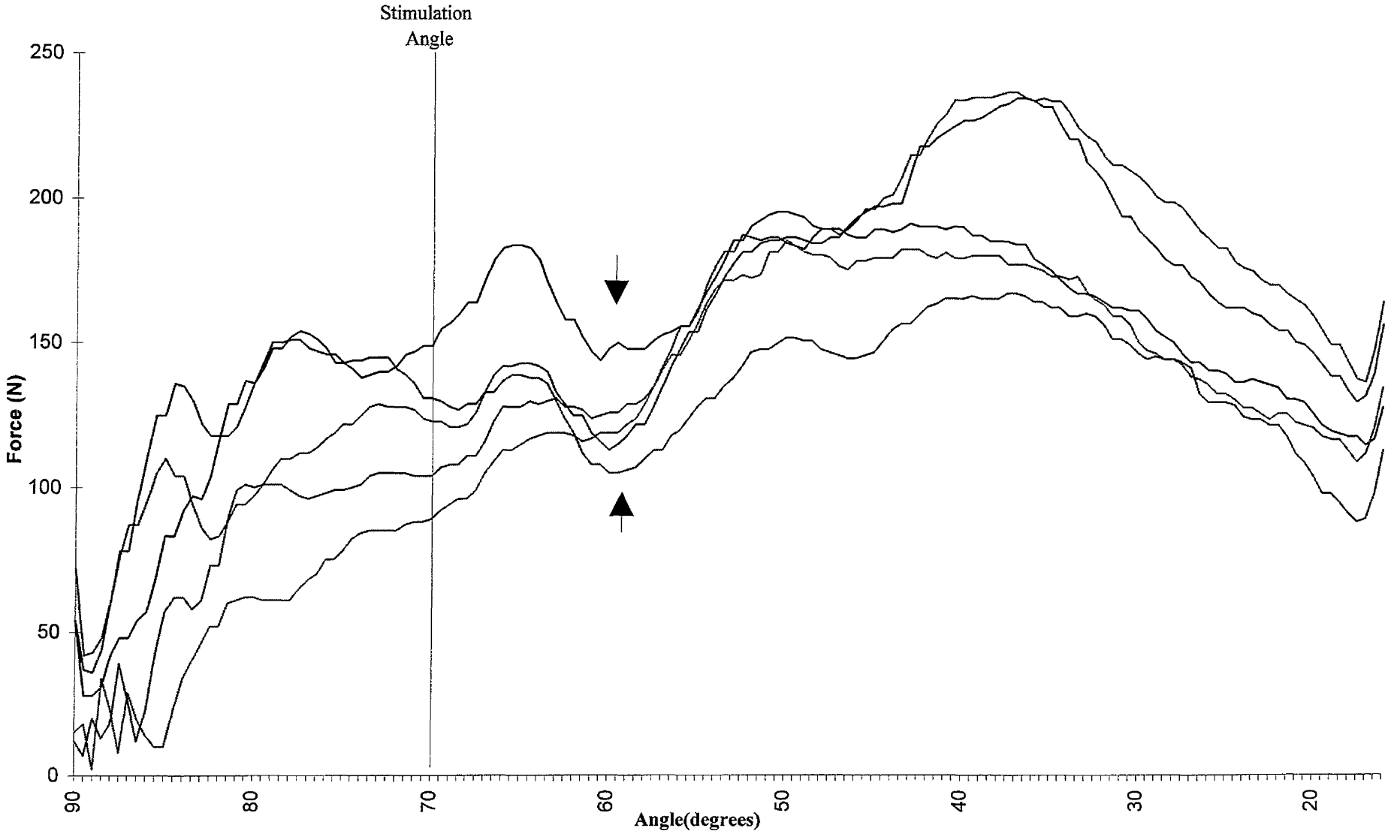
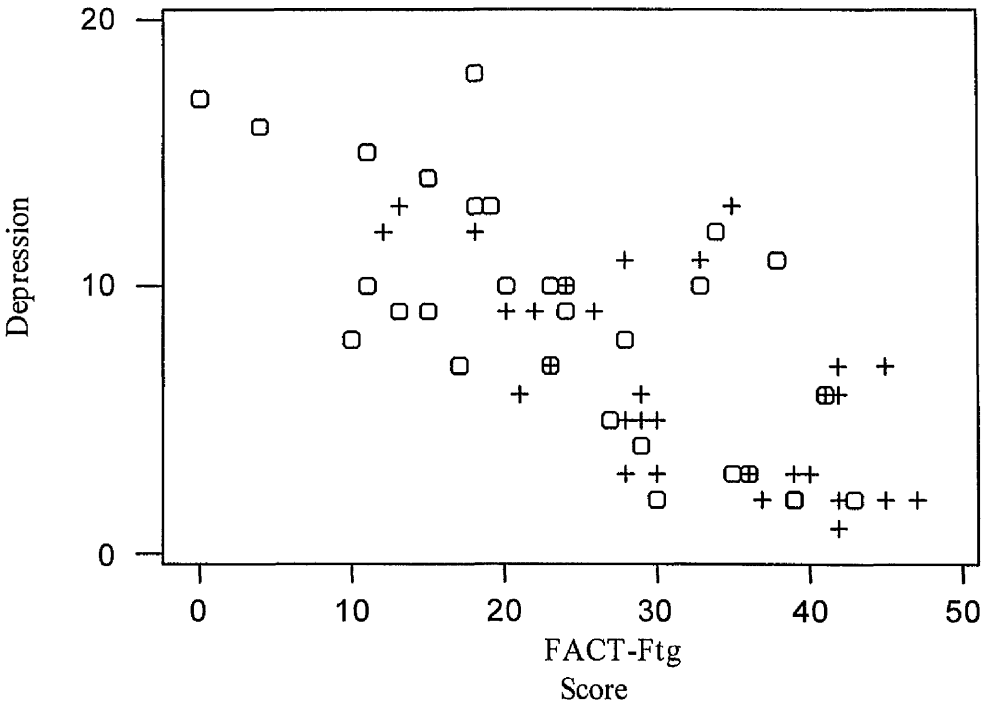


Figure 7.1 Isokinetic Force Tracings With Electrical Stimulation Angle Shown Small arrows show post-stimulation refractory period

Figure 7.2 Isometric Force Tracings With Twitches Shown

Arrows indicate twitches

Figure 7.3 Plot of FACT-Ftg Scores Against Depression Scores



O = Weight-Losing Patients
+ = Weight-Stable Patients

$r = -0.69 \quad p < 0.001$

CHAPTER 8: LONGITUDINAL STUDY OF WEIGHT LOSS, STRENGTH, FUNCTION, WEAKNESS AND FATIGUE, THE INFLAMMATORY RESPONSE AND QUALITY OF LIFE IN PATIENTS WITH ADVANCED CANCER

8.1 Introduction

As has previously been described in chapters 6 and 7, weakness and fatigue are common symptoms in patients with advanced cancer and they are commoner in patients who have lost weight. Weight-losing patients also have reduced muscle strength, compared with weight-stable patients, as well as increased difficulty in performing the activities of daily living. Weight-losing patients have increased psychological distress and poorer quality of life, and these factors seem related to the experience of weakness and fatigue. The presence of weight loss is associated with an inflammatory response, including a raised white cell count and elevated C-reactive protein concentrations.

The studies described in chapters 6 and 7 provide snapshot data regarding the continuum which appears to exist from healthy subjects to weight-stable and weight-losing cancer patients. However, such studies have limitations as it is difficult to establish the temporal nature of the relationships between these variables. There are few longitudinal studies in patients with advanced cancer, due to the inevitable attrition rate encountered.

O'Gorman, McMillan and McArdle (1999) reported that as patients with advanced gastrointestinal cancer continue to lose weight, so Karnofsky Performance Status

declines, triceps skinfold thickness falls and C-reactive protein concentrations rise. In addition, they reported that those patients who gained weight over the follow-up period had significantly lower initial C-reactive protein and significantly higher initial albumin concentrations than those who subsequently lost weight.

In the following study, the longitudinal relationships between weight loss, strength, function, performance status, weakness and fatigue, the inflammatory response and quality of life was studied in a group of patients with advanced cancer and in a group of healthy age and sex matched controls.

8.2 Material and Methods

The patients and healthy controls studied were those previously described in chapter 7. Questionnaires, strength tests, functional tests, blood tests and tests of body composition were performed - as previously described in sections 6.2 and 7.2 - at baseline, 6 weeks, 12 weeks and 6 months in the patient group and at baseline and 12 weeks in the controls.

Data is presented as medians, with ranges. Comparisons were carried out where appropriate using Fisher's Exact test and the Mann Whitney U test and analysis of data between different time points was performed using the Wilcoxon signed rank test (SPSS Inc., Chicago, Illinois, USA).

8.3 Results

Fifteen healthy controls completed baseline measurements, as previously described in chapters 6 and 7. Of these subjects, one was unavailable for follow-up assessment at 12 weeks. There was no significant change over the 12 weeks in weight, anthropometrics, handgrip strength, functional tests, Karnofsky Performance Status, weakness and fatigue scores, anxiety and depression scores, blood parameters and EORTC quality of life scale scores (see appendices 3.18-22). However, there was a significant increase in both mid-arm circumference ($p < 0.01$) and mid-thigh circumference ($p < 0.05$), as well as a significant improvement in chair rise time ($p < 0.05$) and in isometric torque ($p = 0.05$). There was also a fall in white cell count ($p < 0.05$).

Sixty eight cancer patients completed baseline measurements, and these have previously been described in chapters 6 and 7. Of these patients, only 32 had follow-up measurements at six weeks. Of the 36 patients with no follow-up, 12 patients were either unavailable (5), refused follow-up (4), or were lost to follow-up for other reasons (3). Of the remaining 24 patients, 19 died and 5 (due to disease progression) were too unwell to undergo follow-up assessment. Of the thirty two patients with follow-up, 12 were weight-losing at baseline and 20 were weight-stable.

The baseline characteristics of the 32 patients with follow-up were compared with the baseline characteristics of the 24 patients with no follow-up due to death or disease progression (Tables 8.1, 8.2). The two groups were similar in terms of age, sex, cancer type, weight and anthropometry. The no follow-up group had lost significantly more of their healthy weight ($p < 0.05$) and had significantly lower handgrip strength ($p < 0.01$,

Table 8.3) and Karnofsky Performance Status ($p < 0.001$, Table 8.1) than the follow-up group. There were too few completed measures in the group with no follow-up to allow meaningful statistical comparison of the isokinetic and isometric dynamometry measurements.

Nine of the patients in the no follow-up group were unable to participate in any of the functional testing, while all of the patients in the follow-up group at least completed the chair stand test ($p < 0.001$). The follow-up group performed significantly better in the chair stand test ($p < 0.05$, Table 8.3) and stair descent ($p < 0.05$). Walking distances were similar between the two groups in those who had completed the 2 minute tests (see appendix 3). There were insufficient numbers in the no follow-up group for statistical comparison of the 6 minute walk distances.

The group with no follow-up had significantly more fatigue, as measured by both the FACT-Ftg scale and the EORTC QLQ-C30 questionnaire ($p < 0.001$, Table 8.4), although linear analogue scale measurements of weakness were similar. This group also had significantly higher anxiety and depression scores than the follow up group ($p < 0.05$).

The no follow-up group had significantly lower albumin ($p < 0.001$, Table 8.5), haemoglobin ($p < 0.01$), zinc ($p < 0.01$), vitamin D ($p < 0.01$), sodium ($p < 0.05$) and creatine kinase ($p < 0.05$) concentrations, as well as significantly higher C-reactive protein concentrations ($p < 0.001$) and white cell count ($p < 0.01$).

The no follow-up group scored more poorly on the physical ($p < 0.001$) and role functioning ($p < 0.01$) scales of the EORTC QLQ-C30 quality of life questionnaire. This group also had more dyspnoea ($p < 0.001$) and constipation ($p < 0.05$) and poorer appetite ($p < 0.05$).

Those 32 patients with follow-up were then grouped according to whether or not they went on to lose weight over the six weeks of study (Tables 8.7-8.9). Twenty four patients had remained weight-stable (median gain 1.0 kg over baseline weight, $p < 0.01$) and 8 patients lost weight as defined by a loss of at least 2.0 kg of their baseline weight, (median -3.3 kg, $p < 0.05$).

At baseline these two groups were not significantly different with regard to age, sex, cancer type, weight, degree of weight loss from healthy weight at study entry, anthropometry, handgrip strength, weakness and fatigue scores, anxiety and depression scores, the majority of the blood parameters and EORTC quality of life scale scores. In contrast, at baseline, the weight-losing group had a significantly lower Karnofsky Performance Status compared with the weight-stable group ($p < 0.05$). The weight-losing group, at baseline, were also slower at the chair stand ($p < 0.05$), stair ascent and stair descent ($p < 0.01$). Baseline C-reactive protein concentrations were higher ($p < 0.05$) in the weight-losing group.

In the group which remained weight-stable there was a significant improvement over the follow up period in mid-arm circumference ($p < 0.05$), arm muscle area ($p < 0.05$), chair stand (median -0.08 (-1.38 to 0.40), $p < 0.05$; see appendix 3), stair ascent (median -0.07 (-1.06 to 0.64), $p < 0.05$; see appendix 3) and FACT-Ftg score ($p < 0.05$).

In the group which lost weight there was a significant reduction in mid-arm circumference ($p < 0.05$). Too few patients completed the chair tests (n=5) or the stair tests (n=3) at the six week assessment for meaningful statistical comparison to baseline (see appendix 3.16).

Twenty three patients were followed up to 12 weeks (See Appendices 3.23-27). Of the thirty two patients who had follow-up measurements performed at 6 weeks, 2 were unavailable, 2 declined any further follow-up, one had died and 4 (due to disease progression) were too unwell to undergo further assessment. Of the twenty three patients, 9 were in the weight-losing group at baseline and 14 were in the weight-stable group. When these patients were grouped according to whether or not they had lost weight over the 12 weeks of study, 18 patients had remained weight-stable and only 5 had lost weight. Due to the small number of patients in the weight-losing group, no further statistical analysis was carried out.

Seventeen patients were followed up to 6 months (see Appendices 3.28-3.32). Of the twenty three patients who had follow-up measurements performed at 12 weeks, one declined any further follow-up, 3 had died and 2 (due to disease progression) were too unwell to undergo further assessment. Of the seventeen patients, 5 were in the weight-losing group at baseline and 12 were in the weight-stable group. When the patients were grouped according to whether or not they subsequently lost weight, there were only 3 patients who had lost weight and therefore no further statistical analysis was appropriate.

8.4 Discussion

In this study, a group of patients with advanced cancer was followed up over a period of 6 months. Only 47% of the original patient group could be followed up to 6 weeks, with this proportion falling to 34% at 12 weeks and only 25% at 6 months. This attrition rate is typical of other longitudinal studies in this patient group (McMillan et al., 1999; Stone et al., 1999) and explains why such studies are uncommon. In contrast, only one healthy subject had dropped out of the study at 12 weeks due to unavailability.

The healthy subjects appeared to remain well over the 12 week study period, with no significant alterations in physical, psychological, biochemical and quality of life parameters. There were improvements in limb circumferences, perhaps reflecting the fact that the 12 week assessments for the healthy subjects were mainly carried out in the summer, when they were likely to be more active and have a greater muscle bulk. This may also explain the improvements in isometric torque and in the chair rise test, although this may also reflect increased familiarity with the tests, an observation previously reported by Gillies and colleagues (1999).

In the published literature, there do not appear to be studies which have compared the baseline characteristics of cancer patients followed up longitudinally, with those who were not followed up due to death or disease progression. Nevertheless, it is clear that the no follow-up group in this study are different to the follow-up group in a number of ways.

The no follow-up group appear to have been at a more advanced stage in their disease process. They had lost a greater proportion of their healthy weight prior to the study, compared to the follow-up group. They had poor subjective physical functioning and observer-rated performance status, as well as being poorer at carrying out the activities of daily living. They also had reduced handgrip strength. Fatigue and psychological distress were greater in this group, compared with the follow-up group. The no follow-up group had a greater symptom burden and were more anaemic. This group also had more deranged biochemistry, with poorer nutritional parameters and a more marked inflammatory response.

In the present study, patients who subsequently lost weight over 6 weeks of follow-up had poorer Karnofsky Performance Status and performed more poorly in the chair and stair tests at baseline. At baseline, degree of weight loss from healthy weight and muscle bulk were not significantly different between the weight-stable and weight-losing groups and there was no correlation between degree of weight loss from healthy weight and performance status, or with performance in any of the functional tests. Therefore, neither weight nor muscle bulk are likely to be the only determinants of functional ability. Weight loss and deterioration in functional ability are both likely to be related to disease progression. Only 62% of the group which lost weight over 6 weeks were able to complete the chair tests at follow-up and only 50% were able to complete the stair tests. Although there was a reduction in mid-arm circumference in the weight-losing group after 6 weeks, there was no reduction in arm muscle area, nor in mid-thigh circumference. Therefore, loss of muscle bulk appears unlikely to be the main reason for this inability to participate in the functional tests. As has previously been discussed in chapter 7, patient performance in functional tests may decline to the point where there is

a transition from being just able to perform an activity to being just unable to perform that activity (Young, 1986). Poor function may, therefore, relate to advancing disease where the threshold is crossed from disability to inability. It is possible that the sequence of events may be reduced muscle strength, leading to reduced activity and muscle disuse, followed by a loss of function.

The group which remained weight-stable improved in the chair rise and stair ascent tests. Although there was a significant gain in weight and in mid-arm circumference and area, there was no gain in thigh circumference, suggesting that the improvement was unlikely to relate merely to increased muscle bulk. The improvement may have been related partly to improved muscle function and, as with the healthy group, part of the improvement may have been due to increased familiarity with the test.

This study found no change in performance status over time. Previous work has reported a fall in Karnofsky Performance Status with continued weight loss (O'Gorman et al., 1999). However, the degree of weight loss between the weight-stable and weight-losing groups at 6 weeks in the present study was less than that reported by O'Gorman and colleagues. Nevertheless, the results of the present study suggest that simple functional tests are more sensitive indicators of decline than observer-rated performance status. They also suggest that it may be possible to maintain function if weight loss can be prevented. Although weight and function are not directly related, the weight-losing group are more unwell and also functionally impaired. Therefore, prevention or slowing of weight loss may contribute to the prolongation of normal function. It could be that slowing of weight loss and of general physical deterioration may lead to increased activity levels, followed by an improvement in level of functioning.

The weight-stable group were also less fatigued at 6 weeks than at baseline, suggesting that future strategies aimed at maintaining weight may have some impact on fatigue. Fatigue is unlikely to be purely related to weight loss, as the weight-losing group was not more fatigued after 6 weeks, although numbers were small. As reported in chapter 6 weight loss and fatigue tend to co-exist and probably relate to disease progression. It was of note that there was no change in depression scores. Given that fatigue and depression are strongly related (see chapter 7), it would seem more likely that depression comes after fatigue and relates to increasing illness and disability of which fatigue is an important feature. If depression had been the most important cause of fatigue, one would have expected a change in both fatigue and depression at follow-up. Larger studies may help to clarify this issue. There was no change in the weakness score in either group, suggesting that a simple linear analogue scale measure is less sensitive to change than a multi-item questionnaire, such as the FACT-Ftg scale.

The group which lost weight had higher C-reactive protein concentrations than the weight-stable group at baseline. Similar results have been recently reported (O'Gorman et al., 1999). Although O'Gorman and colleagues reported further changes in C-reactive protein over time, the results of the present study are consistent with the concept that the presence of an inflammatory response is associated with weight loss and impaired nutritional status. The inflammatory response is also likely to relate to poor prognosis.

In summary, the control group validated the use of the various measures carried out in this study, in that there was little or no change over time. Those patients who were not followed up, due to death or disease progression, had performed or scored less well in a large number of the tests compared to the follow-up group, suggesting that these

measures may be predictive of future outcome. The group which remained weight-stable at follow-up behaved in a similar way to the control group, in that there was little change, or a tendency to improvement with time. In contrast, although there were few statistically significant changes over time in the group which lost weight, this group was clearly becoming less able to perform activities of daily living and had a poorer nutritional status. In addition, these changes were preceded by detectable differences in Karnofsky Performance Status, the functional tests and the inflammatory response. This study highlights the importance of monitoring change in patients with advanced cancer and gives some indication of likely therapeutic targets, e.g., weight, patient functional ability and the inflammatory response. Moreover, monitoring of fatigue levels in patients who either lose or maintain weight may give a better picture of the pattern of fatigue development and whether any therapeutic interventions may reduce patient experience of fatigue.

Table 8.1 Baseline Characteristics in Cancer Patients With and Without Follow-Up at 6 Weeks

	No Follow-up (n=24)	Follow-up (n=32)	p-value
Sex (M/F)	17/7	18/14	NS
Age	69 (38-81)	62 (43-79)	< 0.10
Healthy Weight (kg)	66.8 (45.3-114.3)	63.5 (44.5-101.5)	NS
Current Weight (kg)	58.5 (39.8-85.0)	55.9 (39.0-95.0)	NS
Amount of Weight Loss	12.3 (-4.5-36.3)	6.0 (-18.8-18.0)	< 0.05
Healthy BMI (kgm^{-2})	25.0 (16.8-40.0)	23.8 (15.9-36.0)	NS
Current BMI (kgm^{-2})	20.1 (15.2-29.9)	21.7 (14.8-33.3)	NS
Karnofsky Performance Status	58 (25-80)	78 (50-100)	< 0.001
<u>Cancer Types</u>			
Lung	13	20	NS
Mesothelioma	3	1	NS
Gastrointestinal	7	4	NS
Hormone Dependent	0	5	NS
Others*	1	2	NS

* = One patient each with Non-Hodgkin's lymphoma, cerebral astrocytoma and head & neck cancer

M/F = Male/Female NS = Not Significant

Data presented as median and range

Table 8.2 Baseline Body Composition in Cancer Patients With and Without Follow-Up at 6 Weeks

	No Follow-up (n=22)	Follow-up (n=30)	p-value
Total Body Water (l)	26.7 (21.9-37.7)	27.8 (17.3-41.0)	NS
Triceps Skinfold Thickness (mm)	10.0 (3.5-24.5)	9.5 (3.0-33.5)	NS
Biceps Skinfold thickness(mm)	6.0 (2.5-20.5)	6.0 (2.0-14.5)	NS
Thigh Skinfold Thickness(mm)	13.8 (4.0-36.5)	11.5 (3.5-29.5)	NS
Mid-Arm Circumference(cm)	24.1 (17.6-36.4)	25.2 (17.1-37.0)	NS
Arm Muscle Area (cm^2)	34.7 (20.7-65.6)	36.6 (19.6-76.7)	NS
Mid-Thigh circumference (cm)	42.0 (32.3-52.5)	45.1 (32.5-66.3)	< 0.10
Thigh Muscle Area (cm^2)	133.3 (76.7-184.4)	130.4 (73.1-294.4)	< 0.10

NS = Not Significant

Data presented as median and range

Table 8.3 Baseline Handgrip Strength and Functional Tests in Cancer Patients With and Without Follow-Up at 6 Weeks

	No Follow-up (n=11)	Follow-up (n=25)	p-value
Handgrip Strength (kgW)	17.8 (6.5-43.0)[b]	23.5 (10.0-51.0)[c]	< 0.01
Chair Stand (s)	1.80 (0.80-6.06)[a]	1.37 (0.70-3.18)[c]	< 0.05
Triple Chair Rise (s)	9.01 (5.05-33.30)[a]	7.12 (4.38-19.46)[c]	< 0.10
Stair Ascent (s)	3.78 (2.06-9.28)	2.83 (1.75-8.69)	< 0.10
Stair Descent (s)	3.36 (1.70-8.22)	2.31 (1.46-9.89)	< 0.05

[a] n = 14; [b] n = 24; [c] n = 32

NS = Not Significant

Data presented as median and range

Table 8.4 Baseline Linear Analogue Scales of Weakness and Strength, FACT-Ftg Scale and HAD Scale in Cancer Patients With and Without Follow-Up at 6 Weeks

	No Follow-up (n=23)	Follow-up (n=31)	p-value
Linear Analogue Scales			
Weakness Scale (cm)	5.0 (1.0-8.3)	4.1 (0.4-8.0)	NS
Strength Scale (cm)	4.0 (0.2-9.6)	5.1 (1.9-8.9)	NS
FACT-Ftg Scale	18 (0-39)	29 (17-47)	< 0.001
EORTC Fatigue Scale	66.7 (22.2-100)	44.4 (0-88.9)	< 0.001
HAD Scale			
Anxiety	8 (3-17)	6 (0-11)	< 0.05
Depression	11 (2-12)	6 (1-13)	< 0.01

NS = Not Significant

Data presented as median and range

Table 8.5 Baseline Blood Tests in Cancer Patients With and Without Follow-Up at 6 Weeks

	No Follow-up (n=24)	Follow-up (n=31)	p-value
Haemoglobin (g/l)	117 (91-152)	127 (101-177)	< 0.01
White Cell Count	12.5 (4.9-27.2)	8.1 (4.4-16.1)	< 0.01
Sodium (mmol/l)	136 (123-140)	137 (131-145)	< 0.05
Potassium (mmol/l)	4.4 (3.3-5.1)	4.4 (3.5-5.6)	NS
Urea (mmol/l)	6.3 (2.0-17.6)	6.4 (3.5-13.1)	NS
Creatinine (μmol/l)	82 (62-120)	78 (56-161)	NS
Albumin (g/l)	35 (23-41)	41 (32-46)	< 0.001
Creatine Kinase (IU/l)	26 (10-318)	40 (10-151)	< 0.05
Calcium (mmol/l)	2.43 (2.24-2.58)	2.37 (2.14-3.29)	NS
Magnesium (mmol/l)	0.88 (0.73-1.02)	0.87 (0.65-0.98)	NS
Zinc (μmol/l)	9.4 (5.6-11.8)	10.5 (4.7-15.8)	< 0.01
Copper (μmol/l)	22.1 (10.8-35.3)	21.8 (11.3-37.5)	NS
Vitamin D (nmol/l)	18 (<6-48)	26 (<6-128)	< 0.01
C-Reactive Protein (mg/l)	99 (12-214)	19 (2-201)	< 0.001

NS = Not Significant

Data presented as median and range

Table 8.6 Baseline EORTC QLQ-C30 Quality of Life Questionnaire Scores in Cancer Patients With and Without Follow-Up at 6 Weeks

	No Follow-up (n=22)	Follow-up (n=32)	p-value
Functional Scales:			
Physical	20 (0-60)	60 (20-100)	< 0.001
Role	33.3 (0-83.3)	50 (0-100)	< 0.01
Quality of Life	50 (0-100)	66.7 (25-100)	< 0.10
Symptom Scales			
Fatigue	66.7 (22.2-100)	44.4 (0-88.9)	< 0.001
Nausea & Vomiting	16.7 (0-100)	0 (0-83.3)	< 0.10
Pain	33.3 (0-100)	25 (0-66.7)	< 0.10
Dyspnoea	66.7 (0-100)	33.3 (0-100)	< 0.001
Sleep	33.3 (0-100)	33.3 (0-66.7)	NS
Appetite	33.3 (0-100)	16.7 (0-100)	< 0.05
Constipation	33.3 (0-100)	33.3 (0-66.7)	< 0.05

NS = Not Significant

Data presented as median and range

Table 8.7 Changes in Anthropometrics, Performance Status and Strength in Weight-Stable and Weight-Losing Cancer Patients Over Six Weeks

	Weight-Stable (n=24)		Weight-Losing (n=8)	
	Baseline	Change	Baseline	Change
Weight (kg)	54.0 (39.5-91.0)	1.0 (-1.0 to 5.8)***	71.0 (39.0-95.0)	-3.3 (-8.3 to -2.0)**
Body Mass Index (kgm^{-2})	20.8 (15.3-31.0)	0.4 (-0.4 to 2.4)***	25.5 (14.8-33.3)	-1.1 (-3.1 to -0.80)**
KPS	80 (55-100)	0 (-20 to 15)	63 (50-80)	0 (-20 to 10)
TST (mm)	9.0 (3.0-25.0)	0.5 (-11.5 to 4.0)	14.5 (4.5-33.5)	-1.0 (-4.0 to 10.5)[a]
MAC (cm)	25.0 (18.1-34.0)	0.7 (-1.6 to 3.0)**	27.5 (17.1-37.0)	-1.7 (-3.9 to 0.4)**
AMA (cm^2)	34.2 (22.5-69.8)	2.4 (-6.6 to 15.4)**	41.1 (19.6-76.7)	-4.1 (-21.5 to 0.1)*
Handgrip Strength (kgW)	24.5 (10.0-44.0)	-0.5 (-4.0 to 7.0)	23.5 (14.0-51.0)	-3.3 (-14.5 to 6.0)

KPS = Karnofsky Performance Status TST = Triceps Skinfold Thickness MAC = Mid-Arm Circumference AMA = Arm Muscle Area
[a] n=6 * $p < 0.10$ vs. baseline; ** $p < 0.05$ vs. baseline; *** $p < 0.01$ vs. baseline

Table 8.8 Changes in Fatigue, Weakness, HAD Scale, EORTC Physical Function and Quality of Life in Weight-Stable and Weight-Losing Cancer Patients Over Six Weeks

	Weight-Stable (n=24)		Weight-Losing (n=8)	
	Baseline	Change	Baseline	Change
Weakness Score (cm)	4.0 (0.4-8.0)	0 (-1.7 to 5.6)	4.9 (0.9-7.5)	0.5 (-2.6 to 2.8)
FACT-Ftg Score	30 (22-47)	4 (-9 to 22)**	26 (17-43)	0 (-10 to 6)
EORTC Fatigue	44.4 (0-66.7)	0 (-33.3 to 33.3)	50 (11.1-88.9)	0 (-11.1 to 33.3)
HAD Anxiety	6 (0-11)	-1 (-3 to 4)	7 (0-11)	1 (-1 to 6)
HAD Depression	5 (1-10)	0 (-7 to 4)	7 (2-13)	0 (-1 to 5)
Physical Function	60 (20-100)	0 (-100 to 40)	40 (20-80)	-20 (-40 to 0)*
Quality of Life	66.7 (25-100)	0 (-50 to 25)	58.3 (33.3-83.3)	-12.5 (-25 to 16.7)

* $p < 0.10$ vs. baseline; ** $p < 0.05$ vs. baseline

Table 8.9 Changes in EORTC Pain, Dyspnoea and Appetite Scores, Haemoglobin, White Cell Count, Albumin, Creatine Kinase, Zinc and C-Reactive Protein (CRP) in Weight-Stable and Weight-Losing Cancer Patients Over Six Weeks

	Weight-Stable (n=24)		Weight-Losing (n=8)	
	Baseline	Change	Baseline	Change
Pain	33.3 (0-66.7)	0 (-33.3 to 50)	16.7 (0-66.7)	-16.7 (-33.3 to 50)[b]
Dyspnoea	33.3 (0-100)	0 (-33.3 to 33.3)	33.3 (0-100)	33.3 (-66.7 to 33.3)[b]
Appetite	0 (0-100)	0 (-66.7 to 66.7)	50 (0-66.7)	0 (-33.3 to 33.3)[b]
Haemoglobin (g/l)	129 (101-177)	-3 (-43 to 54)	119 (101-153)[b]	0 (-2 to 12)[b]
White Cell Count	8.1 (4.4-16.1)	0.1 (-10.0 to 10.7)	8.7 (6.2-16.1)[b]	0 (-4.8 to 8.2)[b]
Albumin (g/l)	42 (33-46)	-1 (-10 to 12)	39 (32-43)	-1 (-3 to 1)[b] *
Creatine Kinase (IU/l)	44 (19-131)	-1 (-48 to 92)	34 (13-129)	-3 (-6 to 3)[a]
Zinc (μmol/l)	10.6 (7.3-15.8)	-0.3 (-4.2 to 5.9)	10.2 (4.7-11.6)	0.8 (-3.6 to 5.3)[a]
CRP (mg/l)	9 (2-175)	2 (-157 to 161)	73 (2-169)	-17 (-144 to 13)[a]

[a] n=6; [b] n=7 * $p < 0.10$ vs. baseline

CHAPTER 9: CONCLUSIONS

Weakness and fatigue are the commonest symptoms in patients with advanced cancer. They are symptoms which have largely eluded precise definition, but have been reported to seriously affect quality of life and ability to perform basic daily activities. Reduced muscle bulk due to cancer cachexia and alteration in intrinsic muscle function have been postulated as causes of both reduced muscle strength and subjective weakness and fatigue. It has also been reported that anxiety/depression, reduced haemoglobin concentrations, altered biochemistry and the inflammatory response may contribute to weakness and fatigue. However, the relationship between subjective weakness and fatigue and objective strength in cancer patients is not clear. To date, such relationships have not been studied in cancer patients.

The first aim of the present work was to investigate the importance of weight loss, altered body composition, the inflammatory response, haematological and biochemical parameters in the experience of weakness and fatigue in patients with advanced cancer. Although the healthy control group and the cancer group as a whole were similar in terms of age, sex and pre-illness body weight, at study entry the cancer group were clearly more unwell. The cancer group had lost weight, compared with the healthy group, and this included both fat and lean tissue. Reduced limb muscle area, creatinine excretion and creatine kinase confirmed that muscle was being lost by the cancer patients. The cancer patients had a lower performance status and had significantly more weakness and fatigue, compared with the healthy control group.

Correlations between the weakness scale and the two fatigue scales suggest that weakness and fatigue tend to co-exist. Indeed, the correlations between the weakness scale and almost all the individual questions of the fatigue scales suggests that it is likely that patients use the terms weakness and fatigue synonymously.

It was of interest that patients taking benzodiazepine drugs had higher fatigue scores than those not receiving such drugs. There was no similar relationship with any of the other major drug groups implicated in the aetiology of weakness and fatigue, such as opioid drugs, corticosteroids and antidepressants.

The cancer patients were more anaemic and had lower serum sodium and vitamin D concentrations. They also had evidence of an inflammatory response, with elevated C-reactive protein concentrations and white cell count as well as raised copper concentrations and reduced albumin and zinc concentrations. It is of interest that vitamin D concentration, like other vitamins, was inversely related to the inflammatory response and, therefore, may not be a useful nutritional marker in cancer patients.

The weakness scale score, fatigue scores and reduced albumin concentrations were associated with C-reactive protein concentrations. Low albumin, anaemia and a raised white cell count were associated with fatigue severity. Follow-up data confirmed the importance of haemoglobin, white cell count, albumin and C-reactive protein concentrations, suggesting that anaemia and the inflammatory response are poor prognostic factors and may be aetiological factors in the pathogenesis of weakness and fatigue.

The weight-losing cancer group were clearly less well than the weight-stable group. The weight-losing group had lost significantly more of their pre-illness weight and had lost muscle, particularly from the thigh, compared with the weight-stable group. The weight-losing cancer patients had more weakness and fatigue and from studying the individual questions of the FACT-Ftg scale, it was clear that weight-losing patients had more difficulty in initiating activity, needed more help in activity and needed to rest more than the weight-stable patients. In longitudinal study, weight-stable patients had reduced fatigue. It may, therefore, be possible that by maintaining weight in cancer patients fatigue severity could be alleviated.

Sodium and albumin concentrations were decreased in the weight-losers and white cell count and C-reactive protein were both increased, compared with the weight-stable patients. It would appear, therefore, that the inflammatory response is associated with ongoing weight loss. Although the inflammatory response was associated with both weight loss and subjective weakness and fatigue, there was no linear relationship between degree of weight loss and the severity of weakness or fatigue.

The second aim of this work was to examine the relationships between objective tests of strength and function and measures of weakness and fatigue and patient-related quality of life in patients with advanced cancer. It was evident that the cancer patients were weaker and more fatigued and had lost physical strength compared with the healthy controls. The cancer group also had considerably more difficulty in rising from a chair, stair climbing and walking than the healthy group and had poorer levels of self-rated functioning, an increased symptom burden and poorer quality of life.

The lack of correlation between the weakness scale and the strength measures implies that when a patient complains of weakness, the presence of an objective decrement in strength cannot be assumed. Indeed, some patients rated their level of weakness as high, but had a normal grip strength. However, follow-up data suggests that both fatigue severity and reduction in handgrip strength are important factors indicating a poor prognosis in cancer patients. The cancer patients as a whole had higher levels of weakness and fatigue and lower strength than the healthy group and there were weak relationships between grip strength and both fatigue scales. However, it would appear unlikely that loss of voluntary muscle strength is the only determinant of perceived weakness and fatigue.

Handgrip strength would appear a very useful measure of strength in cancer patients and, unlike the isokinetic/isometric dynamometry, was tolerated by all the cancer patients. Handgrip strength was lower in the weight-losing patients compared with the weight-stable group. The handgrip and quadriceps strength measures were related to each other, suggesting that when strength is lost it is lost in a number of different muscle groups at the same time. These results indicate that reduction in muscle strength in cancer patients is the result of a systemic process and, presumably, is related to disease progression. However, there was no linear relationship between degree of weight loss and strength. Similarly, functional decline seemed to relate to disease progression and affected different activities at the same time.

The use of electrical stimulation to explore whether there were voluntary or central components to muscle strength in cancer patients proved difficult and produced

unreliable results. However, multivariate analysis suggested that muscle bulk, as well as age, was important in determining muscle strength.

Fatigue, as measured by the FACT-Ftg scale correlated well with patient assessed function - as measured by the physical functioning scale of the EORTC quality of life questionnaire - and with the chair tests and 2 minute walk. The weakness scale correlated with patient perceived function and the chair stand only. Grip strength and isometric quadriceps torque were both associated with performance in the chair test. Therefore, those patients who have the most difficulty in activity, and the lowest strength, have more weakness and fatigue than more able patients. There was no relationship between any of the weakness/fatigue scales and performance in the stair tests. Cancer patients were able to rate their own level of functioning accurately, and this implies that the physical functioning scale of the EORTC quality of life questionnaire may be a useful screening tool for functional ability in the palliative care setting and, unlike measures of performance status, has the advantage of being rated by the patient. The FACT-Ftg scale also contains questions on functional activity and may also provide information on cancer patient function.

The weight-losers' poorer scores in the FACT-Ftg questions on activity were confirmed by their poorer self-assessed physical function on the EORTC physical functioning scale and their poorer performance in the chair and stair tests. There was no linear relationship between objective function and the degree of weight loss.

In longitudinal study, although mid-arm circumference and muscle area increased in the group which remained weight-stable and decreased in the group which lost weight, there

was no corresponding change in handgrip strength. Although at baseline muscle bulk was determined to be important factor for handgrip strength, these results suggest that muscle bulk may not be the only determinant of muscle strength in cancer patients. However, it is possible that the change in muscle bulk was insufficient to cause a change in strength. Similarly, although the weight-stable patients improved in the functional tests, there was no corresponding increase in thigh muscle bulk. Nevertheless, it seems clear that the weight-losing group consisted of patients with poorer nutritional status and that lower handgrip strength and poorer function are symptoms of progressing disease, perhaps leading to inactivity and loss of ability.

Karnofsky Performance Status has previously been used as an indicator of functional ability in cross-sectional and longitudinal studies. However, in this work, performance status did not change over time, but performance in the various functional tests did, suggesting that the latter may be more sensitive indicators of a patient's ability to function than performance status.

Patient-rated global quality of life was correlated with fatigue, weakness, the chair stand time and depression. Therefore, it is likely that poor quality of life, in part, is the result of weakness and fatigue and poorer functioning. Depression was strongly correlated with the FACT-Ftg fatigue scale and was the strongest single predictor for fatigue on multi-variate analysis. In longitudinal study, the weight-stable cancer patients became less fatigued and yet there was no alteration in depression scores. Therefore, it is possible that, chronologically, fatigue comes first and contributes to a lowering of mood in cancer patients. Further study is necessary to further explore the relationship between fatigue and depression in this patient group.

Weight-losing patients had more severe symptoms than the weight-stable patients, with more nausea and vomiting, pain and bowel dysfunction, as well as poorer appetite and poorer sleep. Those who had lost weight also had more anxiety and depression. Many of the symptom scores of the EORTC questionnaire were correlated with the weakness and fatigue scores. The reason for this may be that cancer patients often have multiple symptoms and become increasingly symptomatic as the illness progresses, but it is also possible that other symptoms may contribute to the pathogenesis of weakness/fatigue. Pain and dyspnoea also explained some of the variance in weakness/fatigue scores on multivariate analysis, although these factors were not as strongly related as depression.

Patients who could not be followed up due to a deterioration in condition had poorer Karnofsky Performance Status, slower chair stand and stair descent, increased anxiety and depression, poorer scores on the physical functioning scale, more dyspnoea and constipation and reduced appetite compared to the group followed up to 6 weeks. These are, thus, likely to be poor prognostic factors and require further study.

In previous research in the elderly, a more striking relationship was demonstrated between strength and functional ability. However, it is clear that, from this work, cancer patients were a more rapidly changing group than the healthy elderly and this may explain the differences between the two groups. Moreover, small decrements in strength could lead to a large deterioration in function as the patient crosses the threshold of ability to inability.

Research in the elderly has suggested that functional training, i.e., practising the tasks the individual needs to perform, may be more beneficial than strength training and it may be that this approach would also be useful in the cancer population.

In conclusion, this work has confirmed that weakness and fatigue are common problems in patients with advanced cancer who are not receiving active treatment. Patients tend to use the terms weakness and fatigue synonymously. Weakness/fatigue become more severe with increasing weight loss and illness progression. Weight-losing cancer patients are more unwell than weight-stable patients and have lost muscle mass and muscle strength and are more functionally disabled. Weight-losers have poorer quality of life and are more depressed. It is evident that these parameters change together, but the longitudinal relationships between strength, function, weakness/fatigue, weight loss and quality of life require further study. The relationship between depression and fatigue is strong and the basis of this relationship warrants further investigation.

Future research is required in several areas. The relationship between objective measures of strength and ability and the subjective experience of weakness/fatigue requires to be teased out further, to establish whether there are sub-groups with either predominantly subjective symptoms or predominantly physical impairment. There is likely to be a spectrum in between these two extremes. The longitudinal relationships between strength, function, weakness/fatigue, weight loss and depression appear to be important and require further investigation. Possible areas for future intervention include the cachexia process and the inflammatory response, as it seems clear that weight-losing patients with inflammation are a group with a poor prognosis. The role of

exercise in cancer remains to be established. However, functional training in the cancer population may be an alternative, or additional, strategy to exercise.

It is clear that future research, and in particular longitudinal studies, will need to consider the issue of patient attrition, as this will remain a major challenge for any studies in the palliative care population. It will also be important that research in this area is truly multi-disciplinary and involves not only medical and nursing staff, but also physiotherapists and occupational therapists, as they will bring their own perspectives to what are complex, and important, problems for patients with advanced cancer.

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APPENDIX 1: QUESTIONNAIRES AND SCALES USED IN STUDY

Karnofsky Performance Status

Definition	%	Criteria
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires the equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled, requires special care and assistance.
	30	Severely disabled, hospitalisation is indicated although death not imminent.
	20	Hospitalisation necessary, very sick, active supportive treatment necessary.
	10	Moribund, fatal processes progressing rapidly.
	0	Dead.

EORTC QLQ-C30 (Version 2.0)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _____

Your birthdate (Day, Month, Year): _____

Today's date (Day, Month, Year): _____

	No	Yes
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2
2. Do you have any trouble taking a **long** walk?	1	2
3. Do you have any trouble taking a **short** walk outside of the house?	1	2
4. Do you have to stay in a bed or a chair for most of the day?	1	2
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2

During the past week:

	Not at all	A little	Quite a bit	Very much
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

Sample copy

During the past week:

	Not at all	A little	Quite a bit	Very much
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
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 your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

Sample copy

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

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Scoring Information for EORTC QLQ-C30 Version 2.0 Questionnaire

Functional Scales

Physical Functioning (Questions 1-5):

Add scores of Q1-Q5 and divide by number of items:

PF = (Q1+ Q2 + Q3 + Q4 + Q5)/5

Convert to 0-100 score using the equation:

100 - ((PF-1) x 100)

Role Functioning (Questions 6 & 7)

Add scores of questions 6 & 7 and divide by number of items:

RF = (Q6+Q7)/2

Convert to 0-100 score:

100- ((RF-1) x 100/3)

Emotional Functioning (Questions 21-24)

Add scores of questions 21-24 and divide by number of items:

EF = (Q21+Q22+Q23+Q24)/4

Convert to 0-100 score:

100 - ((EF-1) x 100/3)

Cognitive Functioning (Questions 20 & 25); Social Functioning (Questions 26 & 27)

Scored as Role Functioning scale

Global Health Status/Quality of Life (Questions 29 & 30)

Add scores of questions 29 & 30 and divide by number of items:

QL = (Q29+Q30)/2

Convert to 0-100 score:

(QL-1) x 100/6

Symptom Scales/Items

Fatigue Scale (Questions 10,12, 18)

FA = (Q10+Q12+Q18)/3

Convert to 0-100 scale:

(FA-1) x 100/3

Nausea & Vomiting Scale (Questions 14 & 15)

NV = (Q14+Q15)/2

Convert to 0-100 scale:

(NV-1) x 100/3

Pain Scale (Questions 9 & 19)

Scored as nausea & vomiting scale

Single Items:

Dyspnoea (Question 8):

Convert to 0-100 scale:

(DY-1) x 100/3

Sleep (Question 11); Appetite (Question 13); Constipation (Question 16); Diarrhoea (Question 17); Financial (Question 28):

All scored as dyspnoea question

FACT-Ftg (Version 3)

Below is a list of statements that other people with your illness have said are important. **By circling one number per line, please indicate how true each statement has been for you during the past 7 days.**

	not at all	a little bit	some-what	quite a bit	very much
1. I feel fatigued	0	1	2	3	4
2. I feel weak all over	0	1	2	3	4
3. I feel listless ("washed out")	0	1	2	3	4
4. I feel tired	0	1	2	3	4
5. I have trouble starting things because I am tired	0	1	2	3	4
6. I have trouble finishing things because I am tired	0	1	2	3	4
7. I have energy	0	1	2	3	4
8. I am able to do my usual activities	0	1	2	3	4
9. I need to sleep during the day	0	1	2	3	4
10. I am too tired to eat	0	1	2	3	4
11. I need help doing my usual activities	0	1	2	3	4
12. I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
13. I have to limit my social activity because I am tired	0	1	2	3	4

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HAD SCALE

Name:	Trial No:
Hospital No:	Date:

Doctors are aware that emotions play an important part in most illnesses. If your doctor knows about these feelings he will be able to help you more.

This questionnaire is designed to help your doctor to know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week.

Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought-out response.

Tick only one box in each section

I feel tense or 'wound up':
- Most of the time ☐
- A lot of the time ☐
- Time to time, occasionally ☐
- Not at all ☐

I still enjoy the things I used to enjoy:
- Definitely as much ☐
- Not quite so much ☐
- Only a little ☐
- Hardly at all ☐

I get a sort of frightened feeling as if something awful is about to happen:
- Very definitely and quite badly ☐
- Yes, but not too badly ☐
- A little, but it doesn't worry me ☐
- Not at all ☐

I can laugh and see the funny side of things:
- As much as I always could ☐
- Not quite so much now ☐
- Definitely not so much now ☐
- Not at all ☐

Worrying thoughts go through my mind:
- A great deal of the time ☐
- A lot of the time ☐
- From time to time but not too often ☐
- Only occasionally ☐

I feel cheerful:
- Not at all ☐
- Not often ☐
- Sometimes ☐
- Most of the time ☐

I can sit at ease and feel relaxed:
- Definitely ☐
- Usually ☐
- Not often ☐
- Not at all ☐

I feel as if I am slowed down:
- Nearly all the time ☐
- Very often ☐
- Sometimes ☐
- Not at all ☐

I get a sort of frightened feeling like 'butterflies' in the stomach:
- Not at all ☐
- Occasionally ☐
- Quite often ☐
- Very often ☐

I have lost interest in my appearance:
- Definitely ☐
- I don't take so much care as I should ☐
- I may not take quite as much care ☐
- I take just as much care as ever ☐

I feel restless as if I have to be on the move:
- Very much indeed ☐
- Quite a lot ☐
- Not very much ☐
- Not at all ☐

I look forward with enjoyment to things:
- As much as I ever did ☐
- Rather less than I used to ☐
- Definitely less than I used to ☐
- Hardly at all ☐

I get sudden feelings of panic:
- Very often indeed ☐
- Quite often ☐
- Not very often ☐
- Not at all ☐

I can enjoy a good book or radio or TV programme:
- Often ☐
- Sometimes ☐
- Not often ☐
- Very seldom ☐

Scoring Information For Hospital Anxiety and Depression Scale

Questions numbered 1 to 14, reading down left hand column first, then down right hand column. Alternate questions are questions relating to anxiety or depression, i.e., questions 1,3,5,7,9,11,13 make up the anxiety subscale and questions 2,4,6,8,10,12,14 make up the depression subscale. Each component of each question is assigned a score of 0-3 in the order shown below. Each scale is summed to give a total out of 21.

Q1	3	Q2	0	Q3	3	Q4	0
	2		1		2		1
	1		2		1		2
	0		3		0		3
Q5	3	Q6	3	Q7	0	Q8	3
	2		2		1		2
	1		1		2		1
	0		0		3		0
Q9	0	Q10	3	Q11	3	Q12	0
	1		2		2		1
	2		1		1		2
	3		0		0		3
Q13	3	Q14	0				
	2		1				
	1		2				
	0		3				

Medical Research Council (MRC) Grades of Muscle Weakness

Grade 0 - No contraction

Grade 1 - Flicker of contraction

Grade 2 - Active movement with gravity eliminated

Grade 3 - Active movement against gravity

Grade 4 - Active movement against gravity and resistance

Grade 5 - Normal power

(Ref: Griggs and Bradley, 1994)

APPENDIX 2: DATA FROM STRATHCARRON HOSPICE PATIENTS WITH CANCER WHO DIED BETWEEN 1ST JUNE AND 30TH NOVEMBER 1996

There follows the raw data taken from the casenotes of the 229 Strathcarron Hospice patients with cancer who died between 1st June and 30th November 1996 and which is discussed in Chapter 5. Below is a list of abbreviations used in the tables:

F = Female

M = Male

N = No

NK = Not known

No. = Patient Number

NSAIDs = Nonsteroidal anti-inflammatory drugs

Y = Yes

Appendix 2.1 Characteristics of Strathcarron Hospice Patients Who Died Between 1st June 1996 and 30th November 1996

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
1	Ovarian	F	75	75	NK	NK	NK	Hospital
2	Breast	F	79	79	NK	NK	Toiletting difficult	Home
3	Myeloma	M	70	70	Y	Y	Reduced mobility	Hospice
4	Lung	F	87	87	NK	Y	NK	Hospital
5	Breast	F	79	79	Y	Y	Reduced mobility	Relative's Home
6	Unknown primary	F	87	87	NK	Y	Reduced mobility	Hospice
7	Unknown primary	F	59	59	NK	Y	Reduced mobility	Hospice
8	Colorectal	M	48	48	Y	NK	Reduced mobility	Hospice
9	Abdominal Liposarcoma	M	83	83	Y	NK	NK	Hospice
10	Primary cerebral	M	86	86	NK	NK	NK	Hospice
11	Unknown primary	F	71	71	Y	NK	Fatigue; reduced mobility	Hospital
12	Larynx	M	63	63	N	NK	NK	Hospital
13	Lung	F	67	67	Y	Y	None	Home
14	Colorectal + Bladder	F	86	86	N	NK	None	Hospital
15	Colorectal	F	59	59	Y	Y	Reduced mobility	Home
16	Prostate	M	63	64	Y	Y	Leg Weakness	Hospital
17	Non Hodgkin's Lymphoma	F	66	66	N	NK	Reduced mobility	Hospice
18	Bladder	F	65	65	N	NK	None	Hospice
19	Breast	F	74	75	N	NK	None	Hospice
20	Lung + Bladder	M	78	78	Y	Y	Leg Weakness	Hospice
21	Small Cell Lung Cancer	M	70	70	N	NK	None	Home
22	Bladder	M	78	78	N	NK	NK	Hospice
23	Colorectal	F	66	66	N	NK	Weak and frail	Home
24	Colorectal	M	64	64	Y	Y	NK	Hospice
25	Non Small Cell Lung Cancer	F	66	66	Y	Y	Weak; reduced mobility	Home
26	Colorectal	F	69	70	Y	NK	Reduced mobility	Hospice
27	Bladder	M	65	65	Y	Y	None	Hospice
28	Carcinoid of Liver	M	74	74	Y	Y	None	Hospital
29	Non Small Cell Lung Cancer + Prostate	M	62	65	Y	Y	Weak	Hospice

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
30	Non Small Cell Lung Cancer	M	76	76	Y	Y	Leg Weakness	Hospice
31	Mediastinal Sarcoma	M	65	65	NK	Y	Weak	Home
32	Larynx	F	71	71	Y	Y	Weak and tired	Home
33	Pancreas	M	81	82	NK	NK	Tired and frail	Hospice
34	Unknown primary	M	58	58	N	NK	Weak	Hospice
35	Unknown primary	M	46	47	NK	Y	None	Hospice
36	Unknown primary	F	60	60	NK	NK	Leg Weakness	Hospice
37	Melanoma	M	80	80	NK	NK	Frail; leg weakness	Hospice
38	Non Hodgkin's Lymphoma	M	65	65	Y	Y	Reduced mobility	Home
39	Lung	F	75	75	Y	Y	Weak	Hospital
40	Lung	M	77	77	Y	Y	Reduced mobility	Hospital
41	Breast	F	74	74	N	NK	Reduced mobility	Hospice
42	Unknown primary	M	76	76	NK	Y	Tired	Hospital
43	Colorectal	F	63	63	Y	Y	Reduced mobility	Hospital
44	Small bowel	F	65	65	N	NK	NK	Nursing Home
45	Renal	M	71	72	NK	NK	Reduced mobility	Hospice
46	Cervical	F	81	82	Y	NK	Weak; lethargic	Hospice
47	Lung	M	70	70	N	NK	NK	Hospice
48	Lung	F	69	69	Y	Y	None	Home
49	Breast	F	81	81	NK	NK	Weak	Hospice
50	Primary cerebral	M	60	60	NK	Y	Leg Weakness	Hospice
51	Unknown primary	F	80	80	NK	Y	Weak	Home
52	Non Small Cell Lung Cancer	M	57	57	NK	Y	Difficulty in rising from chair	Hospice
53	Non Small Cell Lung Cancer	M	65	65	Y	NK	Leg Weakness	Hospital
54	Ovarian	F	69	69	NK	NK	Tired	Hospital
55	Cholangiocarcinoma	M	75	75	Y	NK	None	Home
56	Unknown primary	F	94	94	NK	Y	NK	Hospital
57	Breast	F	71	71	Y	NK	Reduced mobility	Hospice
58	Unknown primary	M	54	54	N	NK	Reduced mobility	Home

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
59	Prostate	M	73	73	N	NK	None	Hospital
60	Prostate	M	65	65	NK	Y	NK	Hospice
61	Small Cell Lung Cancer	M	63	63	Y	Y	None	Hospital
62	Small Cell Lung Cancer	F	65	66	N	NK	NK	Home
63	Lung	M	72	72	NK	NK	Reduced mobility	Hospital
64	Colorectal	M	70	70	Y	Y	Weak	Hospital
65	Bladder	F	66	66	N	NK	Weak	Hospice
66	Lung	M	73	73	NK	Y	Reduced mobility	Home
67	Breast	F	59	59	Y	NK	NK	Hospice
68	Oesophagus	M	63	63	Y	NK	None	Hospice
69	Lung	F	69	69	Y	NK	None	Home
70	Small Cell Lung Cancer	F	73	73	Y	NK	Reduced mobility	Home
71	Non Hodgkin's Lymphoma	F	67	68	Y	NK	Reduced mobility	Hospice
72	Non Small Cell Lung Cancer	F	61	61	NK	NK	Reduced mobility	Hospital
73	Oesophagus	F	81	82	Y	Y	Reduced mobility	Hospice
74	Gastric	M	70	70	NK	Y	NK	Home
75	Unknown primary	M	67	67	NK	Y	Weak	Hospital
76	Lung	M	69	69	Y	NK	Reduced mobility	Hospice
77	Unknown primary	F	70	70	Y	Y	Reduced mobility	Hospice
78	Pancreas	F	52	53	NK	Y	Weak; tired	Home
79	Unknown primary	F	65	65	NK	Y	NK	Hospital
80	Palate	M	54	54	NK	NK	None	Home
81	Thyroid	F	49	50	NK	Y	None	Hospice
82	Pancreas	M	56	56	NK	NK	Reduced mobility	Hospital
83	Prostate	M	79	80	Y	Y	Reduced mobility	Hospital
84	Non Small Cell Lung Cancer	F	57	58	Y	Y	Reduced mobility	Home
85	Lymphoma	M	48	48	Y	NK	Reduced mobility	Home
86	Ovarian	F	58	58	Y	Y	Weak; tired	Hospice
87	Non Small Cell Lung Cancer	M	67	67	Y	Y	Reduced mobility	Hospice

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
88	Unknown primary	M	54	54	NK	Y	NK	Hospital
89	Renal	F	73	74	Y	Y	Frail	Hospice
90	Prostate	M	55	55	N	NK	NK	Home
91	Colorectal	F	82	82	NK	Y	Reduced mobility	Hospice
92	Breast	F	66	66	NK	Y	Reduced mobility	Hospital
93	Non Small Cell Lung Cancer	F	82	82	Y	Y	Weak	Hospice
94	Unknown primary	M	64	64	Y	NK	NK	Home
95	Synovial Sarcoma	M	36	36	Y	NK	Weak	Hospice
96	Gastric	M	73	74	Y	NK	None	Hospital
97	Non Hodgkin's Lymphoma	M	52	52	Y	Y	Reduced mobility	Hospice
98	Melanoma	F	56	56	N	NK	NK	Hospice
99	Caecum	F	74	74	NK	Y	Reduced mobility	Home
100	Colorectal	F	54	54	Y	Y	None	Hospital
101	Small Cell Lung Cancer	F	67	68	NK	Y	Reduced mobility	Hospital
102	Lung	M	78	78	NK	Y	Frail	Home
103	Non Hodgkin's Lymphoma	F	57	58	N	NK	Weak; tired	Hospice
104	Breast	F	69	69	N	NK	Reduced mobility	Hospital
105	Non Hodgkin's Lymphoma + Bladder	M	77	77	N	NK	Reduced mobility	Hospice
106	Prostate	M	76	76	NK	NK	Tired	Nursing Home
107	Pancreas	M	80	80	Y	Y	Weak	Hospice
108	Small Cell Lung Cancer	F	73	73	NK	NK	Reduced mobility	Hospital
109	Colorectal	M	84	84	Y	Y	Reduced mobility	Home
110	Oesophagus	M	72	72	Y	Y	NK	Home
111	Unknown primary	F	65	65	Y	Y	None	Home
112	Pancreas	M	65	65	N	NK	None	Hospital
113	Breast	F	72	72	NK	Y	Exhausted	Hospice
114	Non Small Cell Lung Cancer	M	70	70	NK	Y	Reduced mobility	Hospital
115	Unknown primary	M	76	76	Y	Y	Reduced mobility	Home
116	Gastric + Prostate	M	91	91	Y	Y	Frail	Home

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
117	Lung	F	76	76	NK	Y	Reduced mobility	Home
118	Caecum	F	80	80	Y	Y	Weak; frail	Hospice
119	Unknown primary	M	59	59	NK	Y	Reduced mobility	Home
120	Lung	M	59	59	N	NK	NK	Hospital
121	Colorectal	M	40	40	Y	Y	NK	Home
122	Colorectal + Endometrial	F	61	61	NK	Y	Reduced mobility	Hospice
123	Colorectal	F	74	74	Y	NK	Tired; frail	Hospice
124	Colorectal	F	76	76	Y	Y	Frail	Hospice
125	Renal	M	64	65	N	NK	Reduced mobility	Hospice
126	Unknown primary	M	69	69	NK	NK	NK	Hospital
127	Small Bowel	F	35	36	Y	NK	Weak	Hospital
128	Cholangiocarcinoma	F	68	68	NK	NK	NK	Hospital
129	Breast	F	48	48	NK	Y	Reduced mobility	Hospital
130	Tonsil	M	64	65	Y	Y	Weak; frail	Hospice
131	Gastric	M	75	76	Y	Y	Weak	Hospice
132	Primary cerebral	F	75	75	N	NK	None	Hospital
133	Unknown primary	M	75	75	Y	Y	Reduced mobility	Hospice
134	Oesophagus	M	69	69	Y	NK	Reduced mobility	Home
135	Anus	M	73	73	N	NK	Reduced mobility	Home
136	Lung	F	67	68	Y	Y	Reduced mobility	Home
137	Oesophagus	F	62	62	Y	Y	Tired	Hospice
138	Oesophagus	F	53	53	Y	Y	Tired; frail	Home
139	Breast	F	82	83	N	NK	NK	Hospice
140	Primary cerebral	M	72	73	Y	Y	NK	NK
141	Renal	M	45	45	Y	NK	None	Hospital
142	Breast	F	86	86	Y	Y	Weak; tired; exhausted	Hospice
143	Colorectal	F	85	85	Y	Y	NK	Home
144	Cholangiocarcinoma	F	75	75	Y	Y	Weak; frail	Home
145	Lung	M	59	59	Y	NK	Reduced mobility	Nursing Home

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
146	Caecum	M	73	73	Y	NK	Weak; tired	Hospital
147	Unknown primary	M	84	84	NK	NK	NK	Hospital
148	Oesophagus	F	80	80	NK	Y	Weak	Hospice
149	Oesophagus	F	69	69	Y	Y	Tired	Hospice
150	Breast	F	72	72	N	NK	None	Hospital
151	Breast	F	58	59	N	NK	Reduced mobility	Hospice
152	Non Small Cell Lung Cancer	M	74	74	N	NK	None	Hospital
153	Unknown primary	M	82	82	N	NK	NK	Hospital
154	Primary cerebral	F	51	51	NK	NK	None	Home
155	Non Small Cell Lung Cancer	M	55	55	Y	NK	Reduced mobility	Home
156	Lung	M	68	68	NK	Y	NK	Home
157	Oesophagus	M	65	65	Y	Y	Exhausted	Hospice
158	Prostate	M	55	56	NK	Y	NK	Hospital
159	Lung	M	56	57	Y	Y	NK	NK
160	Unknown primary	F	67	67	Y	Y	Reduced mobility	Home
161	Vulva	F	63	63	Y	Y	Frail	Hospice
162	Gastric	M	63	63	Y	Y	Frail	Hospice
163	Unknown primary	M	78	79	Y	NK	None	Hospice
164	Colorectal	M	54	54	Y	NK	Weak	Hospice
165	Breast	F	68	68	Y	Y	Frail	Hospital
166	Prostate	M	81	81	NK	NK	Reduced mobility	Home
167	Breast	F	37	38	Y	NK	None	Hospital
168	Pancreas	F	75	75	Y	Y	Weak; frail	Hospice
169	Breast	F	44	44	N	NK	Tired	Hospital
170	Colorectal	M	54	54	Y	Y	None	Home
171	Pancreas	M	68	68	Y	Y	Weak	Hospital
172	Gastric	F	67	67	Y	NK	None	Hospice
173	Prostate	M	75	75	Y	NK	NK	Hospital
174	Lung	F	75	75	NK	Y	NK	Hospital

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
175	Pharynx	M	68	68	NK	NK	Reduced mobility	Hospice
176	Breast	F	69	70	NK	NK	Reduced mobility	Hospital
177	Larynx	M	84	84	N	NK	Frail	Home
178	Non Small Cell Lung Cancer	M	68	68	Y	Y	None	Home
179	Colorectal	F	68	69	Y	Y	Weak	Home
180	Caecum	M	69	69	Y	NK	Weak	Hospice
181	Acute Lymphocytic Leukaemia	M	58	58	NK	Y	Reduced mobility	Home
182	Prostate	M	73	73	Y	Y	Reduced mobility	Hospital
183	Prostate	M	77	78	Y	Y	None	Hospital
184	Lung + Myeloma	F	79	79	Y	Y	Reduced mobility	Hospice
185	Pancreas	F	85	85	Y	Y	NK	Hospice
186	Breast	F	64	64	NK	Y	Weak; exhausted	Hospice
187	Pancreas	F	68	69	Y	Y	Weak	Nursing Home
188	Tonsil	M	69	69	Y	NK	Weak	Hospice
189	Breast	F	58	58	NK	Y	NK	Hospice
190	Gastric	F	70	70	Y	Y	Reduced mobility	Hospice
191	T Cell Lymphoma	F	69	71	Y	NK	Weak	Hospice
192	Lung	M	59	59	Y	NK	Reduced mobility	Hospital
193	Breast	F	81	81	NK	NK	Reduced mobility	Hospice
194	Lung	M	79	79	Y	Y	Frail	Home
195	Oesophagus	F	63	63	Y	Y	NK	Home
196	Non Small Cell Lung Cancer	F	73	74	Y	Y	Reduced mobility	Hospice
197	Prostate	M	81	81	Y	NK	None	Hospital
198	Lung	M	70	70	Y	NK	Reduced mobility	Hospital
199	Ovarian	F	92	92	NK	NK	Tired	Hospital
200	Lung + Cholangiocarcinoma	M	85	85	Y	NK	Leg Weakness	Hospice
201	Breast	F	80	80	Y	Y	Reduced mobility	Hospital
202	Palate	F	65	66	Y	NK	Weak; tired	Home
203	Lung	M	88	88	Y	NK	Frail	Hospice

No.	Cancer	Sex	Age at involvement	Age at death	Weight Loss	Anorexia	Weakness/Fatigue/ Mobility	Place of death
204	Non Small Cell Lung Cancer	F	80	80	Y	Y	Reduced mobility	Hospital
205	Unknown primary	M	86	86	NK	NK	Leg Weakness	Hospital
206	Prostate	M	66	66	Y	Y	Reduced mobility	Hospital
207	Unknown primary	F	68	69	N	NK	None	Hospital
208	Mesothelioma	M	65	65	N	NK	NK	Hospice
209	Cervical	F	59	59	NK	Y	Weakness; reduced mobility	Hospice
210	Melanoma	F	82	82	Y	NK	None	Hospice
211	Colorectal	F	69	69	NK	Y	Reduced mobility	Home
212	Small Cell Lung Cancer	F	55	55	N	NK	Reduced mobility	Hospice
213	Colorectal + Vipoma	M	79	79	Y	Y	Weak; frail	Hospice
214	Ovarian + Caecum	F	35	35	Y	NK	Weak; reduced mobility	Hospice
215	Breast	F	75	75	N	NK	Reduced mobility	Hospital
216	Small Cell Lung Cancer	M	79	80	Y	Y	Reduced mobility	Hospice
217	Non Small Cell Lung Cancer	M	51	51	Y	Y	Reduced mobility	Hospital
218	Colorectal	M	NK	72	NK	NK	NK	NK
219	Colorectal	F	60	61	Y	Y	Reduced mobility	Hospice
220	Bladder	F	81	81	NK	Y	Reduced mobility	Hospital
221	Small Cell Lung Cancer	M	78	78	NK	NK	Reduced mobility	NK
222	Non Small Cell Lung Cancer	M	81	81	Y	NK	NK	Home
223	Lung	M	54	54	Y	Y	Exhausted	Hospice
224	Primary cerebral	F	54	54	NK	Y	Leg Weakness	Hospital
225	Pancreas	M	68	68	Y	Y	Reduced mobility	Home
226	Breast	F	69	69	Y	Y	NK	Home
227	Lung	M	79	79	Y	Y	Reduced mobility	Home
228	Renal	M	65	65	Y	NK	Weak; reduced mobility	Hospice
229	Larynx	M	69	69	NK	Y	None	Hospital

Appendix 2.2 Length of Hospice Involvement and Drugs Prescribed to Strathcarron Hospice Patients Who Died Between 1st June 1996 and 30th November 1996

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
1	10	Y	N	N	N	N	N	N	
2	12	N	N	N	N	N	N	N	
3	46	N	Y	Y	Y	N	Y	N	
4	1	Y	Y	N	N	N	N	N	
5	7	N	N	N	N	N	N	Y	Tamoxifen
6	16	N	N	N	Y	Y	Y	Y	
7	9	Y	Y	N	N	N	N	N	
8	212	N	Y	N	Y	Y	N	Y	
9	59	N	N	Y	N	N	N	N	
10	79	N	Y	N	N	N	N	N	
11	26	N	Y	N	N	Y	N	Y	
12	8	Y	N	N	N	N	N	N	Carbamazepine
13	67	Y	Y	N	N	N	Y	N	
14	153	Y	N	N	N	N	N	N	
15	2	Y	Y	N	N	Y	N	N	
16	386	Y	Y	N	Y	N	N	N	
17	18	N	N	Y	N	N	Y	N	
18	115	Y	Y	N	N	N	Y	N	
19	282	N	N	N	Y	N	N	N	
20	88	N	N	N	N	N	N	N	Megestrol acetate
21	45	N	Y	N	N	N	N	Y	Megestrol acetate
22	154	N	Y	N	N	N	N	N	
23	1	N	N	N	N	N	N	N	
24	4	Y	N	Y	N	N	Y	Y	
25	25	Y	Y	N	N	N	N	N	
26	151	Y	Y	N	N	N	N	N	
27	75	Y	Y	N	Y	N	N	N	
28	79	Y	Y	Y	N	N	Y	N	
29	1017	Y	N	N	Y	N	N	N	

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
30	16	Y	Y	Y	Y	N	N	N	
31	3	N	N	N	N	N	N	N	
32	21	Y	Y	N	N	N	N	N	
33	61	Y	Y	Y	N	Y	N	N	
34	42	Y	Y	N	N	N	Y	N	
35	141	Y	N	N	Y	N	N	N	
36	22	Y	Y	Y	N	N	N	N	
37	324	Y	N	N	N	N	Y	N	
38	2	N	Y	N	N	N	N	Y	
39	5	Y	Y	N	Y	Y	N	N	
40	27	N	Y	N	N	N	N	N	
41	66	Y	N	Y	N	N	N	N	
42	22	Y	N	N	Y	N	N	N	
43	17	Y	Y	N	Y	N	N	N	Haloperidol/Carbamazepine
44	52	Y	Y	Y	Y	N	Y	N	
45	114	Y	N	N	Y	N	Y	N	
46	472	Y	N	N	Y	N	N	N	Haloperidol
47	159	Y	N	Y	N	N	N	N	
48	23	Y	Y	N	N	Y	N	N	
49	58	N	Y	Y	N	N	N	Y	
50	44	Y	Y	N	N	N	N	N	
51	5	N	Y	Y	N	N	N	N	
52	17	Y	Y	N	N	N	Y	N	
53	39	N	Y	N	N	N	N	N	
54	32	N	N	Y	Y	Y	N	N	Thioridazine
55	104	N	N	Y	N	N	N	Y	
56	54	N	Y	Y	N	N	N	N	
57	1	Y	Y	N	N	N	N	N	
58	7	Y	Y	N	Y	N	Y	N	Carbamazepine

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
59	87	Y	Y	N	Y	N	N	N	
60	179	Y	N	N	Y	N	Y	N	Megestrol acetate
61	12	Y	Y	N	Y	N	N	N	
62	333	N	Y	Y	Y	N	N	Y	
63	61	Y	N	N	Y	N	N	N	Thioridazine/Carbamazepine
64	31	Y	N	Y	N	N	N	N	
65	71	Y	Y	N	N	N	N	N	
66	3	Y	N	N	N	Y	N	N	Thioridazine
67	41	N	Y	N	Y	Y	Y	N	Anastrozole
68	110	Y	N	N	Y	N	Y	N	
69	27	Y	Y	Y	N	N	Y	N	
70	8	Y	Y	N	N	N	N	N	
71	27	N	Y	N	Y	Y	N	Y	
72	16	N	Y	N	N	N	N	N	
73	21	Y	N	Y	N	Y	N	N	
74	49	Y	Y	N	N	N	N	N	
75	44	Y	N	N	Y	N	Y	N	Carbamazepine
76	120	N	Y	N	N	N	N	Y	
77	107	Y	N	N	Y	N	Y	N	Carbamazepine
78	105	Y	N	N	N	N	Y	N	Haloperidol
79	4	N	N	N	N	N	N	N	Prochlorperazine
80	24	Y	N	N	Y	Y	Y	N	
81	163	Y	Y	N	Y	N	N	N	
82	10	Y	N	N	N	N	N	N	Methotrimeprazine
83	293	N	Y	N	N	N	N	Y	
84	49	N	Y	N	N	Y	Y	N	Anastrozole
85	3	Y	N	N	N	N	N	N	Methotrimeprazine
86	49	Y	N	N	Y	N	N	N	
87	13	Y	Y	N	N	Y	N	N	

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
88	9	N	Y	N	N	Y	N	N	
89	13	Y	N	Y	N	Y	N	N	
90	33	Y	Y	N	Y	N	Y	N	
91	69	Y	Y	Y	Y	N	Y	N	
92	22	Y	N	Y	Y	N	N	N	
93	20	N	Y	Y	N	Y	N	Y	
94	19	N	Y	N	N	N	N	Y	
95	11	Y	Y	N	N	Y	N	N	
96	337	N	Y	Y	N	N	N	N	
97	105	Y	N	N	Y	Y	Y	N	Megestrol acetate
98	130	Y	Y	N	N	N	N	N	Tamoxifen/Norethisterone
99	34	Y	N	Y	N	N	N	N	
100	130	N	N	N	N	N	Y	Y	
101	23	Y	Y	N	Y	N	N	N	
102	98	Y	Y	N	Y	N	N	N	
103	279	N	Y	Y	N	N	N	N	Chlorpromazine
104	20	N	Y	N	N	Y	N	Y	Tamoxifen
105	8	N	Y	Y	N	Y	N	N	
106	54	Y	N	Y	Y	Y	Y	N	
107	1	N	N	N	N	N	N	N	
108	8	Y	Y	N	N	N	N	N	
109	13	Y	N	Y	N	N	N	N	
110	153	N	N	N	N	N	N	N	
111	66	Y	N	N	Y	N	N	N	
112	17	Y	Y	N	N	N	N	N	
113	5	N	N	N	N	Y	N	Y	Tamoxifen
114	27	N	N	Y	N	Y	N	N	
115	8	N	Y	N	N	N	N	Y	
116	17	N	Y	N	N	N	N	N	

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
117	32	Y	Y	Y	N	N	N	N	
118	21	Y	Y	Y	N	N	N	N	
119	44	N	Y	Y	N	N	N	N	
120	48	Y	N	N	Y	N	N	N	Methotrimeprazine
121	12	Y	Y	Y	N	N	N	N	
122	117	Y	Y	N	N	N	N	N	
123	38	N	N	N	N	N	N	Y	
124	16	Y	N	N	N	Y	N	N	
125	412	Y	Y	N	Y	N	Y	N	Sodium valproate
126	5	Y	Y	N	Y	Y	Y	N	
127	344	Y	N	N	N	N	N	N	
128	10	Y	Y	N	N	N	N	N	
129	91	Y	N	N	Y	N	N	N	
130	269	Y	N	N	Y	N	N	N	Megestrol acetate
131	35	Y	N	N	N	N	N	N	Promethazine
132	101	N	Y	N	N	N	N	N	
133	27	Y	N	Y	N	Y	N	N	Haloperidol
134	42	N	Y	N	N	Y	N	N	
135	2	Y	Y	N	N	N	Y	N	
136	33	Y	Y	Y	N	N	N	N	
137	114	N	Y	N	N	N	Y	N	
138	18	N	N	N	N	N	N	N	
139	58	Y	Y	Y	N	Y	Y	N	
140	66	NK	NK	NK	NK	NK	NK	NK	NK
141	274	Y	Y	Y	Y	N	N	N	
142	21	N	N	Y	N	N	N	N	Thioridazine/Tamoxifen
143	4	N	N	N	N	N	N	Y	
144	7	N	N	N	N	N	N	Y	
145	20	Y	N	N	N	N	N	N	Carbamazepine

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
146	98	N	Y	Y	N	N	N	Y	
147	10	Y	N	N	N	N	N	N	
148	5	N	N	Y	N	N	N	Y	
149	29	Y	Y	Y	N	N	N	N	
150	55	N	N	Y	N	N	N	Y	Anastrozole
151	354	Y	N	Y	Y	N	Y	N	Thioridazine/Anastrozole
152	52	N	Y	Y	N	N	Y	Y	
153	60	Y	N	Y	Y	N	N	N	Carbamazepine
154	4	N	Y	N	Y	N	N	N	Carbamazepine
155	46	Y	Y	N	Y	N	N	N	
156	20	Y	Y	N	N	N	N	N	
157	43	Y	N	Y	N	N	N	N	
158	251	Y	N	Y	Y	N	N	N	
159	208	Y	Y	Y	Y	Y	Y	N	
160	8	Y	N	N	N	N	N	N	Megestrol acetate
161	37	Y	N	N	N	N	Y	N	Chlorpromazine/Haloperidol/Carbamazepine
162	31	N	N	Y	N	N	N	Y	
163	47	Y	N	N	Y	N	N	N	Carbamazepine
164	402	Y	Y	Y	Y	N	Y	N	
165	80	N	Y	Y	Y	Y	N	Y	
166	4	Y	Y	Y	N	N	N	N	
167	189	Y	Y	N	N	N	Y	N	Megestrol acetate
168	96	Y	Y	N	N	N	N	N	
169	7	Y	N	N	N	Y	N	N	
170	15	Y	Y	Y	N	Y	N	N	
171	13	Y	N	Y	N	Y	N	N	
172	89	Y	N	N	N	Y	Y	N	Thioridazine
173	7	Y	N	N	N	N	N	N	
174	27	Y	Y	N	N	Y	N	N	

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
175	40	Y	Y	N	Y	Y	Y	N	
176	91	N	N	N	N	N	N	N	
177	106	N	N	Y	N	N	N	N	
178	38	Y	Y	Y	N	N	N	N	
179	343	Y	N	Y	N	N	N	N	
180	4	N	Y	N	N	N	N	Y	Methotrimeprazine
181	17	N	N	N	N	N	N	N	
182	3	Y	N	N	N	N	N	N	
183	326	Y	Y	Y	N	N	N	N	Goserelin acetate
184	150	Y	N	N	Y	N	N	N	
185	21	Y	Y	N	N	N	N	N	
186	25	N	Y	N	N	N	N	N	
187	122	Y	Y	N	N	N	N	N	Haloperidol
188	41	Y	N	N	N	N	Y	N	
189	44	Y	Y	N	Y	Y	Y	N	Haloperidol/Megestrol acetate
190	11	Y	N	N	N	N	Y	N	
191	693	N	Y	N	Y	Y	Y	N	
192	40	Y	Y	N	N	N	N	N	Phenytoin
193	28	Y	Y	N	N	N	N	N	Thioridazine
194	11	Y	N	N	Y	N	N	Y	
195	39	Y	N	N	N	N	N	N	Megestrol acetate
196	98	N	Y	Y	N	N	N	N	
197	48	N	N	Y	N	N	N	N	
198	38	N	Y	N	N	N	N	N	
199	5	NK	NK	NK	NK	NK	NK	NK	NK
200	240	N	Y	N	Y	Y	N	Y	
201	14	Y	N	Y	N	Y	N	N	Megestrol acetate/Carbamazepine
202	580	Y	N	Y	Y	N	Y	N	Carbamazepine
203	110	N	Y	N	N	N	N	N	

No.	Time Hospice Involved (Days)	DRUGS Strong Opioids	Steroids	Diuretics	NSAIDs	Benzodiazepines	Antidepressants	Weak Opioids	Other Drugs
204	24	N	N	N	N	N	N	N	
205	6	N	Y	N	N	N	N	N	Carbamazepine
206	60	Y	N	N	Y	N	N	N	Flutamide
207	87	Y	N	N	N	N	N	N	Tamoxifen
208	43	Y	Y	N	N	N	N	N	
209	48	Y	Y	Y	N	N	N	N	
210	11	Y	Y	N	N	N	N	N	Thioridazine
211	36	Y	N	N	N	Y	N	N	
212	19	N	Y	Y	Y	Y	Y	Y	
213	11	N	N	N	N	N	N	N	
214	106	Y	N	N	N	Y	Y	N	Haloperidol/Methotrimeprazine
215	3	Y	N	N	N	Y	N	N	Megestrol acetate
216	39	N	Y	Y	N	N	Y	N	
217	16	Y	Y	N	N	N	N	N	
218	NK	N	Y	N	N	Y	N	N	
219	183	Y	N	Y	N	N	N	N	Megestrol acetate/Methotrimeprazine
220	144	N	N	Y	Y	N	N	N	
221	3	N	N	Y	N	N	N	N	
222	8	N	N	N	N	N	N	Y	
223	53	Y	Y	N	Y	Y	N	N	Phenytoin
224	144	Y	Y	N	Y	N	N	N	
225	1	Y	Y	N	N	N	N	N	
226	25	Y	N	N	Y	N	N	N	Tamoxifen
227	16	Y	Y	N	N	Y	N	N	Haloperidol
228	136	Y	N	N	Y	N	Y	N	Megestrol acetate
229	42	Y	N	N	N	Y	N	N	Haloperidol

APPENDIX 3: DATA FROM HEALTHY SUBJECTS AND CANCER PATIENTS FROM STUDIES DESCRIBED IN CHAPTERS 6-8

There follows the raw data from the 15 healthy subjects (V1-V15) and 68 cancer patients who participated in the studies described in chapters 6-8. Below is a list of the abbreviations used in the tables:

AMA = Arm Muscle Area
BMI = Body Mass Index
BST = Biceps Skinfold Thickness
cm = centimetres
cmsq. = Square centimetres
DED = Dexamethasone Equivalent Dose (24 hours)
EORTC = European Organisation for the Research and Treatment of Cancer
F = Female
FACT-Ftg = Functional Assessment of Cancer Therapy Fatigue Subscale
g/l = grams per litre
HAD = Hospital Anxiety and Depression Scale
icf/ecf ratio = intracellular fluid/ extracellular fluid ratio
IU/l = International Units per litre
kg = kilograms
kgW = kilogram Watts
KPS = Karnofsky Performance Status
LASA = Linear Analogue Self-Assessment Scale
LN = Lymph Nodes
m = metres
M = Male
MAC = Mid-Arm Circumference
max. = maximum
MED = Morphine Equivalent Dose (24 hours)
mg/l = milligrams per litre

min. = minutes

mm = millimetres

mmol/l = millimoles per litre

MTC = Mid-Thigh Circumference

N & V = Nausea and Vomiting

ND = Non-Dominant

NK = Not Known

Nm = Newton metres

nmol/l = nanomoles per litre

NSAIDs = Nonsteroidal Anti-Inflammatory Drugs

Pred. Vecf/Vtbw/Vicf (l) = Predicted volume of extracellular fluid/total body water/ intracellular fluid (litres)

QOL = Quality of life

Qu. = Question

s = seconds

Study No. = Study Number

ThST = Thigh Skinfold Thickness

TMA = Thigh Muscle Area

TST = Triceps Skinfold Thickness

V = Volunteer (Healthy Control Subject)

WL = Weight-Losing at Study Entry

WS = Weight-Stable at Study Entry

Y = Yes

24hr creat. = 24 hour urinary creatinine excretion

Appendix 3.1 Baseline Anthropometrics & Body Composition in Healthy Subjects

Study No.	Sex	Age	Height cm	Current weight kg	Current BMI	% ideal BMI	Pred. Vecf (l)	Pred. Vtbw (l)	Pred. Vicf (l)	icf/ecf ratio	TST mm	BST mm	ThST mm	MAC cm	AMA cmsq.	MTC cm	TMA cmsq.	24hr creat mmol/l
V1	M	61	177.5	79.50	25.2	109.7	21.6	39.5	17.9	0.83	13.0	7.5	15.5	29.3	50.6	54.3	194.6	19.2
V2	F	58	158.5	52.50	20.9	90.9	13.3	24.7	11.4	0.85	13.0	7.0	28.0	25.6	36.9	49.7	133.2	12.6
V3	M	68	174.5	78.50	25.8	112.1	19.6	34.8	15.2	0.78	20.0	10.0	14.0	32.5	54.7	47.3	146.6	16.4
V4	M	66	165.0	66.25	24.3	105.8	17.8	31.5	13.6	0.76	17.0	4.5	19.0	29.8	47.6	47.4	136.7	11.3
V5	M	65	176.5	87.00	27.9	121.4	23.3	41.5	18.1	0.78	12.5	7.5	9.0	31.8	61.9	54.0	208.5	10.3
V6	M	69	177.5	74.50	23.7	102.8	20.2	36.4	16.1	0.80	8.0	6.0	9.0	29.5	58.0	49.9	176.4	14.5
V7	F	68	163.5	68.00	25.4	110.6	16.8	28.8	12.0	0.71	23.0	18.0	38.0	31.2	45.8	53.2	135.6	9.6
V8	F	58	167.0	62.50	22.4	97.4	16.4	28.1	11.8	0.72	18.0	11.0	17.5	28.8	42.7	52.0	172.2	11.2
V9	F	66	172.5	77.50	26.0	113.2	18.3	29.9	11.6	0.63	32.0	29.5	56.5	33.5	43.8	59.1	136.2	-
V10	F	64	165.5	67.25	24.6	106.7	15.3	26.3	11.0	0.71	23.0	16.5	37.5	31.2	45.8	56.7	160.7	9.3
V11	F	50	152.5	52.00	22.4	97.2	13.2	23.8	10.6	0.81	15.5	11.5	32.0	27.5	40.8	44.8	96.2	7.0
V12	M	74	171.0	82.00	28.0	121.9	23.6	39.4	15.8	0.67	12.5	5.5	9.5	32.6	65.5	49.4	171.5	13.2
V13	F	46	169.0	66.50	23.3	101.2	18.0	34.1	16.1	0.89	22.5	15.0	-	31.9	49.1	51.3	-	10.6
V14	M	46	166.0	60.50	22.0	95.5	18.9	37.8	18.9	1.00	6.5	3.5	8.5	29.4	59.6	49.7	176.1	15.4
V15	F	62	159.5	73.50	28.9	125.6	17.0	31.3	14.3	0.84	19.0	17.0	32.5	33.4	59.9	55.8	165.5	15.0

Appendix 3.2 Baseline Blood Tests in Healthy Subjects

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	Vitamin D nmol/l	C-reactive protein mg/l
V1	147	7.2	139	4.2	5.3	89	44	124	2.34	0.93	9.4	16.9	53	30
V2	142	5.5	138	4.4	4.7	92	46	156	2.33	1.03	9.1	23.1	66	2
V3	154	6.8	139	3.8	7.5	95	44	101	2.34	0.79	11.8	16.3	41	3
V4	145	6.0	138	4.8	7.4	97	46	199	2.28	0.69	13.3	18.2	22	2
V5	158	6.7	140	4.4	6.2	88	45	105	2.30	0.81	15.5	18.4	31	8
V6	161	6.8	141	4.5	5.2	88	42	152	2.44	1.02	13.7	17.1	44	3
V7	128	5.4	137	4.7	8.1	79	41	141	2.25	0.81	12.1	27.5	40	9
V8	145	4.1	141	4.1	5.8	95	44	111	2.31	0.78	14.3	11.4	82	9
V9	138	4.7	139	3.9	5.2	91	43	86	2.27	0.97	12.4	18.2	24	3
V10	123	4.9	139	4.0	7.3	83	45	95	2.37	0.93	14.5	25.6	25	2
V11	132	8.4	144	-	3.8	89	46	87	2.31	0.87	18.5	18.6	21	-
V12	123	5.6	144	3.6	17.7	323	43	38	2.38	1.00	13.0	16.4	24	10
V13	132	7.7	138	4.0	5.2	74	43	91	2.25	0.83	9.6	18.0	50	7
V14	156	6.5	138	4.5	4.3	94	47	189	2.23	0.85	10.7	12.4	35	1
V15	144	6.8	138	4.7	5.5	90	43	84	2.52	0.82	11.8	21.9	23	4

Appendix 3.3 Baseline Linear Analogue Scales of Weakness and Strength, FACT-Ftg and EORTC Fatigue Scales, Handgrip Strength and Quadriceps Torque in Healthy Subjects

Study No.	LASA Weak cm	LASA Strength cm	FACT-Ftg	EORTC-Fatigue	Handgrip strength kgW	ND Handgrip strength kgW	Max. isokinetic torque Nm	Max. isometric torque Nm
V1	0.1	10.0	51	0	46.0	-	222.7	200.0
V2	0.1	10.0	51	0	25.5	-	143.9	168.6
V3	0.8	6.1	46	22.2	35.5	40.5	76.2	177.0
V4	2.0	7.0	51	0	32.5	28.5	232.2	185.4
V5	0.2	9.8	51	0	49.0	50.5	241.8	236.2
V6	0.1	9.2	49	0	49.0	48.5	251.2	268.2
V7	3.3	6.8	43	33.3	23.0	18.0	81.2	130.8
V8	0.4	10.0	43	11.1	26.5	23.5	166.5	130.2
V9	1.0	10.0	50	22.2	20.0	21.0	181.4	148.2
V10	1.1	6.7	50	11.1	22.0	20.5	71.9	73.8
V11	1.0	9.4	49	11.1	27.5	27.0	117.0	104.0
V12	1.4	9.7	46.58	22.2	26.0	25.0	79.0	225.7
V13	3.3	6.4	48	0	34.0	36.0	302.4	248.9
V14	2.7	6.3	44	0	40.0	37.5	213.9	213.9
V15	0.3	4.8	50	0	28.5	28.0	238.1	249.4

Appendix 3.4 Baseline Activity Level, Karnofsky Performance Status and Performance in Functional Tests in Healthy Subjects

Study No.	Activity Level	KPS	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
			s	s	s	s	2 min. distance (m)	6 min. distance (m)
V1	3	100	0.95	5.06	1.44	1.42	194	574
V2	2 to 3	100	0.85	3.02	1.80	1.70	198	598
V3	1 to 2	90	1.60	10.71	2.59	2.23	149	445
V4	2	100	1.15	5.00	2.25	1.91	214	580
V5	2	100	0.84	4.35	1.84	1.20	200	602
V6	2 to 3	100	1.08	4.19	1.80	1.53	209	614
V7	2	100	0.90	5.46	2.08	1.68	180	540
V8	2	100	0.90	4.10	2.25	1.61	188	571
V9	2	100	1.15	5.46	1.76	1.57	185	566
V10	2	90	1.10	6.55	2.51	2.04	145	431
V11	2	100	0.97	4.22	1.96	1.64	149	440
V12	1 to 2	90	1.45	6.66	2.36	2.40	122	361
V13	2	100	1.16	4.90	2.29	1.66	180	551
V14	3	100	0.97	3.60	2.16	1.40	185	581
V15	1 to 2	100	0.81	5.70	2.09	1.80	162	485

Appendix 3.5 Baseline Scores for EORTC Questionnaire and HAD Scale in Healthy Subjects

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales									HAD Scale	
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
V1	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	0	0
V2	100	100	100	100	100	100	0	0	0	0	0	0	0	0	0	1	0
V3	60	100	100	83.3	66.7	75	22.2	0	0	33.3	0	0	0	0	0	1	3
V4	100	83.3	100	100	83.3	100	0	0	16.7	0	0	0	0	0	0	0	1
V5	100	100	91.7	100	100	100	0	0	0	0	0	0	0	33.3	0	4	1
V6	100	100	83.3	100	100	83.3	0	0	0	33.3	33.3	0	0	33.3	0	6	3
V7	100	66.7	66.7	83.3	100	66.7	33.3	0	33.3	0	0	0	0	0	0	8	5
V8	100	100	100	83.3	100	100	11.1	0	0	0	33.3	0	33.3	0	0	4	2
V9	100	100	100	66.7	100	83.3	22.2	0	0	0	33.3	0	0	0	0	2	0
V10	80	83.3	100	100	100	91.7	11.1	0	50	0	0	0	0	0	0	3	1
V11	80	100	66.7	100	100	83.3	11.1	16.7	33.3	0	33.3	0	33.3	0	0	6	0
V12	60	66.7	75	83.3	83.3	66.7	22.2	0	33.3	0	0	0	33.3	0	0	1	3
V13	100	100	100	83.3	100	83.3	0	0	0	0	0	0	0	0	0	1	0
V14	100	100	91.7	83.3	100	66.7	0	0	0	0	33.3	0	0	33.3	0	10	1
V15	100	100	91.7	83.3	100	100	0	0	0	0	0	0	0	0	0	1	0

Appendix 3.6 Baseline Characteristics of, and Drugs Used By, Cancer Patients

Study No.	Sex	Age	Group	Cancer	Metastatic sites	Activity Level		KPS	Drugs								
						Pre-illness	Current		Strong opioids	MED	Benzodiazepines	Antidepressants	Diuretics	NSAIDs	Steroids	DED	Megestrol
1	M	43	WL	Non Small Cell Lung Cancer	Brain & Lung	2	1	85	N	-	N	Y	N	N	N	-	N
2	F	83	WS	Non Hodgkin's Lymphoma	-	2	1	60	N	-	Y	N	N	N	Y	0.5	N
3	F	69	WL	Non Small Cell Lung Cancer	-	2	0	40	N	-	Y	Y	N	N	N	-	N
4	M	75	WS	Colon	Liver	2	1	60	N	-	Y	Y	N	N	Y	0.5	N
5	M	52	WS	Mesothelioma	-	3	1 to 2	80	Y	50	N	N	N	Y	N	-	N
6	M	64	WS	Lung (No Histology)	-	2	1	85	N	-	N	N	N	N	N	-	N
7	M	62	WL	Lung (No Histology)	-	2	1	65	Y	60	N	N	Y	N	N	-	N
8	F	51	WL	Non Small Cell Lung Cancer	LN	2	1	80	Y	60	Y	Y	N	N	N	-	N
9	F	54	WL	Small Cell Lung Cancer	Bone	2	1	65	Y	2000	N	N	N	Y	N	-	N
10	M	51	WL	Pancreas	-	2 to 3	1	45	Y	360	Y	Y	N	N	N	-	N
11	M	69	WL	Non Small Cell Lung Cancer	-	2	1	55	Y	120	Y	Y	Y	N	Y	2	N
12	F	58	WS	Stomach	Bone	2	1	70	Y	200	Y	Y	Y	Y	N	-	N
13	M	42	WL	Mesothelioma	-	3	1	60	Y	360	N	N	N	N	N	-	N
14	F	67	WL	Breast	Bone	2	1	75	Y	60	N	Y	N	Y	N	-	Y
15	M	67	WS	Mesothelioma	-	1	1	60	Y	120	N	N	N	N	N	-	N
16	F	72	WS	Non Small Cell Lung Cancer	Lung, Liver, LN	2 to 3	2	90	Y	20	N	N	N	N	N	-	N
17	F	69	WS	Breast	Bone	2 to 3	1 to 2	90	N	-	N	Y	Y	N	N	-	N
18	F	52	WL	Pancreas	-	2	1	75	Y	15	N	N	N	N	N	-	N
19	F	65	WL	Oesophagus	-	1	1	55	N	-	N	N	N	N	N	-	N
20	M	63	WS	Colon	Liver & LN	2	1	80	N	-	N	N	N	N	N	-	Y
21	M	47	WS	Astrocytoma	-	2 to 3	1	80	N	-	Y	N	N	N	N	-	N
22	M	66	WL	Oesophagogastric	-	1	0	25	Y	90	N	N	N	N	N	-	N
23	F	69	WL	Non Small Cell Lung Cancer	-	1 to 2	0 to 1	50	N	-	Y	N	N	N	N	-	N
24	M	64	WL	Non Small Cell Lung Cancer	-	2	1	50	Y	30	N	N	N	N	N	-	N
25	F	62	WS	Non Small Cell Lung Cancer	-	2	2	90	Y	360	N	N	N	Y	Y	1	N
26	F	58	WS	Ovary	-	2	1	80	N	-	Y	Y	Y	Y	N	-	N
27	M	57	WL	Non Small Cell Lung Cancer	-	2	1	70	Y	32	N	N	N	N	N	-	N
28	F	64	WS	Ovary	-	2	1	75	N	-	N	N	N	Y	N	-	N
29	M	72	WS	Non Hodgkin's Lymphoma	-	NK	1	60	N	-	N	Y	N	Y	Y	0.5	N
30	F	58	WS	Breast	Liver & Bone	2	1 to 2	80	Y	200	N	Y	N	Y	N	-	N
31	M	38	WL	Colon	-	3	1 to 2	80	Y	40	Y	Y	N	Y	Y	6	Y
32	F	64	WL	Small Cell Lung Cancer	Bone	2	1	55	Y	20	Y	N	N	Y	N	-	N
33	M	55	WS	Non Small Cell Lung Cancer	-	2 to 3	1 to 2	80	N	-	N	N	N	N	N	-	N
34	M	80	WL	Colon	-	NK	0	40	Y	60	Y	N	Y	N	Y	2	N

Study No.	Sex	Age	Group	Cancer	Metastatic sites	Activity Level		KPS	Drugs								
						Pre-illness	Current		Strong opioids	MED	Benzodiazepines	Antidepressants	Diuretics	NSAIDs	Steroids	DED	Megestrol
35	F	65	WL	Non Small Cell Lung Cancer	-	2	1	80	N	-	Y	N	Y	N	N	-	N
36	M	60	WS	Non Small Cell Lung Cancer	Brain	3	1	50	Y	20	Y	N	Y	N	Y	8	N
37	M	71	WS	Non Small Cell Lung Cancer	-	2	1	65	N	-	N	N	N	Y	Y	2	N
38	M	61	WS	Small Cell Lung Cancer	Bone	2	1	80	N	-	N	N	N	N	N	-	N
39	F	74	WS	Small Cell Lung Cancer	Liver	2	2	100	N	-	N	N	N	N	N	-	N
40	M	69	WL	Non Small Cell Lung Cancer	Renal	2	1	70	Y	120	N	N	N	N	Y	4	N
41	M	74	WL	Small Cell Lung Cancer	-	1 to 2	1	60	N	-	N	N	N	N	N	-	N
42	F	69	WS	Non Small Cell Lung Cancer	LN	2	1	60	Y	60	Y	N	N	Y	N	-	N
43	M	77	WS	Small Cell Lung Cancer	LN	2	0	40	Y	15	Y	N	N	Y	N	-	N
44	M	60	WL	Non Small Cell Lung Cancer	Bone	2	1	70	Y	400	Y	N	N	Y	Y	4	N
45	M	75	WS	Prostate/Head & Neck	Bone	2 to 3	1	60	N	-	N	N	N	N	N	-	Y
46	M	66	WS	Non Small Cell Lung Cancer	-	2	1	80	N	-	N	N	Y	N	N	-	N
47	M	59	WS	Non Small Cell Lung Cancer	Brain	3	2	90	N	-	N	N	N	N	Y	1	N
48	F	73	WS	Non Small Cell Lung Cancer	-	NK	1	60	N	-	Y	N	Y	N	Y	2	N
49	M	57	WL	Non Small Cell Lung Cancer	Brain	2 to 3	1	70	N	-	N	N	N	N	Y	4	Y
50	M	72	WL	Non Small Cell Lung Cancer	Lung	2	0	35	Y	40	N	N	Y	N	Y	3	N
51	F	63	WS	Non Small Cell Lung Cancer	-	1 to 2	1	75	N	-	N	N	Y	N	N	-	N
52	F	77	WL	Non Small Cell Lung Cancer	-	1	0 to 1	60	Y	300	Y	Y	N	Y	Y	4	N
53	M	59	WS	Head & Neck	-	2	1	65	Y	240	Y	Y	N	N	N	-	N
54	M	83	WS	Prostate	Bone	1 to 2	1	65	N	-	Y	N	Y	Y	N	-	N
55	F	81	WL	Lung (No Histology)	Liver & Lung	2	0	30	N	-	N	N	N	N	N	-	Y
56	F	67	WL	Colon	Bladder & Lung	1 to 2	1	70	Y	600	Y	N	N	Y	N	-	N
57	M	71	WL	Mesothelioma	-	2	0	30	Y	15	N	Y	N	N	N	-	Y
58	M	62	WL	Non Small Cell Lung Cancer	Peritoneal & Liver	2	1	60	NK	NK	NK	NK	NK	NK	NK	NK	NK
59	M	44	WL	Colon	Peritoneal	2	1 to 2	80	Y	480	N	N	N	N	Y	8	N
60	M	79	WS	Non Small Cell Lung Cancer	-	2	1	60	N	-	N	N	N	N	Y	2	N
61	F	45	WS	Breast	Liver & Bone	2	1	80	Y	160	N	Y	Y	Y	N	-	N
62	M	53	WL	Non Small Cell Lung Cancer	-	2	1	55	Y	90	Y	N	N	N	Y	8	N
63	F	72	WS	Non Small Cell Lung Cancer	-	1	0 to 1	55	Y	60	Y	N	N	Y	Y	2	N
64	M	51	WS	Non Small Cell Lung Cancer	-	3	1 to 2	90	Y	20	N	N	N	N	N	-	N
65	M	61	WS	Colon	Peritoneal	2	1	60	Y	200	N	N	N	N	Y	1.5	N
66	F	51	WL	Non Small Cell Lung Cancer	Bone	2	1	60	Y	5	N	N	Y	Y	Y	4	N
67	M	64	WS	Non Small Cell Lung Cancer	-	2	1	80	Y	120	N	N	N	Y	N	-	N
68	M	76	WS	Colon	Lung	2	0	45	N	-	Y	N	N	N	N	-	N

Appendix 3.7 Baseline Anthropometrics & Body Composition in Cancer Patients

Study No.	Height cm	Healthy weight kg	Healthy BMI	Current weight kg	Current BMI	% ideal BMI	Pred. Vecf (l)	Pred. Vtbw(l)	Pred. Vicf(l)	icf/ecf ratio	TST mm	BST mm	ThST mm	MAC cm	AMA cmsq.	MTC cm	TMA cmsq.	24hr ur. creat mmol/l
1	167.0	57.00	20.4	46.25	16.6	72.1	-	-	-	-	3.0	2.0	3.5	20.5	30.5	38.5	111.4	-
2	159.5	50.00	19.7	35.00	13.8	59.8	-	-	-	-	3.0	2.0	3.0	16.5	19.3	30.6	70.0	-
3	156.0	58.50	24.0	48.25	19.8	86.2	11.2	22.1	10.8	0.97	17.0	7.5	14.5	26.0	34.0	40.0	100.0	-
4	173.0	57.25	19.1	58.00	19.4	84.3	17.4	27.9	10.5	0.61	5.5	2.5	12.5	21.0	29.6	42.0	115.4	-
5	177.0	79.50	25.4	78.00	24.9	108.2	18.9	36.8	18.0	0.95	17.0	6.5	12.0	31.2	53.3	50.4	173.1	15.3
6	165.0	51.00	18.7	49.25	18.1	78.7	13.2	21.2	8.0	0.61	8.5	5.5	5.5	21.8	29.1	36.8	97.9	6.9
7	164.5	76.25	28.2	63.50	23.5	102.0	17.5	29.0	11.5	0.66	14.5	11.0	16.0	27.2	40.8	45.1	127.9	9.5
8	152.0	48.00	20.8	39.50	17.1	74.3	10.7	18.9	8.2	0.76	9.5	5.0	11.5	19.8	22.6	38.5	96.9	3.0
9	151.0	82.00	36.0	76.00	33.3	144.9	15.0	28.6	13.6	0.91	33.5	10.5	-	29.0	27.2	-	-	-
10	178.0	95.00	30.0	63.00	19.9	86.5	21.1	35.8	14.8	0.70	5.0	3.0	-	17.7	20.7	-	-	-
11	159.0	69.75	27.6	59.00	23.3	101.5	14.9	24.4	9.6	0.64	13.0	6.0	14.5	24.7	33.8	38.4	91.2	1.4
12	159.0	60.25	23.8	72.00	28.5	123.8	16.0	29.8	13.8	0.86	34.5	20.5	-	31.0	32.4	60.7	-	-
13	163.0	59.75	22.5	44.00	16.6	72.0	12.5	21.9	9.4	0.75	6.5	4.5	6.5	19.8	25.1	34.1	81.8	8.2
14	149.0	65.25	29.4	49.00	22.1	96.0	15.2	25.1	9.9	0.65	14.0	6.5	8.5	23.3	28.5	46.8	155.1	-
15	165.0	76.00	27.9	75.00	27.6	119.8	23.1	35.7	12.5	0.54	10.5	6.5	13.0	26.6	43.2	45.3	135.3	10.5
16	150.5	53.00	23.4	54.00	23.8	103.7	12.5	22.8	10.3	0.82	25.0	6.0	20.0	28.2	33.0	51.1	159.9	7.9
17	159.5	55.00	21.6	55.50	21.8	94.9	12.8	22.6	9.9	0.77	20.5	7.5	22.0	25.3	28.3	45.1	116.1	-
18	171.5	59.00	20.1	53.50	18.2	79.1	14.4	27.1	12.7	0.88	12.5	7.5	19.0	25.1	35.7	44.6	118.8	6.1
19	161.0	47.75	18.4	41.00	15.8	68.8	12.8	22.9	10.1	0.79	7.0	4.0	8.5	20.3	26.1	33.6	76.2	-
20	176.0	76.25	24.6	75.00	24.2	105.3	19.8	37.7	17.8	0.90	8.0	3.0	6.0	28.9	55.4	53.2	209.7	10.5
21	174.0	95.25	31.5	91.00	30.1	130.7	20.9	41.0	20.1	0.96	14.0	8.5	22.5	34.0	69.8	59.4	218.1	17.3
22	170.0	95.25	33.0	59.00	20.4	88.8	17.9	34.0	16.1	0.90	8.0	3.5	15.5	23.2	34.1	45.7	132.7	-
23	153.0	66.75	28.5	54.50	23.3	101.2	-	-	-	-	17.5	4.0	18.0	27.1	37.2	50.3	158.7	-
24	164.0	74.00	27.5	58.00	21.6	93.8	18.1	28.6	10.4	0.58	8.0	6.0	12.5	25.1	40.6	41.8	114.2	-
25	157.0	52.50	21.3	56.50	22.9	99.7	15.0	26.1	11.1	0.74	22.0	8.0	23.0	29.8	41.7	51.4	155.5	9.5
26	162.0	82.50	31.4	73.00	27.8	120.9	16.2	31.2	14.9	0.92	25.5	16.5	39.5	37.1	67.4	55.9	150.6	14.6
27	174.0	101.50	33.5	95.00	31.4	136.4	21.3	37.5	16.2	0.76	19.0	9.5	17.5	37.0	76.7	57.1	212.0	-
28	164.0	59.00	21.9	46.75	17.4	75.6	12.9	22.5	9.6	0.74	7.5	9.0	13.5	23.0	33.9	41.5	110.5	7.2
29	168.0	78.00	27.6	79.50	28.2	122.5	18.0	30.9	12.9	0.71	10.0	3.5	8.5	27.9	48.8	47.3	158.5	-
30	160.0	61.75	24.1	80.50	31.5	136.7	19.5	32.8	13.3	0.68	25.0	14.5	17.5	34.4	56.1	66.3	294.4	11.4
31	181.5	82.50	25.0	71.25	21.6	94.0	19.1	34.1	15.0	0.79	11.5	5.5	12.0	29.8	54.6	51.9	184.4	-
32	154.5	58.00	24.3	40.00	16.8	72.9	10.6	17.3	6.8	0.64	8.5	4.0	10.0	22.8	32.3	36.2	87.0	-
33	162.5	64.50	24.4	62.75	23.8	103.3	17.8	32.5	14.7	0.82	9.0	5.0	13.5	28.1	50.9	49.3	161.7	20.4
34	166.0	-	-	61.75	22.4	97.4	16.9	26.7	9.9	0.59	12.0	8.0	20.0	27.1	43.3	44.0	113.3	-

Study No.	Height	Healthy weight	Healthy BMI	Current weight	Current BMI	% ideal BMI	Pred.	Pred.	Pred.	icf/ecf	TST	BST	ThST	MAC	AMA	MTC	TMA	24hr ur. creat
	cm	kg		kg			Vecf (l)	Vtbw (l)	Vicf (l)	ratio	mm	mm	mm	cm	cmsq.	cm	cmsq.	mmol/l
35	163.5	60.00	22.4	56.50	21.1	92.0	13.7	23.0	9.3	0.68	13.0	11.0	18.5	26.0	38.2	46.5	131.8	3.7
36	180.5	89.00	27.3	92.50	28.4	123.0	22.2	36.1	13.9	0.63	23.0	7.5	29.5	33.4	54.6	54.4	162.2	-
37	172.0	64.75	21.9	65.75	22.2	97.0	18.2	26.6	8.4	0.46	17.5	12.5	15.0	27.4	38.2	44.7	127.3	6.8
38	168.5	63.50	22.4	56.25	19.8	86.0	14.5	24.6	10.1	0.70	6.5	4.5	7.0	23.6	37.0	40.7	118.0	-
39	162.0	59.00	22.5	50.00	19.1	83.0	12.5	21.7	9.3	0.74	13.0	7.0	20.5	24.8	34.2	45.6	122.1	6.9
40	169.5	63.50	22.1	50.75	17.7	77.0	14.8	23.3	8.5	0.58	5.5	3.5	6.5	22.1	33.0	35.8	90.7	-
41	157.5	63.50	25.6	47.50	19.2	83.0	14.5	24.5	9.9	0.68	7.5	4.0	10.0	23.8	36.6	42.7	124.6	-
42	162.0	50.50	19.2	39.75	15.2	66.0	-	-	-	-	4.0	3.0	5.0	17.6	21.3	33.3	80.2	-
43	162.0	76.25	29.1	78.50	29.9	130.0	24.1	33.7	9.7	0.40	-	-	-	-	-	-	-	-
44	154.5	71.00	29.7	48.50	20.3	88.0	15.8	25.6	9.8	0.62	10.0	7.5	11.0	24.2	35.3	39.5	103.4	-
45	146.0	57.25	26.9	35.00	16.4	71.0	12.3	20.9	8.6	0.70	2.5	2.0	3.0	18.0	23.6	28.0	58.3	-
46	176.0	86.00	27.8	83.50	27.0	117.0	21.7	33.6	11.9	0.55	16.0	5.5	26.0	30.2	50.5	55.2	176.1	12.8
47	167.0	60.00	21.5	65.50	23.5	102.0	17.1	30.0	12.9	0.75	14.0	7.5	7.5	31.0	56.4	48.1	166.6	10.3
48	165.5	60.00	21.9	64.50	23.6	102.0	-	-	-	-	12.0	12.5	18.0	28.8	49.9	51.1	164.5	-
49	180.0	79.50	24.5	82.75	25.5	111.0	21.7	33.9	12.2	0.56	15.5	13.5	20.0	30.2	51.1	49.5	148.7	-
50	169.5	57.25	19.9	49.25	17.1	75.0	-	-	-	-	3.5	2.5	4.0	18.1	23.0	32.3	76.7	-
51	144.5	70.75	33.9	64.75	31.0	135.0	-	-	-	-	-	-	-	33.5	-	55.7	-	6.2
52	164.0	45.25	16.8	41.50	15.4	67.0	12.8	22.7	10.0	0.78	6.0	3.0	12.0	19.5	24.7	35.2	78.7	-
53	176.0	63.50	20.5	47.25	15.3	66.0	17.5	25.3	7.8	0.44	4.0	3.0	4.0	18.9	24.8	33.1	80.7	-
54	170.0	69.75	24.1	63.50	22.0	96.0	-	-	-	-	8.0	6.5	6.5	24.8	39.6	42.0	127.1	-
55	162.5	63.50	24.1	51.00	19.3	84.0	-	-	-	-	6.0	4.5	15.0	18.8	22.8	40.3	100.8	-
56	162.0	76.25	29.1	61.25	23.3	101.0	13.8	22.6	8.8	0.64	20.5	14.0	23.0	28.9	40.2	42.1	96.9	-
57	183.0	85.25	25.5	65.00	19.4	84.0	-	-	-	-	-	-	-	-	-	-	-	-
58	167.0	69.75	25.0	53.50	19.2	83.0	14.3	22.8	8.5	0.60	8.5	8.5	11.5	24.0	36.2	38.5	96.9	-
59	182.0	85.75	25.9	64.00	19.3	84.0	16.4	26.6	10.2	0.62	13.0	-	15.5	26.5	40.0	42.9	115.2	-
60	167.5	44.50	15.9	43.00	15.3	67.0	12.3	23.0	10.7	0.87	4.0	2.5	7.0	18.1	22.6	32.5	73.1	-
61	149.5	51.75	23.2	47.00	21.0	91.0	13.9	20.9	7.0	0.51	8.0	5.0	15.5	22.9	33.1	41.5	106.8	8.1
62	169.0	114.25	40.0	85.00	29.8	129.0	21.3	35.7	14.5	0.68	24.5	20.5	36.5	36.4	65.6	52.5	134.1	-
63	154.0	63.50	26.8	50.25	21.2	92.0	13.9	22.1	8.2	0.59	11.0	6.5	14.5	21.8	26.8	38.7	92.8	-
64	165.5	63.50	23.2	54.00	19.7	86.0	17.2	33.0	15.7	0.91	6.5	4.5	5.5	23.9	38.0	44.7	147.0	16.5
65	178.0	71.75	22.7	65.25	20.6	90.0	20.6	34.0	13.4	0.65	8.0	7.5	10.0	25.6	42.4	44.5	136.2	9
66	162.5	53.00	20.1	39.00	14.8	64.0	11.0	19.9	9.0	0.81	4.5	3.0	6.0	17.1	19.6	34.2	83.1	6.4
67	171.0	71.75	24.5	66.00	22.6	98.0	21.9	32.2	10.3	0.47	10.0	7.5	11.5	26.0	41.6	45.4	139.0	7.3
68	168.0	72.50	25.7	66.50	23.6	102.0	16.8	37.7	20.9	1.25	10.0	10.5	12.5	26.7	44.2	45.5	137.6	-

Appendix 3.8 Baseline Blood Tests in Cancer Patients

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	Vitamin D nmol/l	C-reactive protein mg/l
1	127	6.5	131	4.5	7.1	78	37	-	2.32	0.71	-	-	-	175
2	99	16.7	140	4.7	6.2	83	41	-	2.20	0.84	-	-	-	-
3	109	9.2	132	4.2	2.0	62	36	-	2.49	-	-	-	-	207
4	121	4.9	138	3.6	3.7	101	38	47	2.24	0.79	-	-	-	-
5	152	5.7	141	4.4	7.7	78	42	59	2.35	0.93	10.5	18.7	120	21
6	154	7.3	137	3.7	5.1	121	45	100	2.31	0.58	13.7	21.2	34	8
7	133	12.7	137	4.5	4.9	93	39	39	2.58	0.88	9.5	37.5	16	120
8	123	9.4	142	3.5	7.7	71	44	36	2.53	0.78	10.6	11.3	68	35
9	116	10.4	139	3.9	4.7	95	39	27	2.37	0.93	11.6	29.7	20	160
10	91	10.2	135	5.1	7.6	96	27	40	2.32	0.88	9.4	10.8	18	49
11	122	19.4	136	3.6	6.7	89	39	24	2.46	0.63	8.7	26.9	15	21
12	123	5.0	140	4.5	8.6	161	42	205	2.18	0.81	12.2	29.0	31	23
13	108	11.0	137	4.9	6.9	67	37	23	2.52	0.88	10.0	28.9	45	117
14	131	8.6	141	4.0	6.8	98	42	131	2.14	0.85	12.2	23.0	33	9
15	119	7.5	137	3.5	3.1	67	37	29	2.30	0.82	11.8	35.3	30	106
16	115	12.4	134	4.5	3.8	74	42	89	2.32	0.84	11.9	23.4	19	49
17	144	4.4	140	4.4	7.8	78	41	59	2.41	0.88	15.8	21.3	53	8
18	102	12.7	134	4.4	3.5	65	33	22	2.42	0.83	11.0	20.5	21	68
19	126	8.4	138	4.7	9.2	69	40	32	2.35	0.90	10.9	18.6	29	5
20	141	11.2	138	4.4	4.2	94	44	110	2.40	0.81	10.4	20.0	128	13
21	177	11.7	140	4.3	5.1	111	46	50	2.40	0.79	12.1	21.8	35	22
22	122	18.2	137	3.6	6.1	73	30	35	2.36	0.90	9.5	19.0	48	99
23	123	5.8	123	4.5	6.5	111	40	35	2.33	0.84	7.2	31.2	27	66
24	101	16.1	134	4.8	7.2	99	35	40	3.29	0.88	8.7	23.4	36	56
25	104	6.8	140	4.4	8.0	107	40	63	2.33	0.73	11.0	17.8	22	9
26	112	6.3	140	-	7.3	134	44	74	2.41	0.87	11.5	33.0	18	8
27	131	7.8	136	3.8	8.9	161	43	46	2.31	0.89	11.2	28.8	43	59
28	136	10.9	135	5.6	13.1	98	43	19	2.61	0.79	11.9	25.8	21	9
29	135	6.2	136	4.7	8.9	81	43	28	2.22	0.95	10.5	15.6	23	6
30	127	6.2	140	4.1	7.1	75	41	129	2.22	0.89	11.2	20.6	43	15
31	114	22.0	137	4.3	5.6	109	36	27	2.33	0.99	10.1	16.4	21	77
32	145	7.0	136	3.7	4.4	72	37	151	2.46	0.81	7.6	37.5	27	40
33	163	10.4	145	4.4	3.9	85	43	83	2.45	0.79	11.2	18.6	55	7
34	120	27.2	131	4.7	13.1	98	35	14	2.28	0.79	11.1	15.4	16	28

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	Vitamin D nmol/l	C-reactive protein mg/l
35	151	8.3	139	4.7	5.1	79	43	31	2.50	0.70	9.4	18	38	3
36	119	8.7	137	4.1	4.3	78	39	20	2.41	0.90	7.5	26.5	21	87
37	110	16.9	134	4.3	5.8	73	37	17	2.50	1.02	7.1	21.2	15	133
38	143	6.5	141	3.6	8.8	94	44	38	2.44	0.81	10.0	20.6	30	2
39	120	5.8	135	5.0	7.8	97	44	75	2.33	0.87	8.2	23.8	16	2
40	120	8.1	139	4.4	4.9	116	40	36	2.24	0.93	9.3	22.8	50	46
41	153	8.1	141	4.5	6.2	109	39	49	2.40	0.93	11.4	17.2	22	2
42	112	8.9	139	3.5	4.9	74	32	28	2.34	0.87	7.2	23.3	22	91
43	126	7.8	137	4.2	7.5	70	31	97	2.47	0.94	9.6	28.1	26	204
44	101	17.6	137	4.7	10.0	95	28	16	2.58	0.98	6.4	20.1	9	173
45	121	9.5	140	4.0	3.3	79	40	79	2.42	0.85	8.8	15.7	27	1
46	126	5.6	137	4.3	9.3	160	40	19	2.31	0.87	9.5	20.3	6	19
47	132	6.1	135	4.5	5.0	76	42	46	2.44	0.87	14.8	14.7	22	11
48	152	10.6	135	3.9	7.8	93	41	20	2.53	0.80	5.7	24.2	18	39
49	113	10.2	144	3.4	3.6	74	39	26	2.36	0.78	6.4	20.0	12	133
50	142	9.0	136	4.6	11.2	94	29	24	2.28	0.96	5.6	20.0	6	129
51	161	10.8	135	3.5	6.5	62	45	35	2.31	0.71	11.8	21.8	26	8
52	107	16.5	132	4.7	5.9	62	30	29	2.33	-	-	-	-	214
53	110	7.2	137	4.5	2.2	70	31	24	2.49	0.75	10.5	18.6	19	64
54	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55	123	26.2	135	3.3	17.6	120	23	318	2.44	0.99	-	-	6	66
56	125	10.0	142	3.7	4.1	92	35	30	2.41	0.89	12.4	18.5	10	19
57	100	16.0	137	4.4	12.4	108	34	18	2.51	0.96	8.3	25.6	27	174
58	121	14.1	135	4.2	4.0	69	35	10	2.49	0.73	9.6	28.3	6	201
59	126	20.2	132	4.3	7.0	85	41	23	2.41	0.93	9.4	22.1	6	12
60	125	5.1	142	-	5.2	56	36	44	2.31	0.90	9.8	11.6	12	-
61	102	5.6	136	4.0	5.7	67	33	46	2.26	0.65	7.3	24.8	63	7
62	96	18.9	136	4.4	6.4	78	40	-	2.47	0.73	-	-	7	91
63	96	14.3	140	4.5	5.0	72	31	17	2.30	0.81	9.4	18.7	6	22
64	123	12.7	138	4.5	8.6	66	38	35	2.38	0.97	13.1	23.4	22	4
65	110	5.5	142	3.9	8.7	93	39	24	2.19	0.91	9.9	19.6	14	5
66	109	15.1	133	4.2	4.2	70	33	13	2.32	0.80	4.7	36.7	23	169
67	-	-	135	4.8	4.1	70	32	16	2.37	0.98	9.2	27.2	11	158
68	142	7.9	134	4.5	5.2	91	32	71	2.51	0.92	9.9	25.0	35	118

Appendix 3.9 Baseline Linear Analogue Scales of Weakness and Strength, FACT-Ftg and EORTC Fatigue Scales, Handgrip Strength and Quadriceps Torque in Cancer Patients

Study No.	LASA Weak	LASA Strength	FACT-Ftg	EORTC	Handgrip strength ND	Handgrip strength	Max isokinetic torque	Max isometric torque
	cm	cm		Fatigue	kgW	kgW	Nm	Nm
1	8.0	6.6	41	16.7	33.0	-	86.8	-
2	-	-	22	55.6	15.0	-	-	-
3	7.5	2.0	4	55.6	7.0	-	-	-
4	1.9	0.2	28	55.6	21.0	-	-	-
5	4.7	6.2	29	55.6	39.0	-	223.5	270.3
6	3.8	2.9	36	66.7	18.0	-	120.6	149.8
7	3.1	2.6	38	33.3	22.5	-	-	-
8	5.6	3.6	24	66.7	16.0	-	73.1	95.7
9	2.3	3.2	28	33.3	22.0	-	-	-
10	1.3	0.4	15	66.7	16.0	-	-	-
11	8.1	3.8	34	55.6	15.0	-	-	-
12	1.4	4.9	42	22.2	21.0	-	-	-
13	6.3	5.8	13	100	23.0	-	-	-
14	3.9	4.4	27	66.7	18.0	-	-	-
15	6.2	2.6	13	83.3	28.0	-	-	-
16	0.9	7.0	41	33.3	14.5	-	129.6	91.8
17	5.7	5.0	39	33.3	20.5	-	64.3	110.7
18	5.1	5.8	28	66.7	20.0	-	107.2	103.9
19	4.3	3.6	24	55.6	14.0	-	-	-
20	4.8	8.8	30	44.4	34.0	-	-	232.3
21	1.7	5.7	28	66.7	44.0	-	157.8	204.0
22	5.0	0.2	1	-	7.5	-	-	-
23	7.2	3.9	18	66.7	14.0	-	-	-
24	5.7	4.7	23	88.9	24.5	-	-	-
25	0.6	10.0	45	33.3	24.0	-	93.9	60.1
26	6.2	3.7	21	77.8	28.5	-	169.3	187.9
27	5.1	4.2	17	77.8	51.0	46.0	162.8	198.1
28	2.5	8.2	30	44.4	16.0	-	85.3	92.5
29	6.8	4.0	23	44.4	26.5	-	-	-
30	0.9	8.1	40	33.3	18.0	-	132.8	118.9
31	4.5	4.2	39	55.6	43.0	-	183.3	-
32	5.2	2.4	23	55.6	10.0	-	-	-
33	2.8	5.4	30	55.6	36.5	-	209.1	241.9
34	1.5	9.2	11	77.8	13.0	-	-	-

Study No.	LASA Weak cm	LASA Strength cm	FACT-Ftg	EORTC Fatigue	Handgrip strength ND kgW	Handgrip strength Max kgW	Max isokinetic torque (Nm)	Max isometric torque (Nm)
35	5.0	3.6	20	55.6	22.0	-	84.0	-
36	7.5	2.9	20	66.7	37.5	-	-	-
37	3.0	7.2	30	50.0	27.5	-	-	-
38	4.7	3.2	26	33.3	36.0	-	135.3	126.3
39	0.7	8.9	42	0	18.0	-	68.9	75.9
40	2.4	6.7	36	33.3	29.0	-	-	-
41	5.4	5.5	43	11.1	22.5	-	-	-
42	1.6	3.8	23	55.6	12.0	12.0	-	-
43	5.9	3.7	18	88.9	16.5	-	-	-
44	7.8	5.6	10	100	22.5	-	87.8	79.4
45	5.8	0.4	21	-	12.0	-	-	-
46	0.4	4.6	42	11.1	31.5	25.0	-	-
47	2.0	7.9	45	22.2	32.0	30.0	181.4	203.3
48	3.4	4.0	-	88.9	21.0	20.5	-	-
49	3.5	5.7	33	33.3	27.5	22.0	-	-
50	-	9.6	38	-	8.5	-	-	-
51	3.6	2.3	29	44.4	21.0	19.5	-	-
52	6.0	3.4	11	100	8.5	5.5	-	-
53	2.1	1.7	12	55.6	27.5	25.0	-	-
54	3.7	5.7	33	55.6	27.0	25.0	-	-
55	4.1	6.8	15	77.8	6.5	2.0	-	-
56	2.3	4.0	29	44.4	18.5	16.0	-	-
57	8.2	4.0	0	100	7.0	4.0	-	-
58	8.3	2.7	18	66.7	20.5	19.0	-	-
59	5.4	9.4	30	22.2	29.0	30.5	147.2	89.3
60	5.2	1.9	24	55.6	22.5	19.5	-	-
61	2.7	5.1	47	22.2	17.0	-	62.1	82.9
62	3.8	2.5	35	44.4	29.0	28.0	-	-
63	1.0	8.9	35	55.6	10.0	10.0	-	-
64	2.8	6.2	37	44.4	29.0	29.0	150.9	119.0
65	4.0	2.4	22	55.6	28.0	33.5	-	-
66	4.7	5.1	19	66.7	14.0	13.0	-	-
67	2.5	8.8	42	33.3	27.0	27.0	91.1	161.8
68	6.0	8.0	28	77.8	19.0	18.0	-	-

Appendix 3.10 Baseline Scores for Individual Questions of EORTC Fatigue Scale and FACT-Ftg Scale in Cancer Patients

Study No.	EORTC Fatigue Scale			FACT-Ftg Scale												
	Qu. 10 (Rest)	Qu. 12 (Weak)	Qu. 18 (Tired)	Qu. 1	Qu. 2	Qu. 3	Qu. 4	Qu. 5	Qu. 6	Qu. 7	Qu. 8	Qu. 9	Qu. 10	Qu. 11	Qu. 12	Qu. 13
1	2	1	-	3	4	4	3	3	3	3	3	2	4	4	3	2
2	2	3	3	1	1	0	1	1	1	2	1	2	4	3	1	4
3	2	2	4	0	0	0	0	-	0	0	0	2	2	0	0	0
4	2	3	3	1	-	2	0	3	3	2	2	2	3	4	3	1
5	3	2	3	2	1	2	1	2	3	2	3	1	4	4	3	1
6	3	3	3	2	4	3	1	2	1	3	1	4	4	4	3	4
7	2	2	2	3	4	3	3	3	3	1	-	3	4	4	3	1
8	3	3	3	1	1	1	1	2	2	1	2	3	4	3	1	2
9	2	2	2	3	3	3	3	2	2	0	1	1	2	3	3	2
10	2	4	3	1	2	2	2	0	0	-	0	2	2	2	1	0
11	3	3	2	3	4	3	1	3	3	1	0	3	4	3	3	3
12	2	1	2	4	4	4	3	3	3	2	1	4	4	4	3	3
13	4	4	4	1	1	1	1	0	1	1	3	1	1	1	1	0
14	3	3	3	2	4	3	3	1	1	0	1	3	4	2	1	2
15	3	-	4	0	0	1	2	1	1	1	0	1	2	4	0	0
16	-	2	2	4	3	3	3	4	4	1	1	4	4	4	3	3
17	2	2	2	3	3	3	3	3	3	3	3	3	1	4	4	3
18	3	3	3	1	2	2	1	2	2	1	3	4	4	3	2	1
19	3	2	3	1	2	1	1	2	2	1	1	1	4	4	1	3
20	2	3	2	1	2	2	2	2	2	2	3	3	4	4	1	2
21	3	3	3	2	3	2	2	3	2	2	1	1	4	3	1	2
22	-	-	-	0	0	1	0	0	0	0	0	0	0	0	0	0
23	-	3	3	1	1	1	1	4	4	0	0	1	4	1	0	0
24	4	4	3	2	1	1	3	1	1	1	4	3	4	0	0	2
25	2	2	2	4	4	4	3	4	4	3	0	3	4	4	4	4
26	3	4	3	1	2	1	3	-	1	1	1	2	4	0	1	2
27	3	3	4	1	2	2	1	1	0	1	0	2	4	2	1	0
28	3	2	2	1	3	1	2	3	2	2	2	-	3	3	3	3
29	2	3	2	1	2	2	1	3	2	1	2	2	4	2	1	0
30	2	2	2	3	3	4	3	4	4	1	1	3	4	4	3	3
31	3	2	3	2	3	3	3	4	2	3	2	3	4	4	4	2
32	3	3	2	1	3	3	1	1	1	2	1	4	4	1	0	1
33	3	2	3	2	3	3	2	1	1	3	2	1	4	4	2	2
34	3	3	4	2	-	0	0	0	0	0	-	3	4	0	0	0

Study No.	EORTC Fatigue Scale			FACT-Ftg Scale												
	Qu. 10 (Rest)	Qu. 12 (Weak)	Qu. 18 (Tired)	Qu. 1	Qu. 2	Qu. 3	Qu. 4	Qu. 5	Qu. 6	Qu. 7	Qu. 8	Qu. 9	Qu. 10	Qu. 11	Qu. 12	Qu. 13
35	2	3	3	3	2	2	1	1	1	2	2	1	3	1	0	1
36	3	3	3	1	1	1	1	1	1	2	0	1	4	3	4	0
37	2	3	-	2	2	2	2	3	2	3	4	2	4	2	1	1
38	2	2	2	3	2	3	1	2	2	2	1	2	4	2	1	1
39	1	1	1	3	4	4	3	4	4	0	0	4	4	4	4	4
40	-	2	2	3	2	3	3	3	3	1	1	4	4	3	3	3
41	2	1	1	4	4	4	4	4	4	0	0	3	4	4	4	4
42	2	4	2	2	1	2	1	3	2	1	1	1	4	2	2	1
43	4	4	3	1	1	1	2	2	1	2	0	3	4	1	0	0
44	4	4	4	0	1	0	1	0	1	1	0	1	2	3	0	0
45	-	-	-	1	2	3	1	3	1	0	1	1	4	1	3	0
46	2	1	1	3	4	4	3	4	4	1	1	3	4	4	4	3
47	1	2	2	3	4	4	3	4	3	3	3	3	4	4	3	4
48	3	4	4	-	-	-	-	-	-	-	-	-	-	-	-	-
49	2	2	2	2	3	3	3	3	3	1	1	3	4	3	2	2
50	-	-	-	2	4	4	4	4	3	3	0	3	4	1	4	2
51	2	2	3	3	-	2	2	1	1	1	2	3	4	4	1	3
52	4	4	4	0	0	0	0	0	0	0	0	4	4	1	1	-
53	3	3	2	1	1	1	2	1	1	0	0	3	1	1	0	0
54	2	3	3	3	3	3	3	2	2	2	1	2	4	3	3	2
55	4	3	3	1	3	1	1	0	3	1	0	1	4	0	0	0
56	2	3	2	2	2	1	1	2	2	2	3	2	4	4	2	2
57	4	4	4	0	0	0	0	0	0	0	0	0	0	0	0	0
58	3	3	3	2	2	1	1	1	1	3	2	1	1	1	1	1
59	2	1	2	2	2	2	3	2	1	3	1	3	2	3	3	3
60	2	3	3	1	1	1	1	1	1	2	2	3	4	3	1	3
61	1	2	2	3	4	4	3	4	4	3	3	4	4	4	4	3
62	3	2	1	1	1	2	4	4	4	1	1	4	4	1	4	4
63	3	3	2	3	4	2	1	-	1	1	4	3	4	4	4	1
64	3	2	2	3	3	3	3	3	3	2	2	3	4	4	2	2
65	3	3	2	1	1	1	2	2	2	1	1	3	2	2	2	2
66	3	3	3	1	2	1	2	2	2	1	0	3	3	2	0	0
67	2	2	2	3	4	3	4	3	3	3	2	4	3	4	3	3
68	3	4	3	1	4	2	0	2	0	2	2	4	4	4	1	2

Appendix 3.11 Baseline Results in Functional Tests in Cancer Patients

Study No.	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
	s	s	s	s	2 min. distance (m)	6 min. distance (m)
1	1.05	4.76	2.40	2.11	139	447
2	1.35	5.98	2.81	2.80	89	-
3	-	-	-	-	-	-
4	1.70	8.48	2.30	2.56	123	-
5	0.70	5.06	1.75	1.46	145	-
6	1.41	8.11	2.58	2.26	140	430
7	1.30	7.69	2.76	2.35	-	-
8	1.50	8.87	2.77	2.86	140	404
9	3.18	19.46	8.69	9.89	-	-
10	1.80	18.67	9.28	8.22	-	-
11	3.80	22.16	6.98	8.25	-	-
12	1.25	5.55	-	-	104	-
13	1.35	6.20	3.06	2.53	-	-
14	1.40	10.78	3.80	-	123	-
15	4.90	33.30	6.96	5.07	30	-
16	1.12	7.08	3.06	2.30	100	286
17	1.66	10.17	2.31	2.31	138	410
18	1.80	10.27	3.46	3.02	130	385
19	1.80	12.54	3.81	2.87	-	-
20	0.90	6.17	2.49	2.27	130	370
21	0.95	4.80	2.19	1.79	130	395
22	-	-	-	-	-	-
23	4.18	23.85	8.65	6.35	-	-
24	2.38	11.66	-	-	-	-
25	1.56	8.94	3.36	2.54	120	380
26	1.46	7.76	2.69	2.47	130	390
27	2.49	10.76	4.17	3.20	70	-
28	1.26	5.90	2.46	2.28	135	385
29	2.96	10.36	-	-	79	-
30	1.15	7.40	4.16	3.34	90	279
31	0.80	5.05	2.06	1.70	194	604
32	1.51	7.15	-	-	-	-
33	1.06	4.38	1.96	1.64	130	376
34	-	-	-	-	-	-

Study No.	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
	s	s	s	s	2 min. distance (m)	6 min. distance (m)
35	1.38	7.98	2.34	2.02	140	-
36	2.46	8.76	-	-	-	-
37	1.41	7.30	-	-	-	-
38	1.26	6.66	2.75	2.13	113	325
39	1.30	7.35	2.77	2.29	160	462
40	1.38	9.85	3.56	3.00	100	-
41	1.66	6.76	5.01	5.34	83	-
42	-	-	-	-	-	-
43	-	-	-	-	-	-
44	1.31	5.15	3.78	3.36	102	-
45	1.85	8.29	8.75	7.94	-	-
46	1.22	9.46	3.06	3.20	130	-
47	1.28	5.05	2.89	2.16	154	456
48	1.27	7.58	-	-	-	-
49	1.56	6.76	2.96	2.92	130	-
50	-	-	-	-	-	-
51	0.98	6.28	3.46	3.26	100	-
52	6.06	-	5.74	7.15	-	-
53	2.10	11.31	4.14	3.77	120	-
54	-	-	-	-	-	-
55	-	-	-	-	-	-
56	1.45	9.07	3.55	3.73	-	-
57	-	-	-	-	-	-
58	2.30	8.21	3.70	2.80	74	-
59	2.24	9.54	3.20	3.03	139	400
60	2.08	6.87	-	-	-	-
61	1.36	6.21	2.64	2.10	151	445
62	2.96	12.95	-	-	-	-
63	1.79	9.95	-	-	-	-
64	1.25	5.76	2.11	1.79	155	433
65	1.38	6.26	-	-	-	-
66	1.56	8.96	3.20	3.40	100	-
67	1.16	5.76	2.77	2.31	128	374
68	-	-	-	-	-	-

Appendix 3.12 Baseline Scores for EORTC Questionnaire and HAD Scale in Cancer Patients

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales									HAD Scale	
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
1	80	100	-	-	-	-	16.7	16.7	33.3	33.3	0	33.3	33.3	-	-	6	6
2	60	66.7	91.7	83.3	100	50	55.6	0	0	66.7	0	0	0	0	0	4	9
3	20	50	91.7	83.3	100	0	55.6	0	0	0	33.3	33.3	0	66.7	0	9	16
4	60	66.7	66.7	66.7	33.3	33.3	55.6	16.7	16.7	66.7	0	33.3	66.7	66.7	0	7	3
5	60	83.3	66.7	50	16.7	58.3	55.6	0	33.3	66.7	0	0	0	0	100	6	5
6	60	16.7	75	50	100	75	66.7	16.7	16.7	0	33.3	33.3	0	0	0	4	3
7	40	50	66.7	66.7	100	58.3	33.3	33.3	16.7	33.3	66.7	100	33.3	0	0	12	11
8	40	33.3	41.7	50	66.7	58.3	66.7	16.7	33.3	0	66.7	100	66.7	33.3	0	9	10
9	20	83.3	75	83.3	66.7	75	33.3	33.3	0	33.3	33.3	66.7	33.3	0	0	11	8
10	20	16.7	41.7	33.3	0	33.3	66.7	16.7	33.3	66.7	0	100	33.3	66.7	33.3	17	9
11	20	83.3	58.3	16.7	100	25	55.6	16.7	83.3	66.7	66.7	33.3	100	33.3	0	6	12
12	40	33.3	75	83.3	50	50	22.2	16.7	50.0	0	0	33.3	0	66.7	0	3	7
13	20	16.7	41.7	66.7	50	16.7	100	66.7	83.3	100	100	100	33.3	0	33.3	13	9
14	60	66.7	83.3	83.3	83.3	66.7	66.7	33.3	16.7	33.3	0	33.3	33.3	33.3	0	8	5
15	0	0	33.3	66.7	66.7	0	83.3	33.3	100	100	66.7	66.7	0	0	33.3	13	13
16	60	66.7	75	100	83.3	100	33.3	0	0	33.3	0	0	0	0	0	8	6
17	80	66.7	66.7	100	66.7	66.7	33.3	33.3	33.3	33.3	-	33.3	33.3	0	0	8	3
18	40	33.3	66.7	100	50	50	66.7	0	33.3	0	0	0	66.7	0	33.3	5	8
19	75	50	75	83.3	83.3	66.7	55.6	0	33.3	33.3	0	33.3	33.3	0	0	6	9
20	80	66.7	83.3	100	83.3	91.7	44.4	0	16.7	100	33.3	0	66.7	33.3	0	3	5
21	40	66.7	50	83.3	50	41.7	66.7	0	0	0	66.7	0	0	0	66.7	5	5
22	-	-	-	-	-	66.7	-	-	-	-	-	-	-	-	-	-	-
23	0	0	66.7	50	0	50	66.7	83.3	83.3	66.7	100	100	100	33.3	0	6	13
24	20	0	83.3	83.3	0	50	88.9	66.7	50	100	-	0	0	0	0	7	7
25	80	83.3	83.3	66.7	100	75	33.3	0	16.7	33.3	33.3	0	0	0	0	8	7
26	60	16.7	58.3	16.7	33.3	50	77.8	16.7	50	33.3	-	0	33.3	0	0	8	6
27	40	0	66.7	83.3	33.3	33.3	77.8	0	66.7	66.7	66.7	33.3	66.7	66.7	0	6	7
28	60	33.3	91.7	50	16.7	41.7	44.4	16.7	33.3	0	0	66.7	33.3	0	0	3	-
29	40	16.7	33.3	83.3	66.7	66.7	44.4	16.7	0	33.3	33.3	0	33.3	0	0	10	7
30	80	50	91.7	83.3	66.7	66.7	33.3	0	0	100	0	0	33.3	0	0	1	3
31	40	16.7	91.7	50	33.3	75	55.6	0	16.7	66.7	0	0	0	66.7	0	3	2
32	20	50	66.7	83.3	66.7	50	55.6	83.3	66.7	33.3	33.3	33.3	66.7	0	0	8	10
33	80	50	58.3	66.7	33.3	83.3	55.6	0	66.7	33.3	66.7	33.3	0	0	33.3	11	3
34	20	0	58.3	33.3	0	100	77.8	0	0	100	0	0	100	0	0	11	10

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales									HAD Scale	
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
35	60	66.7	66.7	83.3	50	33.3	55.6	50	33.3	33.3	66.7	33.3	33.3	0	0	11	10
36	40	16.7	100	66.7	33.3	50	66.7	0	16.7	33.3	0	66.7	0	0	0	0	9
37	60	33.3	100	83.3	66.7	75	50	33.3	66.7	33.3	0	0	33.3	0	100	6	5
38	60	33.3	58.3	83.3	33.3	50	33.3	0	33.3	33.3	33.3	0	0	0	66.7	9	9
39	100	100	75	100	100	83.3	0	0	0	0	0	0	0	0	0	3	1
40	60	33.3	83.3	66.7	66.7	50	33.3	16.7	33.3	33.3	-	33.3	33.3	0	33.3	6	3
41	60	50	100	33.3	100	66.7	11.1	33.3	16.7	0	33.3	0	0	0	0	0	2
42	40	33.3	66.7	50	66.7	33.3	55.6	66.7	66.7	66.7	0	66.7	66.7	0	0	-	-
43	0	50	58.3	50	50	50	88.9	16.7	50	66.7	66.7	66.7	100	0	66.7	11	12
44	20	33.3	0	33.3	16.7	58.3	100	0	100	100	100	33.3	0	100	33.3	11	8
45	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46	20	50	91.7	100	83.3	66.7	11.1	0	0	33.3	0	0	0	0	33.3	0	2
47	100	100	91.7	83.3	83.3	83.3	22.2	0	16.7	0	0	0	0	0	0	7	2
48	60	83.3	91.7	100	100	33.3	88.9	0	0	66.7	100	0	33.3	0	0	-	-
49	60	33.3	83.3	50	66.7	50	33.3	0	16.7	33.3	33.3	66.7	33.3	0	33.3	8	10
50	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
51	60	66.7	83.3	66.7	100	25	44.4	0	33.3	33.3	66.7	33.3	66.7	0	0	5	6
52	25	33.3	33.3	83.3	-	50	100	100	100	100	33.3	33.3	100	0	0	8	15
53	0	16.7	50	33.3	16.7	50	55.6	33.33	50	66.7	66.7	100	66.7	33.3	33.3	8	12
54	40	16.7	66.7	50	50	58.3	55.6	33.33	33.3	33.3	0	66.7	33.3	33.3	33.3	7	11
55	20	16.7	77.8	33.3	33.3	83.3	77.8	0	33.3	33.3	66.7	0	0	0	-	7	14
56	40	50	41.7	66.7	100	58.3	44.4	33.33	66.7	33.3	66.7	66.7	0	0	0	8	4
57	0	0	41.7	33.3	50	0	100	50	16.7	100	33.3	100	100	33.3	0	17	17
58	40	33.3	41.7	50	0	33.3	66.7	66.67	66.7	66.7	33.3	66.7	100	66.7	33.3	8	18
59	60	66.7	91.7	100	83.3	83.3	22.2	16.67	16.7	0	0	33.3	33.3	33.3	0	8	2
60	40	16.7	66.7	66.7	50	50	55.6	0	16.7	66.7	0	0	0	0	0	4	10
61	80	50	88.9	83.3	33.3	75	22.2	0	0	33.3	0	0	0	0	0	2	2
62	20	0	100	100	0	50	44.4	0	33.3	66.7	66.7	33.3	66.7	0	33.3	3	3
63	60	33.3	58.3	83.3	66.7	75	55.6	0	16.7	100	33.3	33.3	33.3	0	0	5	13
64	60	66.7	100	100	66.7	83.3	44.4	0	16.7	33.3	33.3	0	0	0	0	8	2
65	60	50	100	66.7	66.7	33.3	55.6	16.67	33.3	0	33.3	66.7	0	0	0	8	9
66	40	66.7	75	100	0	33.3	66.7	0	66.7	33.3	66.7	66.7	66.7	0	0	8	13
67	80	16.7	75	83.3	50	83.3	33.3	50	16.7	33.3	66.7	66.7	33.3	0	0	7	6
68	20	50	25	100	100	41.7	77.8	16.7	0	66.7	0	0	0	0	0	5	11

Appendix 3.13 Karnofsky Performance Status, Anthropometrics & Body Composition in Cancer Patients at 6 Weeks

Study No.	KPS	Height cm	Current weight kg	Current BMI	Pred. Vecf (l)	Pred. Vtbw(l)	Pred. Vicf(l)	icf/ecf ratio	TST mm	BST mm	ThST mm	MAC cm	AMA cmsq.	MTC cm	TMA cmsq.	24hr ur. creat mmol/l
1	75	167.0	46.25	16.6	14.5	24.6	10.1	0.70	4.0	3.5	4.0	19.6	26.8	36.1	96.7	4.0
5	85	177.0	79.00	25.2	20.3	35.5	15.3	0.75	17.5	8.0	13.5	31.6	54.3	51.7	179.3	15.4
8	60	152.0	45.00	19.5	11.8	20.6	8.8	0.75	13.0	9.0	17.5	21.8	25.0	46.0	130.7	2.1
9	65	151.0	74.00	32.5	15.5	32.2	16.7	1.07	-	-	-	29.4	-	60.9	-	-
14	70	149.0	49.00	22.1	14.4	24.4	10.0	0.69	10.5	5.0	8.0	25.0	37.5	43.6	134.4	-
16	90	150.5	53.50	23.6	13.1	23.4	10.3	0.79	13.5	8.0	17.5	28.9	48.4	52.3	174.3	6.6
17	90	159.5	54.50	21.4	12.9	23.9	11.0	0.85	24.5	11.0	23.0	26.3	27.6	45.4	116.0	-
18	85	171.5	55.00	18.7	14.6	26.9	12.3	0.84	12.0	8.5	19.5	25.3	36.9	46.6	130.4	-
19	70	161.0	42.00	16.2	13.7	25.1	11.4	0.83	7.0	4.0	8.5	19.8	24.7	37.3	95.5	-
20	75	176.0	79.75	25.8	19.8	38.6	18.8	0.95	8.5	8.5	-	30.0	59.5	53.4	-	6.2
21	80	174.0	91.00	30.1	21.6	41.0	19.4	0.90	11.0	8.0	22.5	33.2	70.4	56.9	197.7	14.2
24	35	164.0	49.75	18.5	-	-	-	-	-	-	-	23.1	-	-	-	-
27	60	174.0	90.75	30.0	20.7	35.2	14.5	0.70	15.0	17.0	15.0	33.1	64.2	53.1	186.4	-
28	80	164.0	50.25	18.7	14.0	23.9	9.9	0.71	8.5	5.0	16.0	23.4	34.2	43.1	115.4	6.8
29	65	168.0	79.50	28.2	20.1	31.6	11.5	0.57	11.5	8.0	8.0	29.2	52.1	48.5	168.4	-
30	80	160.0	78.50	30.7	17.4	36.4	19.0	1.09	35.5	21.5	17.5	32.0	34.6	59.6	233.1	7.2
32	60	154.5	39.75	16.7	-	-	-	-	9.0	7.5	9.0	21.2	26.9	34.7	80.9	-
33	80	162.5	62.50	23.7	17.4	32.1	14.7	0.85	10.5	5.5	13.0	28.5	50.6	48.4	156.4	5.7
36	60	180.5	90.00	27.6	23.3	37.1	13.8	0.59	21.0	11.0	24.0	31.5	49.4	50.5	147.0	-
38	80	168.5	56.25	19.8	13.5	25.8	12.3	0.91	6.5	3.0	7.0	24.3	39.4	40.1	114.4	-
39	90	162.0	52.50	20.0	12.7	24.0	11.3	0.90	11.5	9.5	22.5	26.9	43.2	47.2	128.2	7.9
40	80	169.5	52.50	18.3	15.1	24.4	9.3	0.62	4.5	2.5	5.0	22.5	35.4	36.4	96.6	-
41	65	157.5	45.50	18.3	13.5	22.3	8.8	0.65	6.5	4.0	-	23.5	36.7	40.6	-	-
46	85	176.0	84.75	27.4	21.7	36.5	14.9	0.69	19.5	10.5	-	30.8	48.5	55.3	-	7.7
47	90	167.0	66.25	23.8	16.0	29.2	13.2	0.82	14.0	6.5	7.5	29.4	49.8	46.3	153.8	9.3
51	80	144.5	64.50	30.9	11.7	22.7	11.0	0.95	23.5	17.5	42.5	32.5	50.2	54.3	133.5	5.7
60	70	167.5	48.00	17.1	13.7	22.5	8.8	0.64	4.5	3.0	8.5	20.3	28.4	35.5	85.8	-
61	90	149.5	49.25	22.0	13.2	22.9	9.7	0.74	11.0	8.5	20.0	25.7	39.4	43.3	109.1	6.3
64	90	165.5	58.00	21.2	17.9	30.9	12.9	0.72	8.5	5.5	8.5	25.8	42.6	47.1	157.2	15.3
65	60	178.0	71.00	22.4	20.0	40.3	20.3	1.01	11.5	10.5	12.0	28.6	49.7	48.2	157.2	7.1
66	40	162.5	35.00	13.3	9.7	16.3	6.6	0.68	4.0	2.0	-	15.7	16.6	-	-	-
67	80	171.0	60.00	20.5	-	-	-	-	9.0	5.5	10.0	25.0	39.1	42.7	124.6	-

Appendix 3.14 Blood Tests in Cancer Patients at 6 weeks

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	C-reactive protein mg/l
1	124	3.0	134	4.2	5.1	83	35	17	2.28	0.85	-	-	18
5	115	16.4	131	3.2	5.2	60	32	11	2.32	0.69	10.0	44.4	182
8	93	10.6	142	3.7	11.5	84	36	35	2.52	0.87	11.4	25.8	37
9	116	5.6	140	4.2	5.8	107	37	30	2.20	1.03	9.4	22.7	16
14	122	6.0	137	4.5	8.5	80	41	103	2.30	0.84	9.9	22.8	5
16	150	5.9	141	4.5	4.7	95	39	57	2.30	0.92	11.6	19.2	30
17	135	4.6	140	4.1	6.5	82	40	71	2.41	0.99	12.7	25.3	2
18	116	10.5	138	3.9	3.1	78	37	26	2.40	0.85	6.8	30.3	25
19	138	6.1	139	4.3	8.7	105	43	34	2.33	0.86	11.3	20.6	4
20	135	4.6	140	4.1	6.5	82	40	71	2.41	0.99	12.7	25.3	2
21	134	15.3	137	4.0	7.1	126	42	134	2.29	0.89	11.0	16.9	17
24	113	24.2	130	4.5	6.4	92	33	-	3.35	-	-	-	-
27	132	7.8	141	4.4	8.7	167	44	41	2.44	0.88	7.6	20.0	33
28	178	13.4	140	-	4.9	113	46	67	2.40	0.97	13.3	19.2	-
29	121	6.4	137	4.4	6.2	101	41	74	2.30	0.90	8.6	24.9	29
30	125	5.5	140	3.6	6.9	89	40	123	2.19	0.92	11.7	20.4	4
32	114	6.4	140	4.2	3.2	70	38	141	2.56	0.86	7.9	38.8	14
33	125	5.5	140	3.6	6.9	89	40	123	2.19	0.92	11.7	20.4	4
36	117	10.5	140	4.5	3.7	71	38	17	2.36	0.98	8.6	27.2	65
38	152	11.7	142	4.3	4.4	72	44	88	2.48	0.82	9.9	20.3	16
39	147	5.5	139	3.6	7.1	98	47	32	2.35	0.69	14.1	21.5	12
40	117	9.3	137	4.4	4.5	100	41	30	2.68	0.84	6.2	22.9	49
41	152	7.5	135	4.1	5.0	88	36	46	2.23	0.81	13.2	19.5	6
46	126	6.9	136	4.8	8.4	111	45	76	2.29	0.79	9.2	20.9	26
47	128	5.9	137	4.0	7.2	133	41	22	2.36	-	11.0	23.2	13
51	138	10.8	137	4.2	7.0	76	41	32	2.27	0.86	10.6	21.0	45
60	126	6.9	144	3.8	7.8	75	37	47	2.31	1.00	8.4	13.7	11
61	156	12.4	134	3.5	4.9	79	45	22	2.48	0.56	9.7	23.4	14
64	123	4.6	143	4.4	8.2	73	40	68	2.40	0.76	13.8	30.1	6
65	115	7.8	139	4.3	8.2	112	42	23	2.37	0.86	10.5	21.2	11
66	115	16.4	131	3.2	5.2	60	32	11	2.32	0.69	10.0	44.4	182
67	-	-	-	-	-	-	-	-	-	-	-	-	-

Appendix 3.15 Linear Analogue Scale Scores of Weakness and Strength, FACT-Ftg and EORTC Fatigue Scales, Handgrip Strength and Quadriceps Torque in Cancer Patients at 6 Weeks

Study No.	LASA Weak	LASA Strength	FACT-Ftg	EORTC-Fatigue	Handgrip strength ND	Handgrip strength	Max. isokinetic torque	Max. isometric torque
	cm	cm			kgW	kgW	Nm	Nm
1	7.2	5.3	33	33.3	31.0	-	117.8	156.2
5	5.3	6.2	35	66.7	36.5	-	-	-
8	6.7	2.9	33	33.3	15.0	-	-	-
9	2.8	3.6	29	44.4	19.0	-	-	-
14	3.6	5.4	35	33.3	16.5	-	-	-
16	1.8	3.4	39	33.3	13.5	-	103.1	97.7
17	4.8	6.3	38	33.3	19.0	-	67.0	106.4
18	3.4	6.4	42	33.3	22.0	-	91.8	109.2
19	2.6	6.6	40	33.3	14.0	-	-	-
20	7.3	1.3	25	77.8	37.5	-	165.5	241.8
21	7.3	7.7	40	33.3	44.0	-	136.0	-
24	6.3	1.7	-	-	10.0	-	-	-
27	7.9	2.0	7	100	57.0	-	-	-
28	2.5	4.8	32	44.4	-	-	108.8	123.3
29	5.9	4.1	35	33.3	31.5	-	-	-
30	0.8	6.5	46	22.2	24.0	-	143.8	132.0
32	4.1	4.3	25	66.7	10.0	-	-	-
33	4.0	6.6	26	55.6	33.0	36.0	223.0	202.1
36	4.9	4.8	20	66.7	30.5	-	-	-
38	3.4	3.7	30	33.3	35.0	33.5	144.8	168.3
39	2.1	7.5	45	16.7	19.5	18.0	-	-
40	2.7	4.8	34	33.3	28.5	25.0	61.7	124.6
41	7.2	6.1	34	44.4	26.5	-	-	-
46	0.2	7.3	47	33.3	35.5	29.0	-	-
47	2.0	6.5	36	22.2	32.0	30.5	192.3	186.2
51	3.7	3.6	37	33.3	19.5	18.5	84.9	120.8
60	3.9	5.7	34	33.3	23.5	21.0	-	-
61	2.7	6.4	46	33.3	16.5	-	118.8	103.7
64	6.9	5.1	40	33.3	25.0	31.0	156.5	123.5
65	2.6	-	44	33.3	35.0	35.0	-	-
66	5.0	3.9	9	66.7	2.5	1.5	-	-
67	2.9	8.0	42	33.3	23.5	22.5	105.4	186.6

Appendix 3.16 Results in Functional Tests in Cancer Patients at 6 Weeks

Study No.	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
	s	s	s	s	2 min. distance (m)	6 min. distance (m)
1	0.97	5.15	2.36	2.58	131	380
5	0.81	5.46	1.77	1.57	155	458
8	1.55	7.79	2.35	2.39	134	400
9	4.59	17.76	7.58	8.31	57	-
14	1.38	8.71	3.20	2.69	128	-
16	1.25	8.28	3.00	2.56	100	290
17	1.15	9.07	2.95	2.66	120	355
18	1.55	10.19	2.40	2.83	135	391
19	1.55	6.85	3.56	2.78	-	-
20	0.85	5.98	2.21	2.42	120	-
21	1.09	5.49	2.28	2.10	125	370
24	-	-	-	-	-	-
27	-	-	-	-	-	-
28	0.96	4.96	2.40	2.25	150	435
29	1.58	9.50	3.17	2.79	98	-
30	1.08	6.05	3.87	3.81	120	347
32	1.37	7.46	-	-	-	-
33	1.11	4.51	2.06	1.53	128	371
36	1.68	7.65	-	-	-	-
38	0.98	4.36	2.70	2.16	140	-
39	1.44	7.49	2.70	2.51	159	465
40	1.30	8.44	3.40	2.96	-	-
41	1.46	6.89	4.46	4.47	90	-
46	1.21	8.59	3.08	3.65	140	-
47	1.25	4.86	2.98	2.69	159	469
51	0.80	6.27	2.98	2.30	100	282
60	2.48	10.84	-	-	-	-
61	0.98	4.99	2.26	1.84	142	460
64	0.95	3.68	1.95	1.71	145	412
65	1.01	5.97	-	-	-	-
66	-	-	-	-	-	-
67	1.16	5.23	-	-	-	-

Appendix 3.17 Scores for EORTC Questionnaire and HAD Scale in Cancer Patients at 6 Weeks

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales								HAD Scale		
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
1	100	16.7	66.7	83.3	33.3	66.7	33.3	50	16.7	0	-	100	33.3	0	33.3	3	9
5	80	83.3	66.7	83.3	50	66.7	66.7	0	33.3	66.7	0	0	0	0	100	9	9
8	40	50	66.7	66.7	66.7	50	33.3	0	33.3	33.3	33.3	33.3	33.3	33.3	0	6	7
9	0	66.7	66.7	66.7	50	58.3	44.4	33.3	0	66.7	33.3	33.3	0	0	0	12	7
14	60	83.3	91.7	83.3	50	58.3	33.3	33.3	0	66.7	0	33.3	33.3	0	0	6	5
16	60	66.7	66.7	100	66.7	50	33.3	16.7	0	33.3	0	0.0	0	0	0	7	5
17	80	33.3	66.7	100	66.7	50	33.3	0	33.3	33.3	33.3	33.3	0	33.3	0	7	6
18	60	50	91.7	83.3	83.3	50	33.3	0	33.3	0	0	0	0	33.3	33.33	6	6
19	60	83.3	83.3	83.3	83.3	83.3	33.3	0	33.3	33.3	0	0	0	0	33.33	4	8
20	40	83.3	16.7	66.7	66.7	58.3	77.8	16.7	66.7	100	100	0	33.3	0	0	7	5
21	80	83.3	66.7	66.7	100	66.7	33.3	0	33.3	33.3	33.3	33.3	33.3	0	33.3	7	5
24	-	-	-	-	-	25	-	-	-	-	-	-	-	-	-	-	-
27	20	0	58.3	50	0	16.7	100	0	33.3	100	33.3	66.7	66.7	0	0	8	7
28	60	66.7	83.3	50	50	66.7	44.4	0	33.3	0	0	0	33.3	33.3	0	3	8
29	60	66.7	100	83.3	66.7	33.3	33.3	16.7	0	33.3	33.3	0	0	0	0	10	4
30	80	66.7	100	83.3	66.7	83.3	22.2	0	0	33.3	0	33.3	33.3	0	0	0	2
32	20	33.3	58.3	100	100	50	66.7	0	33.3	66.7	33.3	0	66.7	0	0	6	11
33	60	33.3	66.7	83.3	33.3	66.7	55.6	16.7	66.7	66.7	66.7	33.3	0	0	33.3	10	4
36	40	0	100	66.7	16.7	58.3	66.7	0	0	66.7	0	33.3	0	0	0	1	9
38	60	50	50	66.7	67	50	33.3	0	16.7	33.3	33.3	0	0	0	66.7	8	11
39	100	100	83.3	100	100	75	16.7	16.7	0	0	0	0	0	0	0	4	1
40	60	50	83.3	83.3	66.7	50	33.3	0	33.3	-	33.3	0	33.3	0	33.3	5	3
41	60	16.7	91.7	50	83.3	50	44.4	16.7	66.7	33.3	66.7	33.3	0	0	0	6	6
46	40	83.3	91.7	100	66.7	66.7	33.3	0	0	33.3	0	33.3	0	0	33.3	2	4
47	0	83.3	66.7	100	100	83.3	22.2	0	0	33.3	33.3	0	33.3	0	0	5	1
51	60	66.7	83.3	66.7	100	50	33.3	0	33.3	33.3	33.3	33.3	66.7	0	0	4	5
60	60	50	91.7	100	83.3	58.3	33.3	0	16.7	33.3	0	0	0	0	0	3	3
61	80	100	100	100	66.7	75	33.3	0	16.7	0	0	0	0	0	0	2	1
64	60	66.7	75	83.3	50	50	33.3	0	33.3	33.3	33.3	0	0	0	33.3	8	3
65	60	66.7	91.7	100	66.7	33.3	33.3	16.7	33.3	0	33.3	0	0	0	0	7	4
66	0	33.3	100	66.7	16.7	33.3	66.7	33.3	50	33.3	0	66.7	66.7	66.7	0	7	18
67	60	16.7	66.7	83.3	33.3	75	33.3	33.3	0	66.7	0	33.3	0	0	0	8	5

Appendix 3.18 Karnofsky Performance Status, Anthropometrics & Body Composition in Healthy Subjects at 12 Weeks

Study No.	KPS	Height cm	Current weight kg	Current BMI	Pred. Vecf (l)	Pred. Vtbw (l)	Pred. Vicf (l)	icf/ecf ratio	TST mm	BST mm	ThST mm	MAC cm	AMA cmsq.	MTC cm	TMA cmsq.	24hr ur. creat mmol/l
V1	100	177.5	81.00	25.7	22.3	40.9	18.6	0.84	16.5	6.5	14.0	30.6	51.4	53.5	192.0	15.5
V2	100	158.5	53.00	21.1	14.0	26.0	12.0	0.86	14.5	4.5	35.0	26.0	36.6	50.2	122.4	10.9
V3	90	174.5	79.00	25.9	-	-	-	-	18.5	7.5	14.0	34.7	66.5	48.2	152.8	16.8
V4	100	165.0	66.25	24.3	-	-	-	-	17.0	4.5	17.0	31.3	53.7	50.5	162.4	14.6
V5	100	176.5	89.50	28.7	23.8	44.0	20.1	0.84	12.5	6.5	9.5	32.2	63.7	56.4	227.2	18.3
V6	100	177.5	73.50	23.3	21.6	38.2	16.6	0.77	10.0	5.5	10.0	30.7	60.5	52.1	190.9	11.5
V7	100	163.5	68.00	25.4	-	-	-	-	21.0	17.5	24.0	31.6	49.8	54.6	176.4	8.4
V8	100	167.0	62.75	22.5	-	-	-	-	14.5	11.5	17.5	29.8	50.7	53.6	184.2	12.3
V9	100	172.5	74.50	25.0	17.7	29.8	12.1	0.68	23.5	15.0	-	32.9	51.9	58.8	-	6.7
V10	100	165.5	69.00	25.2	15.9	27.7	11.8	0.74	21.5	15.5	31.0	32.3	52.0	59.2	194.8	9.7
V11	100	152.5	53.50	23.0	13.4	23.1	9.7	0.73	15.0	10.0	-	27.8	42.4	48.9	-	8.7
V12	80	171.0	84.50	28.9	24.6	41.0	16.4	0.66	10.0	6.5	10.0	32.6	69.1	52.4	193.2	12.4
V13	100	169.0	65.50	22.9	17.4	32.6	15.2	0.87	21.5	15.0	-	32.0	50.8	49.9	-	12.4
V15	100	159.5	70.25	27.6	16.9	31.1	14.2	0.84	19.0	20.0	40.0	33.9	62.1	54.3	138.7	-

Appendix 3.19 Blood Tests in Healthy Subjects at 12 Weeks

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	C-reactive protein mg/l
V1	150	6.1	140	4.2	5.8	88	43	99	2.28	0.79	13.9	15.2	1
V2	147	6.2	139	-	4.6	85	44	205	2.29	0.76	16.2	30.2	-
V3	149	6.5	143	4.1	7.1	93	40	93	2.31	0.85	11.4	14.8	12
V4	143	6.0	142	4.5	6.7	97	44	167	2.30	0.65	11.6	15.7	10
V5	163	5.6	140	4.5	6.9	103	44	87	2.36	0.81	14.8	17.0	10
V6	148	5.9	142	4.5	5.5	98	40	84	2.49	0.93	11.8	16.8	19
V7	124	5.7	137	4.9	7.1	82	44	171	2.30	0.79	12.5	24.8	12
V8	142	4.0	141	4.4	5.2	101	44	102	2.36	0.80	11.9	11.0	10
V9	132	3.8	140	4.1	3.4	67	41	76	2.35	0.79	11.5	17.3	9
V10	118	4.0	140	4.2	7.5	42	43	128	2.33	0.81	14.0	23.9	8
V11	129	7.5	142	4.1	5.2	89	45	65	2.41	0.88	13.9	15.6	6
V12	118	5.9	144	3.6	15.4	381	42	41	2.34	1.01	12.0	17.2	8
V13	131	7.5	140	4.2	4.8	90	43	78	2.33	0.83	13.7	20.4	7
V15	145	6.7	138	4.1	3.3	83	44	80	2.52	0.89	12.8	24.1	10

Appendix 3.20 Linear Analogue Scales of Weakness and Strength, FACT-Ftg and EORTC Fatigue Scales, Handgrip Strength and Quadriceps Torque in Healthy Subjects at 12 Weeks

Study No.	LASA Weak	LASA Strength	FACT-Ftg	EORTC-Fatigue	Handgrip strength ND	Handgrip strength Max.	isokinetic torque	Max. isometric torque
	cm	cm			kgW	kgW	Nm	Nm
V1	0.2	9.9	52	0	47.0	44.5	233.0	203.5
V2	0.4	10.0	51	0	29.0	27.5	184.7	189.5
V3	6.6	7.3	42	22.2	36.5	38.5	247.0	211.8
V4	0.0	8.8	52	0	32.5	29.5	204.0	269.1
V5	1.5	10.0	51	0	50.0	45.5	262.6	350.3
V6	1.9	9.5	48	11.1	45.0	45.5	279.7	400.0
V7	3.5	8.2	45	11.1	19.0	21.0	128.5	155.7
V8	0.3	10.0	52	0	22.0	22.5	193.1	202.7
V9	0.0	10.0	50	0	25.5	26.5	169.6	179.8
V10	0.2	7.5	50	22.2	19.5	17.5	111.9	118.1
V11	1.8	8.2	45	22.2	24.5	26.0	130.5	-
V12	5.1	9.1	35	33.3	27.0	23.0	56.8	191.5
V13	2.9	7.6	50	0	36.0	36.5	225.7	234.6
V15	1.7	9.5	51	0	25.5	27.0	194.0	204.5

Appendix 3.21 Results in Functional Tests in Healthy Subjects at 12 Weeks

Study No.	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
	s	s	s	s	2 min. distance (m)	6 min. distance (m)
V1	0.79	4.55	1.80	1.30	200	585
V2	0.54	3.09	1.26	1.17	218	643
V3	1.36	8.36	2.76	2.34	162	472
V4	0.81	4.75	2.08	1.63	202	613
V5	0.95	4.58	1.85	1.57	200	605
V6	1.01	4.41	1.86	1.70	225	660
V7	0.90	6.38	2.31	1.54	180	544
V8	0.97	5.15	2.21	1.80	183	540
V9	0.90	4.95	1.91	1.84	194	595
V10	0.90	5.14	2.55	1.78	169	500
V11	0.76	3.81	1.91	2.05	140	428
V12	1.38	5.91	3.00	3.00	111	333
V13	1.06	3.87	2.14	1.93	169	504
V15	0.86	4.56	2.16	1.82	174	514

Appendix 3.22 Scores for EORTC Questionnaire and HAD Scale in Healthy Subjects at 12 Weeks

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales								HAD Scale		
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
V1	100	100	100	100	100	91.7	0	0	0	0	33.3	0	0	0	0	0	0
V2	100	100	100	100	100	91.7	0	0	0	0	0	0	0	0	0	1	0
V3	100	100	100	83.3	66.7	83.3	22.2	0	0	33.3	0	0	0	0	0	5	5
V4	100	100	100	100	100	100	0	0	16.7	0	0	0	0	0	0	0	0
V5	100	100	100	66.7	100	100	0	0	0	0	0	0	33.3	33.3	0	3	1
V6	100	100	100	100	100	91.7	11.1	0	0	0	0	0	0	0	0	3	0
V7	100	100	75	66.7	100	83.3	11.1	0	0	0	0	0	0	0	0	5	2
V8	100	100	100	66.7	100	100	0	0	0	0	33.3	0	33.3	0	0	5	0
V9	100	100	100	83.3	100	83.3	0	0	0	0	33.3	0	0	0	0	0	1
V10	80	100	100	83.3	100	91.7	22.2	0	0	0	0	0	0	0	0	4	1
V11	80	100	75	100	100	83.3	22.2	0	16.7	0	33.3	0	0	0	0	5	0
V12	40	33.3	100	83.3	66.7	66.7	33.3	0	33.3	0	0	0	0	0	0	1	2
V13	100	100	100	83.3	100	100	0	0	0	0	0	0	0	0	0	2	0
V15	100	100	91.7	100	100	100	0	0	0	0	33.3	0	0	0	0	5	0

Appendix 3.23 Karnofsky Performance Status, Anthropometrics & Body Composition in Cancer Patients at 12 Weeks

Study No.	KPS	Height cm	Current weight kg	Current BMI	Pred. Vecf (l)	Pred. Vtbw(l)	Pred. Vicf(l)	icf/ecf ratio	TST mm	BST mm	ThST mm	MAC cm	AMA cmsq.	MTC cm	TMA cmsq.	24hr ur. creat mmol/l
1	85	167.0	47.25	16.9	14.6	25.4	10.7	0.73	4.5	3.5	4.5	20.5	29.0	37.8	105.4	-
5	80	177.0	79.00	25.2	19.6	37.2	17.6	0.90	12.0	5.5	10.5	30.2	55.6	50.7	178.9	12.5
8	40	152.0	43.00	18.6	10.2	18.3	8.0	0.78	12.0	10.5	-	20.7	22.8	42.6	-	-
9	50	151.0	72.00	31.6	15.4	27.3	11.9	0.77	-	-	-	29.9	-	-	-	-
14	50	149.0	51.00	23.0	-	-	-	-	11.0	11.5	8.5	24.0	33.6	39.5	108.0	-
16	85	150.5	53.50	23.6	12.5	21.7	9.2	0.73	13.0	6.0	15.5	29.5	51.4	50.4	165.1	7.9
17	90	159.5	54.50	21.4	12.8	22.2	9.5	0.74	22.0	9.5	34.0	26.1	29.3	45.4	96.0	-
19	70	161.0	41.00	15.8	14.3	24.5	10.2	0.72	5.0	3.5	8.0	19.7	26.2	34.7	82.5	-
20	80	176.0	84.25	27.2	21.0	36.1	15.1	0.72	14.0	12.0	-	31.2	57.2	56.4	-	-
27	70	174.0	91.50	30.2	-	-	-	-	14.0	10.5	18.0	33.9	69.3	56.1	202.6	-
28	85	164.0	51.75	19.2	15.2	25.2	10.0	0.66	9.5	4.0	20.5	23.7	34.2	45.2	119.6	6.0
29	70	168.0	79.75	28.3	19.2	33.1	13.9	0.72	12.5	10.5	6.5	29.2	50.9	48.2	169.6	-
30	85	160.0	77.25	30.2	-	-	-	-	22.0	16.0	-	31.2	47.0	60.5	-	9.2
32	60	154.5	43.50	18.2	-	-	-	-	8.5	5.0	10.5	22.4	31.0	36.2	86.2	-
38	90	168.5	57.75	20.3	14.8	24.5	9.8	0.66	6.5	5.0	8.0	25.0	42.0	42.5	127.3	-
39	100	162.0	54.25	20.7	13.4	23.4	10.1	0.75	14.0	12.0	-	27.2	41.4	48.9	-	7.6
40	60	169.5	50.50	17.6	15.3	25.3	10.1	0.66	4.5	3.5	4.5	22.1	34.1	37.0	100.8	-
41	60	157.5	41.00	16.5	13.3	22.9	9.6	0.73	5.0	3.5	5.0	20.5	28.5	36.4	96.6	-
46	90	176.0	82.50	26.6	22.0	38.8	16.7	0.76	15.0	10.0	24.0	31.5	57.1	55.4	182.4	8.1
51	85	144.5	64.00	30.7	12.2	22.1	9.9	0.81	36.5	15.0	37.5	33.0	36.9	56.8	161.4	6.2
60	50	167.5	44.75	16.0	12.1	21.9	9.8	0.81	5.5	3.0	8.0	19.8	26.0	35.2	85.1	-
64	90	165.5	61.50	22.5	-	-	-	-	11.5	9.5	7.5	27.3	44.7	48.4	168.8	10.3
67	70	171.0	62.00	21.2	19.4	35.5	16.1	0.83	12.0	6.0	9.0	24.3	33.6	44.3	137.0	-

Appendix 3.24 Blood Tests in Cancer Patients at 12 Weeks

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	C-reactive protein mg/l
1	147	3.2	132	5.0	6.6	102	45	30	2.36	0.93	11.0	20.9	27
5	153	6.1	138	4.2	6.5	82	41	64	2.27	0.84	13.8	25.3	8
8	130	9.2	132	4.5	12.2	86	35	25	2.69	0.81	12.4	30.1	71
9	106	7.1	139	4.8	6.0	135	36	37	2.27	0.85	10.5	20.0	10
14	114	6.5	140	4.3	7.4	111	40	-	2.42	0.92	9.3	24.0	23
16	99	11.2	135	4.5	4.3	74	38	83	2.43	1.02	8.0	21.9	53
17	138	5.5	138	4.4	5.7	84	40	60	2.43	0.99	12.5	22.4	2
19	139	8.7	140	4.4	6.2	83	42	62	2.41	0.90	10.3	20.9	2
20	131	15.8	139	4.5	10.0	115	42	111	2.33	0.92	10.3	18.4	19
27	115	8.1	140	4.0	9.9	155	42	37	2.43	0.82	8.3	20.9	55
28	132	8.4	143	4.4	8.2	74	42	34	2.45	0.84	10.1	22.8	18
29	133	4.9	136	4.9	7.5	114	43	120	2.31	0.95	10.3	21.4	19
30	122	5.1	142	4.2	7.3	84	44	121	2.26	0.89	12.0	19.6	5
32	103	4.6	125	3.7	2.8	52	36	51	2.23	0.73	8.3	30.7	20
38	144	4.6	142	4.2	8.5	100	42	27	2.39	0.79	12.6	22.7	13
39	128	6.4	136	4.7	9.6	76	47	108	2.25	0.81	14.5	28.4	10
40	119	13.3	136	4.2	8.0	100	36	33	2.94	0.95	10.2	24.5	54
41	108	4.7	138	4.4	5.3	88	34	20	2.36	0.78	7.7	22.5	24
46	138	5.5	136	4.0	7.8	138	43	32	2.36	0.80	11.9	20.9	12
51	160	16.3	132	3.4	6.1	72	42	31	2.45	0.67	11.3	25.8	4
60	127	6.5	138	-	4.8	67	38	48	2.30	0.85	11.4	19.4	56
64	127	9.5	144	4.8	8.1	99	41	67	2.42	0.88	12.3	18.7	10
67	102	10.0	135	4.5	4.4	76	36	21	2.43	0.90	12.1	27.2	181

Appendix 3.25 Linear Analogue Scales of Weakness and Strength, FACT-Ftg and EORTC Fatigue Scales, Handgrip Strength and Quadriceps Torque in Cancer Patients at 12 Weeks

Study No.	LASA Weak	LASA Strength	FACT-Ftg	EORTC-Fatigue	Handgrip strength ND	Handgrip strength	Max. isokinetic torque	Max. isometric torque
	cm	cm			kgW	kgW	Nm	Nm
1	2.2	6.7	30	33.3	33.5	-	-	-
5	5.4	7.5	36	55.6	39.5	-	195.0	-
8	7.8	0.9	9	88.9	9.5	-	-	-
9	3.8	7.4	36	66.7	22.0	-	-	-
14	7.1	4.1	18	77.8	17.0	-	-	-
16	3.9	4.6	44	33.3	17.0	-	84.8	102.2
17	3.8	5.0	43	33.3	19.0	-	25.9	120.2
19	6.4	6.4	25	66.7	17.5	-	-	-
20	0.8	8.3	31	11.1	34.5	-	173.0	198.4
27	8.2	5.0	23	77.8	53.5	49.0	-	-
28	2.0	3.4	33	44.4	-	-	58.6	111.4
29	3.8	5.2	25	33.3	38.0	34.0	-	-
30	2.2	7.7	49	22.2	24.0	21.0	175.8	173.6
32	3.0	2.5	22	77.8	11.0	-	-	-
38	4.1	6.3	30	33.3	30.0	34.0	142.5	166.0
39	1.4	9.0	46	0	20.0	17.0	77.1	84.4
40	8.0	1.7	27	66.7	27.0	24.0	-	-
41	8.6	1.5	21	66.7	21.0	-	-	-
46	6.7	5.4	37	33.3	37.5	28.5	-	-
51	3.5	3.7	34	22.2	19.0	19.0	159.6	194.2
60	7.3	3.2	25	66.7	22.0	19.0	-	-
64	2.7	6.3	34	44.4	27.0	31.5	205.8	170.5
67	3.1	6.6	28	44.4	25.0	26.5	-	-

Appendix 3.26 Results in Functional Tests in Cancer Patients at 12 Weeks

Study No.	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
	s	s	s	s	2 min. distance (m)	6 min. distance (m)
1	0.79	4.89	1.95	1.97	145	434
5	0.96	5.45	1.76	1.32	166	486
8	-	-	-	-	-	-
9	-	-	-	-	-	-
14	-	-	-	-	-	-
16	1.16	7.30	2.69	2.40	111	308
17	1.27	9.07	2.45	2.20	129	377
19	-	-	3.20	3.00	-	-
20	1.49	6.85	2.79	2.27	111	-
27	1.19	8.90	-	-	-	-
28	0.94	4.46	2.38	2.33	155	445
29	2.51	10.28	4.00	3.75	100	-
30	1.36	5.84	4.00	3.38	121	359
32	-	-	-	-	-	-
38	0.97	4.55	2.55	2.10	136	383
39	1.20	8.36	2.51	2.28	160	464
40	-	-	-	-	-	-
41	-	-	-	-	-	-
46	1.37	8.70	2.90	2.87	140	-
51	0.90	4.16	2.58	2.20	109	303
60	3.19	-	-	-	-	-
64	1.07	4.06	2.11	1.71	145	420
67	-	-	-	-	-	-

Appendix 3.27 Scores for EORTC Questionnaire and HAD Scale in Cancer Patients at 12 Weeks

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales									HAD Scale	
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
1	100	50	83.3	100	66.7	66.7	33.3	33.3	0	33.3	0	66.7	66.7	0	0	4	6
5	60	83.3	66.7	83.3	66.7	50	55.6	0	33.3	66.7	33.3	0	0	0	66.7	6	9
8	20	33.3	41.7	33.3	66.7	83.3	88.9	50	33.3	33.3	100	100	66.7	0	0	-	-
9	40	50	75	83.3	66.7	33.3	66.7	16.7	0	100	0	33.3	33.3	0	0	14	8
14	60	50	66.7	66.7	83.3	33.3	77.8	33.3	50	100	0	33.3	33.3	0	0	9	8
16	60	33.3	66.7	100	100	50	33.3	0	33.3	66.7	0	0	33.3	0	0	8	7
17	80	66.7	66.7	100	100	66.7	33.3	0	33.3	0	66.7	33.3	33.3	33.3	0	7	4
19	60	66.7	58.3	66.7	66.7	58.3	66.7	0	33.3	66.7	0	0	0	0	0	7	9
20	60	66.7	100	83.3	66.7	83.3	11.1	0	0	66.7	33.3	0	0	0	33.3	6	2
27	20	83.3	75	66.7	33.3	50	77.8	0	50	100	33.3	0	66.7	0	33.3	7	7
28	60	50	83.3	66.7	33.3	75	44.4	0	0	0	0	33.3	0	0	0	2	4
29	60	66.7	83.3	83.3	100	41.7	33.3	0	0	33.3	33.3	33.3	33.3	0	0	8	5
30	80	83.3	100	100	83.3	91.7	22.2	0	0	0	0	0	33.3	0	0	0	1
32	40	33.3	50	83.3	66.7	33.3	77.8	33.3	66.7	33.3	66.7	100	66.7	0	33.3	3	11
38	60	50	50	83.3	50	58.3	33.3	0	33.3	33.3	0	33.3	0	0	66.7	8	8
39	100	100	83.3	100	100	91.7	0	16.7	0	0	0	0	0	0	0	6	1
40	40	33.3	83.3	50	50	16.7	66.7	0	66.7	33.3	33.3	33.3	33.3	0	33.3	7	7
41	40	0	100	50	66.7	66.7	66.7	33.3	33.3	66.7	66.7	0	33.3	0	0	4	15
46	40	50	91.7	100	83.3	66.7	33.3	0	0	33.3	0	33.3	33.3	0	33.3	1	7
51	40	50	100	66.7	100	50	22.2	0	33.3	66.7	0	33.3	33.3	0	0	5	3
60	0	0	75	100	66.7	41.7	66.7	0	66.7	66.7	0	66.7	33.3	0	0	5	10
64	60	66.7	66.7	66.7	50	66.7	44.4	16.7	33.3	33.3	33.3	0	33.3	0	33.3	8	2
67	60	33.3	75	66.7	50	50	44.4	33.3	50	100	0	33.3	33.3	0	0	7	5

Appendix 3.28 Karnofsky Performance Status, Anthropometrics & Body Composition in Cancer Patients at 6 Months

Study No.	KPS	Height cm	Current weight kg	Current BMI	Pred. Vecf (l)	Pred. Vtbw(l)	Pred. Vicf(l)	icf/ecf ratio	TST mm	BST mm	ThST mm	MAC cm	AMA cmsq.	MTC cm	TMA cmsq.	24hr ur. creat mmol/l
8	50	152.0	43.50	18.8	13.4	23.4	10.0	1.24	10.5	7.5	22.0	19.7	21.4	42.9	103.1	-
9	65	151.0	75.50	33.1	15.0	25.9	10.8	0.78	-	-	-	29.2	-	-	-	-
16	90	150.5	56.00	24.7	13.6	24.7	11.1	1.00	16.0	11.5	17.5	28.7	44.6	47.8	142.5	6.1
17	90	159.5	56.50	22.2	12.6	23.1	10.5	1.04	25.0	10.5	26.5	26.6	28.0	43.9	100.8	-
19	70	161.0	41.25	15.9	-	-	-	-	5.0	3.5	-	19.9	26.8	-	-	-
20	60	176.0	76.50	24.7	19.7	33.4	13.7	1.35	16.5	9.5	-	30.5	51.0	54.5	-	-
27	60	174.0	85.00	28.1	20.6	36.4	15.8	1.30	17.0	14.5	14.0	34.3	66.8	52.9	187.3	-
28	90	164.0	52.50	19.5	14.6	25.8	11.2	1.32	10.0	10.0	24.0	25.1	38.4	49.6	140.9	9.8
29	80	168.0	81.00	28.7	20.3	35.1	14.8	1.22	14.5	9.0	9.0	30.9	55.3	52.0	192.5	-
30	90	160.0	76.00	29.7	15.9	32.9	16.9	1.11	21.0	21.0	-	32.5	53.4	63.3	-	9.7
32	50	154.5	39.50	16.6	10.3	16.8	6.5	1.01	7.0	3.5	11.0	21.2	28.7	35.2	80.2	
38	80	168.5	61.00	21.5	14.6	25.4	10.8	1.18	7.5	3.0	7.0	26.2	45.3	44.4	141.8	-
39	100	162.0	56.25	21.4	-	-	-	-	14.5	13.0	-	28.9	47.2	48.8	-	8.1
46	80	176.0	84.50	27.3	20.9	35.3	14.4	1.30	17.5	7.5	-	32.8	59.4	58.3	-	9.9
51	80	144.5	63.50	30.4	12.7	23.1	10.5	0.76	23.5	14.0	27.0	33.4	53.9	56.4	182.8	8.4
60	50	167.5	39.50	14.1	-	-	-	-	-	-	-	18.1	-	31.0	-	-
64	90	165.5	66.00	24.1	-	-	-	-	-	-	-	29.9	-	51.5	-	10.1

Appendix 3.29 Blood Tests in Cancer Patients at 6 Months

Study No.	Haemoglobin g/l	White Cell Count	Sodium mmol/l	Potassium mmol/l	Urea mmol/l	Creatinine mmol/l	Albumin g/l	Creatine Kinase IU/l	Calcium mmol/l	Magnesium mmol/l	Zinc mmol/l	Copper mmol/l	C-reactive protein mg/l
8	79	14.4	135	3.6	5.2	66	34	57	2.36	0.91	9.5	29.0	66
9	113	6.8	142	4.2	6.6	91	38	37	2.17	1.10	12.0	21.3	13
16	104	6.1	140	4.2	3.5	60	38	68	2.23	0.86	8.6	19.2	70
17	135	5.2	137	4.1	7.4	86	38	61	2.41	0.90	13.9	20.4	12
19	147	9.5	139	4.5	8.1	77	43	105	2.19	0.86	12.4	23.3	19
20	130	11.7	136	5.0	7.2	118	39	82	2.47	0.83	12.3	24.3	16
27	107	8.1	142	4.9	12.2	153	41	51	2.42	0.80	8.7	27.3	66
28	137	7.8	137	4.5	9.7	84	42	46	2.42	0.83	12.1	25.3	9
29	133	4.8	138	5.0	7.3	114	40	91	2.27	0.91	9.5	22.6	25
30	114	7.2	140	3.0	8.6	92	39	88	2.29	0.93	12.0	28.1	177
32	128	4.7	136	4.6	6.1	85	33	-	2.36	-	-	-	-
38	-	-	141	3.3	6.8	102	45	45	2.29	0.83	17.0	26.4	1
39	126	6.4	136	4.8	6.6	93	43	110	2.36	0.76	10.6	24.7	13
46	139	6.3	141	4.50	8.7	140	42	27	2.36	0.76	10.8	24.0	11
51	155	14.0	137	4.5	3.9	60	43	32	2.47	0.81	9.2	27.0	16
60	125	5.4	143	3.5	5.8	71	31	30	2.25	0.88	7.8	15.3	8
64	124	9.4	142	4.4	6.6	111	44	78	2.36	0.81	11.2	20.8	8

Appendix 3.30 Linear Analogue Scales of Weakness and Strength, FACT-Ftg and EORTC Fatigue Scales, Handgrip Strength and Quadriceps Torque in Cancer Patients at 6 Months

Study No.	LASA Weak	LASA Strength	FACT-Ftg	EORTC-Fatigue	Handgrip strength ND	Handgrip strength Max.	isokinetic torque	Max. isometric torque
	cm	cm			kgW	kgW	Nm	Nm
8	4.7	2.6	26	66.7	10.0	-	-	-
9	0.5	8.3	28	44.4	22.5	-	-	-
16	2.9	6.7	48	11.1	15.5	13.0	32.0	70.2
17	5.6	4.9	38	33.3	19.5	19.0	76.3	112.8
19	4.6	3.6	28	44.4	20.0	11.0	-	-
20	9.1	2.7	10	77.8	26.5	28.5	-	-
27	7.3	4.3	13	88.9	51.5	47.0	-	-
28	0.2	5.1	44	33.3	-	13.5	163.6	146.5
29	3.0	8.1	36	33.3	37.0	33.5	-	-
30	2.5	6.7	47	22.2	25.5	21.0	196.5	186.0
32	2.6	2.7	17	77.8	9.5	10.0	-	-
38	5.9	5.4	30	33.3	30.5	34.5	140.6	171.9
39	0.7	9.0	42	11.1	21.0	20.0	97.2	103.0
46	6.1	5.3	43	22.2	37.5	30.0	-	-
51	6.4	3.0	30	33.3	21.5	21.5	140.9	187.9
60	4.0	4.5	38	44.4	13.0	12.5	-	-
64	2.6	6.1	34	44.4	28.5	29.0	210.3	181.7

Appendix 3.31 Results in Functional Tests in Cancer Patients at 6 Months

Study No.	Chair stand	Triple chair rise	Stair ascent	Stair descent	Walk	
	s	s	s	s	2 min. distance (m)	6 min. distance (m)
8	-	-	-	-	-	-
9	4.28	14.98	5.47	7.58	-	-
16	1.30	6.39	3.47	2.57	111	309
17	1.35	8.16	2.66	2.44	140	383
19	1.55	5.96	-	-	-	-
20	-	-	-	-	-	-
27	-	-	-	-	-	-
28	0.98	4.50	2.06	2.12	162	479
29	1.85	8.58	3.11	2.76	100	-
30	1.17	6.35	3.81	3.39	119	345
32	2.25	12.17	-	-	-	-
38	0.83	4.69	2.11	2.20	140	395
39	1.15	6.58	2.75	2.40	160	479
46	1.39	6.16	2.94	2.90	140	412
51	0.60	4.45	3.25	2.83	100	-
60	-	-	-	-	-	-
64	0.99	4.48	2.11	1.99	140	420

Appendix 3.32 Scores for EORTC Questionnaire and HAD Scale in Cancer Patients at 6 Months

Study No.	EORTC QOL Functional Scales						EORTC QOL Symptom Scales									HAD Scale	
	Physical	Role	Emotional	Cognitive	Social	QOL	Fatigue	N & V	Pain	Dyspnoea	Sleep	Appetite	Constipation	Diarrhoea	Financial	Anxiety	Depression
8	0	16.7	83.3	50	33.3	16.7	66.7	33.3	67	66.7	66.7	33.3	33.3	0	33.3	9	9
9	60	83.3	66.7	66.7	33.3	66.7	44.4	16.7	50	66.7	66.7	33.3	33.3	0	0	12	6
16	60	66.7	100	100	100	66.7	11.1	0	33	33.3	0	0	33.3	0	0	1	5
17	80	50	66.7	83.3	66.7	66.7	33.3	16.7	50	0	33.3	0	0	33.3	0	6	2
19	80	66.7	41.7	66.7	66.7	58.3	44.4	16.7	0	33.3	0	-	33.3	0	0	10	8
20	0	0	41.7	66.7	33.3	8.3	77.8	0	33	100	0	100	100	100	0	8	8
27	20	33.3	75	66.7	33.3	41.7	88.9	0	67	100	33.3	0	0	0	0	13	10
28	80	100	100	83.3	50	83.3	33.3	0	0	0	0	33.3	0	0	0	1	3
29	60	83.3	83.3	83.3	83.3	66.7	33.3	0	0	33.3	33.3	0	33.3	0	0	8	3
30	80	50	100	100	83.3	83.3	22.2	0	17	0	0	33.3	0	66.7	33.3	0	1
32	20	33.3	83.3	83.3	16.7	33.3	77.8	33.3	67	66.7	66.7	33.3	33.3	0	33.3	6	11
38	60	50	58.3	83.3	50	50	33.3	0	33	66.7	0	33.3	33.3	0	66.7	6	9
39	100	100	83.3	100	100	91.7	11.1	16.7	0	0	0	0	0	0	0	5	0
46	60	66.7	91.7	100	100	50	22.2	0	0	33.3	0	0	0	0	0	1	4
51	60	50	66.7	33.3	83.3	50	33.3	33.3	33	66.7	0	0	33.3	0	0	6	7
60	0	50	83.3	83.3	50	66.7	44.4	0	0	66.7	0	0	0	0	0	3	7
64	80	50	66.7	66.7	50	66.7	44.4	16.7	33	33.3	33.3	0	0	0	33.3	8	7

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