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**FATIGUE IN PATIENTS WITH
ADVANCED CANCER**
**aspects of assessment and
measurements**

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ABSTRACT

Symptoms are very common in patients with advanced cancer, with weakness, fatigue, anorexia, pain, and depression reported as the most common and distressing ones. A core issue in palliative care is to provide relief of symptoms, and to be able to do this satisfactorily there is still much to be known about symptom aetiology, prevalence, character and measurement. In this thesis, focus is on fatigue in patients with advanced cancer. Although fatigue is recognised to affect patients during the whole cancer trajectory, few studies have included and compared individuals at different stages of cancer from early treatment to the end of life. The primary aim was to advance knowledge of fatigue in patients with advanced cancer, by exploring to what extent and in what ways these patients experience fatigue, and to investigate aspects of assessment and measurement of fatigue. Both quantitative and qualitative methods have been used. Patients with advanced cancer (paper I-IV), patients receiving curative radiotherapy (Paper II, III), patients visiting a medical outpatient clinic (Paper II), healthy individuals (health care staff, Paper II) and registered nurses at a specialized palliative care facility (Paper V), participated in the different studies. In all studies the participants responded to different self-reporting questionnaires, the quantitative data were analysed with descriptive and parametric statistical methods, the qualitative data was explorative using an interpretive descriptive analysis.

The results indicate that patient with advanced cancer experienced fatigue more intensively than did patients earlier in the cancer trajectory, receiving curative cancer therapy. Our results confirm the multidimensionality of fatigue in patients with cancer. At different stages fatigue was most often experienced as a bodily sensation: as an overall feeling of tiredness, tiring easily, not feeling fit or rested, and lack of energy. Mental aspects of fatigue including ability to concentrate, making plans and do things had less of an impact. Being married or cohabiting was found to be related to higher levels of reported fatigue, which contradicts earlier findings. Forty-four percent of the patients with advanced cancer could be classified as depressed, as compared to about 17% of the patients receiving radiotherapy. There is a common agreement that fatigue negatively influences quality of life. It was shown that the relationship between fatigue and emotional functioning, and with quality of life, varies during the palliative care trajectory, and that the relation decreases in the last month of life. This may reflect that other symptoms and aspects of life become more important when patients are getting closer to death. These correlations were strongest for the group of patients who lived between 61 to 120 days. These findings may be interpreted that the fatigue experience may change at the end of life. We have shown clinical difficulties in making an assessment of quality of life and fatigue with a standardised measurement. This reflects the difficulties to perform these procedures both clinically and for research purposes in palliative care. However, this thesis also demonstrates that fatigue specific instruments are helpful in assessment of fatigue and that patients were able to answer different instruments even very close to death. Future research about fatigue is needed in this group of frail patients comprising physical, psychological, social and existential aspects of fatigue, as well as changes and meaning of fatigue over time.

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

- I. **Lundh Hagelin C.**, Seiger Å., Fürst CJ. Quality of life in terminal care – with special reference to age, gender and marital status. *Supportive Care in Cancer* 2006; 14 (4): 320 – 328
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LIST OF ABBREVIATIONS

ANOVA	Analysis of variance
CI	Confidence interval
CR-10	Category Ratio -10
EAPC	European Association for Palliative Care
EORTC QLQ C-30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
ESAS	Edmonton Symptom Assessment Scale
ESO	European School of Oncology
HADS	Hospital Anxiety and Depression Scale
HRQoL	Health-Related Quality of Life
MFI-20	Multidimensional Fatigue Inventory
NCCN	National Comprehensive Cancer Network (United States)
NCI	National Cancer Institute (United States)
QoL	Quality of Life
OR	Odds Ratio
SOFI	Swedish Occupational Fatigue Inventory
VAS	Visual Analogue Scale
WHO	World Health Organisation
WHOQOL	World Health Organisation Quality of Life Group

INTRODUCTION

My practical work as a clinical nurse in palliative care has contributed to the research questions raised in the present thesis. During my years working with patients at the end of life, the problems of symptoms difficult to treat became central. Patients with advanced cancer experience many symptoms, of which one is fatigue. Fatigue is a symptom I have encountered many times, and I have heard many patients complaining about being tired and not having the strength to participate in daily activities. From a nursing perspective fatigue was not a recognised symptom at that time and patients who complained about fatigue were often simply advised to lie down and rest. In the process of scientifically working with fatigue I have become aware of the complexity of symptoms seen in cancer patients, and especially those associated with fatigue. Interest in, and knowledge of, the field of cancer-related fatigue has increased during the last years, but there is much more to be learned. In exploring fatigue I have mainly focused on fatigue perceived by patients at the end of life by assessing fatigue by using different measurement tools. Although the question raised in this thesis derives from my profession as a registered nurse, I am convinced that we need to tackle fatigue in an interdisciplinary manner.

BACKGROUND

A diagnosis of cancer may dramatically change an individual's life situation. Cancer starts at the molecular and cellular level that leads to a manifest malignancy and series of other processes in the body. This process is not only limited to bodily changes; it will also change the individual's life situation in psychological, social, and existential aspects that may involve the family, relatives and other persons close to the patient. There is an ever increasing demand on those who devote attention to patients with advanced cancer. As early detection and the development of new therapies of cancer have improved, many patients live longer with the disease today than in the past (1). As the general population increases in age, new complex situations including distressing co-morbidities will be added to the demands placed as part of oncology care. However, despite extensive efforts to prevent and cure cancer there are still many patients dying from the disease. Focusing on patients with advanced cancer, this group of patients is shown to have many symptoms (2-4). It has been estimated, that there are up to 1.6 million patients with advanced cancer in Europe experiencing pain each year, and for about one third of these the pain will be severe (1). Fatigue is estimated to reach the same level as pain, and more than 1 of 2 may be affected by anxiety and /or depression, breathlessness, insomnia, nausea, constipation, or anorexia. Many of these symptoms may lead to great suffering for both patients and their families. This thesis is directing attention to the experience of fatigue in patients with advanced cancer, and to aspects of assessment and measurements of fatigue.

CANCER INCIDENCE, PREVALENCE AND MORTALITY IN SWEDEN

Sweden is a small country with a total population of approximately 9 million. Around 50.000 people are diagnosed with cancer in Sweden every year. The prevalence, i.e. the number of persons living, with cancer was in the end of 2006 approximately 375.000, and the survival rate of those diagnosed with a malignant disease has risen steadily since the 1960s (5). The total cancer mortality in Sweden was 22.614 people in 2004 which is approximately 25 % of the total mortality (6). Over half of those diagnosed with cancer are now cured thanks to more intensive diagnostics and better and more effective treatments.

ADVANCED CANCER

For defining the term "advanced cancer" in this thesis three different definitions will be presented: The first is by the United States (US) National Cancer Institute (NCI). "Cancer that has spread to other places in the body and usually cannot be cured or controlled with treatment" (7). The other definition is from the US National Comprehensive Cancer Network (NCCN) (8), "Cancer that has recurred and/or spread to vital organs in the body". Both these definitions are in some way discussible. The first definition by NCI indicates that an advanced cancer cannot be controlled with treatments; it could be argued that palliative care treatments both with radiation and cytotoxic drugs are used for control of tumour or metastatic growth. The definition from NCCN on the other hand, includes the term *spread* which could be understand synonymous with cancer spreading, and where it could be argued that an advanced cancer could be exclusively in a vital organ although advanced. In this thesis the term advanced cancer are define in line with the version of the definition by NCCN as being a "cancer which has recurred and/or involves vital organs in such a way that no curative treatment is effective".

PALLIATIVE CARE - CARE OF PATIENTS WITH ADVANCED CANCER

Historically, care of the dying was of marginal interest in clinical oncology, although now, in the space of only a few decades, the care of patients with an advanced cancer disease and the management of their symptoms has moved to the very centre of modern cancer care (9). The modern development of palliative care can be traced back to Dame Cicely Saunders, who can be regarded as the pioneer of the hospice and palliative care movement in the United Kingdom in the late 1960s (9). In the same period, several theoretical frameworks of death and dying were postulated as described by Copp (10), where the five-stage theory including: denial, anger, bargaining, depression and acceptance, by Kubler-Ross (1969) was featured as the principle paradigm in the area of coping with dying (10). Dying trajectories were presented by Glaser & Strauss (1968) who explored a relationship between the phases of dying and several “death expectations” or trajectories for *certain* or *uncertain* deaths. Glaser and Strauss proposed that individuals dying trajectory comprises two core elements: *time* and *shape*. This means that the course of dying may be rapid or it may be slow or it may plateau with no evident change over time. The shape relates to improvements and relapses. Pattison (1977) continued the work of the dying trajectory in his *living-dying interval/phase theory*, arguing that this trajectory changes when a crisis occurs. Theories from this era have made significant contributions to clinical practise about the dying person. The role of nurses in palliative care was described by Dobratz (11) as: intensive caring, collaborative sharing, continuous knowing and continuous giving (11). Palliative nurses are described by Davies and O’Berle (1990,1992) as being supportive and with multiple dimensions (11, 12). These dimensions include two components of valuing: the first is *global valuing* include being respectful and non-judgemental; the other is *particular valuing* as a more individualised valuing which only occurs when developed a relationship with the patient. More task oriented dimensions of palliative nursing according to Davies and O’Berle is: connecting; empowering; doing for; finding meaning and preserve integrity (11, 12).

Definition

Palliative care as originally defined in 1986 by the World Health Organisation (WHO), comprised only the late palliative phase and the terminal phase of disease. WHO broadened the definition in 2002 (13) to an approach of care of patients with life-threatening illness, emphasising that palliative care is required for various diseases and also stressed the need to commence palliative care earlier in the disease process. The latter definition includes the early palliative phase; rehabilitation and supportive care. The current definition from the WHO, describe palliative care as:

“an approach of care which improves quality of life of patients and their families facing life threatening illness through the prevention and relief of suffering by means of identification and impeccable assessments of pain and other problems, physical, psychosocial and spiritual”.

The definition from WHO has lately been criticised (14, 15). In a position paper, the international working group of the European School of Oncology (ESO) (14) responded to a need to ensure that patients receive the benefits of palliative care at all

appropriate stages and also acknowledged the different skills health care professionals incorporate. The definition of palliative care presented by the ESO (14) is as follows:

“Palliative care is the person-centred attention to physical symptoms and to psychological, social and existential distress and cultural needs in patients with limited prognosis, in order to optimise the quality of life of patients and their families or friends”

This definition describes in detail *how* palliative care is delivered, and also highlights palliative care as *patient-centred*. ESO further defined both basic and specialised palliative care, as follows:

“Basic palliative care is the level of palliative care which should be provided by all health care professionals, in primary or secondary care, within their duties to patients with life-limiting disease”

“Specialised palliative care is the standard of palliative care provided at the expert level, by trained multi-professional team, who must continually update their skills and knowledge, in order to manage persisting and more complex problems and to provide specialised educational and practical resources to other non-specialist members of the primary or secondary care team”

The definition from the ESO points at palliative care as a care and not an approach, being *attentive* to symptoms and *patient-centred*. This definition further reflect the development that has occurred in the developed countries during many years of experience in delivering palliative care, and show the increasing specialisation in the area of palliative care, which has recently been criticised (15, 16), with discussions about “moving back to the grass roots of palliative intentions” (17). A more humble definition of palliative care, and that might respond to the former critique, might be the definition by the European Association for Palliative Care (EAPC) (18), including the interdisciplinary approach:

Palliative care is the active, total care of the patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of social, psychological and spiritual problems is paramount.

Palliative care is interdisciplinary in its approach and encompasses the patient, the family and the community in its scope. In a sense, palliative care is to offer the most basic concept of care – that of providing for the needs of the patient wherever he or she is cared for, either at home or in the hospital.

Palliative care affirms life and regards dying as a normal process; it neither hastens nor postpones death. It sets out to preserve the best possible quality of life until death.

Although palliative care is a relatively new clinical and scientifically area that has developed in the last 40 years, today we assume that the term *palliative care* share the same terminology and purpose, when used. On the contrary it has to be argued that there is not a consensus about definitions and terminology used. Other terms that is

synonymously used with *palliative care* are e.g.; hospice care; end-of-life care and supportive care.

Palliative care in Sweden

Palliative care is organised in different ways in different parts of Sweden today. In some parts of Sweden advanced home care services are highly developed, while less developed in others. Palliative in-patient services may form an integral part of hospital care, may be provided within geriatric medical, or oncology departments. Palliative care may be separate fields of activity in hospices or in specialist palliative clinics. Palliative care may also be provided by local authorities in primary care and old age care facilities. The Swedish National Board of Health and Welfare reported in 2006 (19) that the quality of care at the end of life depended on the place of residence and the disease suffered. There are marked differences in the approach to delivery of care. In some places basic palliative care is provided, delivered by the primary care services. Specialised palliative care is provided for patients who face more complex situations and are therefore in need of care from specialised teams. Teaching palliative medicine and palliative care is not highly prioritised in the education of health professionals. Nor is it provided for nurses or other health care staff who are already concerned with palliative care for their patients (19). This contrasts with the high level of priority accorded to palliative care by the authorities in Sweden (20).

QUALITY OF LIFE

Optimising the quality of life for patients is the primary goal of palliative care. In order to examine quality of life for the patients with advanced cancer who are the subjects of this thesis, I will describe two concepts:

Quality of life

Quality of life (QOL) as a concept is difficult to define (21-23), and may be described with different perspectives for example from sociological or medical perspectives. The World Health Organisation Quality of Life Group (WHOQOL) (24) includes aspects of the individual's perception, expectations, standards and concerns, physical health, psychological state, levels of independence, social relationship, and relation to the environment in their definition. Naming these aspects points to the subjectivity and multidimensionality of the quality of life concept; the different meanings that the concept quality of life has to different people and that it might mean different things to the individual person at different time in life. Quality of life in patients with cancer has been described as the difference between the patients expectations and their perception of the situation, the smaller the gap the better being the quality of life (25).

Health-related quality of life

Health was defined in 1948 by the WHO as: "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (26). This definition placed health in a broader context of human well-being in general. Several definitions occur, although as for *quality of life* there is no general definition. As a concept *health* is more specific than the broader *quality of life*, and the term *Health-related quality of life* (HRQoL) is the patient's experience of quality in life related to e.g. symptoms, physical functioning, and psychosocial well-being this is often used in health care to distinguish the broader concept *quality of life*, in its general sense and to meet the requirements of clinical research and practice (27).

These two concepts are often used in terms of quality of life. Nurses in palliative care seems to have a intuitive appeal on quality of life for the patient, focusing on assisting people to adapt to losses and devastating effects of cancer and its treatment (23). In palliative nursing research quality of life often relates to what makes life more valuable to patients.

SYMPTOM

Patients with cancer, both those receiving curative treatment for cancer and those with advanced disease, report high prevalence of symptoms (28, 29). The symptoms might be caused by the primary tumour, metastases and by the side-effects of treatment, whether it be surgery, radiotherapy, chemotherapy or specific medications used (30). Sometimes these symptoms can be overwhelming for the individual, and extend their reach beyond the patient to people close to the patient, including family members, friends or anyone involved in the care of that person. The term “symptom” can be defined in different ways depending on the perspective of the persons involved (31).

Symptom definition

A well known definition of a symptom proposed by Dodd et al (32) (p.669) defines a symptom as “*a subjective experience reflecting changes in the biopsychosocial functioning, sensations, or cognition of an individual*”, emphasising that a symptom is a subjective experience of changes of the above aspects (32, 33). On the other hand the objective sensation is objective evidence or indication, detectable by the individual or others – which in medical terms can be said to represent a *sign* (32). In Lenz et al’s (34) middle-range theory of unpleasant symptoms, symptoms are defined as “perceived indicators of change in normal functioning as experienced by the patient”. This adds to the above definition that a symptom is subjective, although Lenz et al. conceptualise each symptom as a multidimensional experience, which can be conceptualised and measured separately or in combination with other symptoms. The middle-range theory of unpleasant symptom has three major components: the symptom that the individual is experiencing, the influencing factors that give rise to or affect the nature of the symptom experience and further the consequences of the symptom experience.

Symptom perception

Symptoms can vary in magnitude, severity, persistence and character which reflects the differences in symptom experience (35). *Symptom experience* has been described by Dodd et al. (32) as including *perception, evaluation of symptoms* and also the *response to symptoms*. Dalal et al. (36) points out that the expression of a symptom by the patient involves three steps: *production* is caused mostly by the disease process itself and cannot be measured directly (e.g. host immune cells, cytokines, tumour byproducts), while *perception* takes place at the level of the central nervous system (taking the symptom to the brain), influenced by the action of modulators from drugs (e.g. opioids). Perception, in common with production, cannot be directly measured. *Expression* is the third step and the visible aspect of assessment, the part that guides therapy. Symptom experience is often reported in the literature as the frequency or intensity of the symptom alone (37). These different aspects of symptom and symptom experience reflect the complexity of understanding symptoms, and emphasise the complexity of symptom assessments.

Symptoms in patients with advanced cancer

Symptoms are very common in patients with advanced cancer. It has been reported that the median number of symptoms is 11 with a range between 1 and 18 symptoms per patient at the time of admission to palliative care (2-4). Symptoms such as weakness, fatigue, anorexia, pain, and depression are reported as the most common and also the most distressing among patients with advanced cancer (2, 38). A core issue in palliative care is to provide relief of symptoms, and to be able to do this satisfactorily requires that much must still to be learned about symptoms for these patients. In this thesis, focus is on one of these symptoms, specifically fatigue in patients with advanced cancer.

FATIGUE

Feeling tired, with reduced energy and loss of strength is a common complaint, which is expressed by people in general (39). Almost everyone experiences fatigue on a daily basis, this feeling is generally remedied by rest or a good night's sleep. Fatigue is an umbrella term that originates from the Latin *fatigare*, meaning tired out (30). In English and French, the word fatigue is used to articulate feelings of extreme, unusual tiredness, while many other languages lack a word for fatigue (40). The word fatigue has no equivalent translation in Swedish, and for the purposes of talking to patients about fatigue Swedish words for tiredness or weakness are often used instead. Fatigue in healthy individuals is believed to provide protection and/or satisfying response to physical and psychological stress (41).

Definition

Defining fatigue in relation to cancer has challenged clinicians and researchers for many years, with many definitions proposed where fatigue is described as a subjective, exhaustive experience, that in some way interferes with the capacity to function(42-45). This may be seen in one of the latest definitions (2007) by National Comprehensive Cancer Network® (NCCN) (45)

Cancer-related fatigue is a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning

This definition points to varies in fatigue intensity, which is a major component in screening and management of fatigue. The guidelines of the NCCN provide information how to handle fatigue based on levels of intensity (45).

Fatigue in patients with cancer

Fatigue is experienced by patients with various diseases, e.g chronic obstructive pulmonary disease, rheumatoid arthritis, AIDS, heart disease (3, 41, 46-48), although it has been demonstrated as more likely to be reported among patients with cancer than by any other patients (49). For many patients with cancer, during cancer treatment and with the progress of the disease, fatigue is not alleviated by rest or sleep, and the unpleasant fatigue experience becomes unwieldy (41, 50-52). The sensation of fatigue may be characterised by some as constant and unrelenting while others experience fatigue as unpredictable, coming on suddenly (53). Fatigue is reported as the most common and distressing symptom amongst patients with cancer (54, 55). Although

fatigue is recognised to affect patients during the whole cancer trajectory, few studies has include and compare individuals at different stages of cancer disease (50).

Aetiology

The basic mechanisms that cause fatigue in the population with cancer are poorly understood. Multiple potential factors seem to coexist and are interrelated (56-58). Aspects of cancer-related fatigue caused by physically distinct mechanism, or as a consequence of underlying pathophysiology have been proposed. It has been posed that e.g. anemia, cachexia, infections, metabolic disorders, mood disturbances and stress could lead to physiological changes potentially underlying fatigue, or as a physiological response to cancer therapy (59). Olson (60), conceptualises two theories about the aetiology of fatigue that have been used; “*fatigue as a marker for alertness or functional status*”, where fatigue is a part of a feedback system in the central nervous system (CNS), composed of the mechanisms responsible for action, and decreased inhibition. The other theory brought up is “*fatigue as a stress response*”; where fatigue in cancer is connected to response to stress, and becomes a coping mechanism. From this stress response theory, Olson et al. (61) developed the *Edmonton Fatigue Framework* (EFF) of fatigue. This Framework is built on their *Fatigue Adaptation Model* (FAM), where a distinction was made between tiredness, fatigue and exhaustion, and the continuum between these concepts is described as an adaptation, and where one of the included concepts could serve as warning signs for the other. Olson et al. (61) proposed that stressors associated with advanced cancer and its supportive treatment trigger declines in four systems – cognitive functioning; sleep quality; nutrition; and muscle endurance. The aetiology of fatigue is also considered in terms of two broad main mechanisms, as presented by Ryan et al. (62): One is *peripheral* and concerns the possibility to perform a task in the muscular junctions and muscle tissues, in response to central stimulation. The second mechanism for developing fatigue is considered to be a *central* response; which develops in the central nervous system, as a result of failure to transmit impulses, resulting in difficulty in maintaining self motivated activities, both physical and mental. Although, it has been indicated that the aetiology of fatigue in patients with cancer include, for example, direct tumour effects, observed as an increase in proinflammatory cytokines, peptides, or hormones, but few studies have been performed that directly address this (59). Cancer treatment with chemotherapy, radiotherapy, immunotherapy, and with or without surgery are reported to cause fatigue, and interrelationships with other symptoms such as e.g. pain, anemia, dyspnoea, cachexia and psychological factors – anxiety, depression, stress, cognitive and mood disturbances also contribute (30, 56-58). Many patients with advanced cancer want to focus entirely on interventions that may reduce the symptom rather than the underlying conditions, although an evaluation of potential treatable causes of fatigue must be considered (63).

Prevalence

Prevalence of fatigue in patients with cancer varies between 17 – 96% (41, 50-52, 58), and depends on the timing of the questions and the criteria used (50). Fatigue is reported to follow patients over the trajectory of the cancer care period, from diagnosis (64, 65), during curative treatment (66-73), in disease free cancer patient years after treatment (74-76) and in patients with advanced cancer (77-79). Much research has

been focusing on fatigue during anticancer treatment, while research of fatigue in patients with advanced cancer is less common.

Fatigue perception

Although there is not yet any consensus, there is broad agreement that fatigue is a pervasive subjective experience (50, 58, 80) that is multidimensional, with physical, emotional, and mental sensations affected (62). Fatigue is reported to vary in the degree of unpleasantness, duration, and intensity (81, 82). Fatigue is further described as a symptom with an adverse effect on daily functioning and perceived quality of life (41, 50, 52, 83, 84). The relationship between the experience of fatigue and age is not well defined: age is thought to be a risk factor for fatigue, although data are inconsistent (77, 85). There have been reports of a possible gender difference in the experience of fatigue, some indicating that women generally report more fatigue than men (78, 86), while others suggest that there is no such gender difference (77). According to type of cancers and fatigue, the same lack of consistency is seen in the evidence, where a few studies have reported an association between the site of primary cancer site and fatigue, while others do not find such an association (30).

Management of fatigue in patients with advanced cancer

Patients with advanced cancer may have hope but not expectations of overcoming fatigue and coping strategies normally helpful to individuals with fatigue may be of limited use for these patients (87). The management of fatigue in palliative care is challenging, since the palliative care trajectory varies during the period of time prior to death. Some individuals play an active part in the last period of life both physically and socially, while others have minimal activities at the end of life (88). The NCCNs Clinical Practice Guidelines in Oncology (45, 89), presents interventions for managing fatigue in cancer patients that include: treatment of identifiable aetiology; non-pharmacological strategies, i.e. education/counselling, coping strategies, lifestyle modification, and exercise; pharmacological management i.e. psychostimulants, antidepressants or corticosteroids. Specific management of fatigue at the end of life comprised in the guidelines from the NCCN of: information about expected end-of-life symptoms, no daily self-monitoring, and energy conservation strategies such as eliminating non-essential activities and optimising instead of maintaining optimal levels of activity. As shown by the guidelines from the NCCN, interventions to deal with fatigue are usually divided in two main categories. Although, it is argued that both these categories of strategies are lacking in evidence. The first of which includes pharmacological strategies, where glucocorticoids are common and indicated to relief fatigue (90), with additional pharmacological interventions proposed such as using methylphenidate or modafinil, although there is a lack of evidence of the benefits of this strategy (91). The other category of strategies includes non-pharmacological strategies of which exercise is the strategy for which there is the strongest evidence of benefits. There is however few studies that have examined this intervention used among patients with advanced cancer (92). Other non-pharmacological strategies such as education, energy conservation, distraction, acupressure, acupuncture have not been fully evaluated (91).

ASSESSMENT OF FATIGUE

The definition of palliative care by WHO (13) makes the aspect of clinical assessment central and a broad range of aspects need to be addressed. In palliative care clinical assessment of actual and potential problems, disease management, symptoms, physical, psychological, social, spiritual, and practical assessments, as well as assessments of expectations, needs, hopes, fears, end of life care/death management, loss and grief are to be addressed (93-95). All these aspects mirror the multidimensional evaluation that has to be made and although each health care discipline has expertise and skills for specific assessments, useful for the holistic framework of the interdisciplinary team, clinical judgements have to be made of what is essential to measure. These assessment can be made in various ways (93, 95) including: by interview, observations, listening, or by using assessment scales, physical examination or laboratory and/or radiology procedures. In the field of symptom assessments it has been demonstrated that physical symptoms may be detected more often by nurses, than psychosocial symptoms (96). A “diffuse” problem such as fatigue and impaired well-being seems to be less noted by nurses than reported by patients. Pain and poor physical functioning on the other hand are recognised by nurses in the same amount that patients report them (96). Symptom management is of major concern in nursing. In way of managing symptoms, they have to be recognised, and requires understanding of the individual patients experience and meaning of each specific symptom (97), and is a necessity in able to plan and supply the best available care for patients and their families. As described by Polit and Beck (98) clinical nursing practice relies on different sources of evidence, which vary in dependability and validity. They describe: tradition, authority, clinical experience and exemplifies trial and error as sources, further logical reasoning both inductive and deductive, assemble information and disciplined research as sources for knowledge in nursing practice. Polit and Beck (2004) further describes that many nursing interventions are based on tradition, customs, and a “unit culture”. Haworth and Dluhy (97) describe how the interaction between an individual patient and nurse leads to a type of symptom management which produces knowledge which can then be used for management of the same symptom among other patients. de Haes and Teunissen (99) argues that a good relationship between the patient and health care provider is prerequisite for effective communication, and that trust is important in creating a good relationship. Both the patient and nurse bring personal attributes including age, gender, culture, primary language, socioeconomic status, explanatory models, education, knowledge, health beliefs, values, expectations and communication style into a patient - nurse interaction phase, as described by Haworth and Dluhy (97). This interaction is part of the health care encounter, where context, history, environment and time are essential for the interaction. In this interaction aspects of mutuality, respect and trust has its impact on the outcome. If this creates a good relationship (99) it leads to accuracy of diagnosis, agreement on course of action and symptom relief (97). Although fatigue as an essential element in the field of oncology is increasingly recognised by nurses (100, 101) and other members of the team attending to patients (102), it is still under-diagnosed and under-treated (45), and health care staff lack intervention strategies (83, 103), which points to the need for further research in the area.

MEASUREMENTS OF FATIGUE

As mentioned earlier there are many factors that need to be assessed. In developing procedures to make these assessments the development and use of measurement tools has increased. When using a measurement, one has to consider what is to be measured; is it to be assessed objectively or subjectively, and for which purposes the measurement is used. Is it to be used in clinic and/or for research? Although there is a lack of approved definitions of the concepts symptoms and quality of life, it is evident that measurement must take into account that general agreement about the subjectivity of symptoms and quality of life. Tools for measuring subjective sensations are usually presented in the form of questionnaires that may be completed by interviewing the patient or by patients self-reporting (104). Hence, fatigue, due to its subjectivity nature, is recommended to be measured by patient's self-report (105). Measurements could be for general use, *generic*, in a broad range of conditions, and these might be used for comparison with patients with various diseases, or even with the general population. These instruments do not focus on issues of particular concern to patients with a specific disease. For detecting differences in different diagnostic groups *disease-specific instruments* can be used. In order to explore issues of particular interest *specific instruments*, for measuring e.g. anxiety, depression, functions and fatigue (27) exist. Measurement of fatigue is incorporated as a subscale in symptom or quality of life instruments, e.g. Edmonton Symptom Assessment Scale (ESAS) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30), or single items (unidimensional instrument), e.g. visual analogue scale (VAS) or Borg's Category Ratio (CR) might be used. These scales are focusing on global fatigue severity. Multidimensional fatigue instruments, e.g. Multidimensional Fatigue Inventory (MFI-20), Schwartz Cancer Fatigue Scale, Brief Fatigue Inventory, and Piper Fatigue Scale, provide information about fatigue characteristics other than intensity (58). Due to the diverse definitions of fatigue, a broad range of instruments has been developed, where these multidimensional instruments measure different aspects of fatigue. This may contribute to the inconsistency of reports of fatigue, while on the other hand making it possible to consider more different aspects. Answers in response to questions posed could be on a VAS, which is a straight line with the anchors labelled as the extreme limits of the sensation or feeling being measured, or answers could be in a Likert scale, where the respondent is asked to specify the extent to which the particular statement relates to them (104), answers could be made on a different amount of categories, where five and seven categorical response alternatives are common. Using a measurement often implies a quantification of the attribute that is to be measured (104), and it may be difficult for some patients to provide a numerical score and for the staff to employ these scores in a meaningful way (30). However, when used in research they can supply important information useful in designing new approaches and interventions (106). In the selection process of a measurement tool, both for research and/or clinical practice, it must be ensured that the instrument fulfils the basic psychometric criteria of validity and reliability (106). Validity of a measurement represents the degree to which an instrument measures what it is intended to measure (104, 106). Reliability of an instrument is the extent to which fatigue is measured in a consistent way, with accuracy and with stability (104, 106). Consideration of the validity of measurements in terms of cultural application is also an essential aspect (106). Many instruments are translated into other languages without

consideration of cultural factors that may influence interpretations of questions or statements. Special consideration and preparation are needed when translating a measurement (107) or using an instrument among a new population different from that for which the psychometric test was developed. To use a fatigue measurement among patients with advanced cancer the instrument needs to fulfil the basic psychometric criteria, and must also be easy to administer and easy for the patients to score, and not be tiring to use. For the assessment of the patient's perceived fatigue in this thesis, a disease specific quality of life instrument, including a fatigue subscale, as well as a unidimensional and two multidimensional fatigue measurements has been used.

Measurements of fatigue in Swedish cancer care

The efforts to obtain an overview of fatigue-specific measurements used among patients with cancer in Sweden, resulted in 12 studies using 8 different fatigue instruments, see Table 1. Aspects of reliability and validity were in some reports demonstrated or discussed, while others used the measurement with limited consideration given to reliability and validity, see Table 1.

Abbreviations: MFI-20=Multidimensional fatigue Inventory; CR-10=Category Ratio; KSS=Karolinska Sleepiness Scale; SOFI= Swedish Occupational Fatigue Inventory; DT-scale= Delighted-Terrible Face scale; FQ=Fatigue Questionnaire; FSI=Fatigue Symptom inventory. NA=not applicable. *Ahlberg present in her thesis (2004) Cronbachs alpha ranging 0.82-0.90.

Table 1. Fatigue instruments used among patients with cancer in Sweden.

Reference	Sample, design of study	Instrument	Psychometric concerns
Fürst, CJ & Åhsberg, E Supportive Care Cancer 2001; 9:355-360	Radiotherapy, n=81, Prospective, nonexperimental	MFI-20 CR-10 KSS	Cronbach's alpha 0.75 – 0.94 NA NA
Åhsberg, E & Fürst, CJ Acta Oncol. 2001; 40 (1):37-43	Radiotherapy, n=81 Prospective, Nonexperimental	SOFI, CR-10 KSS	Cronbach's alpha 0.73 – 0.97 NA NA
Avemark et al. Vård I Norden 2003; 67 (23): 42-46	Palliative home care n=27 Prospective, Nonexperimental	DT-Scale	Refer to Bowling, A (1991). Discuss face validity
Ahlberg et al. Biol Research Nursing, 2004; 5 (3): 203-210	Radiotherapy, n=15 Prospective, Nonexperimental, Descriptive	MFI-20	Refer to Smets et al. (1995) and Fürst, CJ & Åhsberg, E (2001).*
Ahlberg et al . J. of Adv. Nurs. 2004; 45 (2): 205-213	Radiotherapy, n=60 Descriptive	MFI-20	Refer to Smets et al. (1995) and Fürst, CJ & Åhsberg, E (2001).*
Ahlberg et al. Onc.Nurs. Forum. 2005; 32 (3): 633-640	Radiotherapy, n=60 Prospective, Nonexperimental Deskriptive	MFI-20	Refer to Smets et al. (1995) and Fürst, CJ & Åhsberg, E (2001).*
Ahlberg et al. Int. J. Nurs. Stud. 2005; 42; 377-386	Radiotherapy, n=60 Prospective, Nonexperimental Deskriptive	MFI-20	Refer to Smets et al. (1995) and Fürst, CJ & Åhsberg, E (2001).*
Lindemalm et al. Supportiv Care Cancer 2005; 13: 652-657	Cancer, after treatment n=61 healthy controls n=9 Quasi-experimental	FQ	Not discussed
Hartvig et al. J Oncol Pharm Practice. 2006; 12 (3): 155-164	Chemotherapy n =147 healthy controls n=47 Prospective, Nonexperimental.	FSI	Refer to Hann et al 1998
Hartvig et al. J.Oncol. Pharm. Practice 2006; 12 (4); 183-191	Chemotherapy n =74 Randomised controlled longitudinal	FSI	Refer to Hann et al 1998 and 2000
Östlund et al. Eur. J. Onc. Nurs. 2007; 11 (2): 133-140	Methodology	PFS	Refer to Piper et al., 1989, 1998 The translation procedure and cultural adaptation is seen as a process of validation
Lundh Hagelin et al. Acta Oncol. 2007; 46:97-104	Cancer palliative care n=229 Radiotherapy n=81 Non cancer patients n=114 Healthy individuals n=160	MFI-20 CR-10	Inter-item correlation 0.21-0.90 Item-to-total correlation, Cronbach's alpha 0.67-0.94, convergent validity (CR-10) (p≤0.001) NA

AIM

The overall aim of this thesis was to describe and explore to what extent and in what ways patients with advanced cancer experience fatigue, and to investigate aspects of the assessment and measurement of fatigue for these specific patients.

The specific aims of the papers included in the thesis were:

- to measure symptoms and other QoL aspects in relation to age, gender, marital status and type of cancer diagnosis in a patient population with a short expected time of survival referred to palliative care (study I)
- to investigate the validity and reliability of the Swedish version of the Multidimensional Fatigue Inventory (study II)
- to describe and to explore the prevalence and pattern of cancer-related fatigue; in patients with advanced cancer at the end of life and in outpatients undergoing curative radiotherapy. The aim was also to explore the association of anxiety and depression with fatigue (study III)
- to explore the association between multidimensional aspects of fatigue, with emotional functioning, and with quality of life in patients with advanced cancer (study IV)
- to explore the perspective of nursing staff with regard to their systematic assessments using a quality of life instrument in palliative care (study V)

METHODS

DESIGN AND METHOD

This thesis includes non-experimental research that is based on quantitative (Papers I-IV) and qualitative (Paper V) approaches. Papers I-IV are based on a cross-sectional design, and all papers included questionnaires (figure 1), with predefined response alternatives in papers I-IV, and open ended questions for written answers in paper V. Characteristic of studies comprised in this thesis are described in Table 2.

Table 2. Characteristics of studies included in the thesis.

Study	I	II	III	IV	V
Aim of study	Measure symptoms and other QoL aspects in relation to age, gender, marital status and type of cancer diagnosis	Investigate the validity and reliability of the Swedish version of the Multidimensional Fatigue Inventory	Describe and explore the prevalence and pattern of cancer-related fatigue; primarily illness related, and also to explore the association of anxiety and depression with fatigue	Explore the association between multi-dimensional aspects of fatigue, with emotional functioning, and with quality of life	Explore the perspective of nursing staff with regard to their systematic assessments using a quality of life instrument in palliative care
Design	Non experimental Cross-sectional	Non experimental Cross-sectional	Non experimental Cross-sectional	Non experimental Cross-sectional	qualitative explorative
Measurement	EORTC QLQ C-30	MFI-20 CR-10	CR-10 MFI-20 HADS	CR-10 MFI-20 SOFI EORTC QLQ C-30	Study specific
Sample	278 pts. with a short expected time of survival referred to palliative care	229 pts. with advanced cancer. 81 pts. with cancer undergoing curative radiotherapy. 114 pts at a medical out patient clinic 160 healthy individuals	228 pts with advanced cancer 81 pts. with cancer undergoing curative radiotherapy.	228 pts with advanced cancer	26 nurses working in palliative cancer care
Analysis	Descriptive, Student's t-test ANOVA, Multiple entered linear regression analysis	Descriptive, Psychometric (investigating aspects of reliability and validity): using item-analysis, Cronbach's alpha and Persons correlation coefficients	Descriptive, Student's t-test, paired sample t-test ANOVA, Multivariate logistic regression, Persons correlation coefficients	Descriptive, ANOVA, Persons correlation coefficients	Interpretive description

Abbreviations: EORTC QLQ C-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; MFI-20 = Multidimensional Fatigue Inventory; CR-10 =Category Ratio; HADS = Hospital Anxiety and Depression Scale; SOFI=Swedish Occupational Fatigue Inventory

QUESTIONNAIRES

To ensure assessments, the measurements used need to fulfil basic validity and reliability criteria (106), and special considerations of the questionnaires used in this thesis were that they were easy to administer and easy for the patients to score. For the purposes of this thesis six different questionnaires have been used, which are presented below. Internal consistency of measurements based on subscales, including two or more items, has been considered and calculated where appropriate and presented in Table 3.

EORTC QLQ C-30 (Paper I and IV)

Symptoms and other QoL aspects were assessed using the Swedish version of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (108). The instrument was designed as a 30-item core instrument to cover a range of QoL areas related to cancer patients participating in clinical trials. This self-reporting instrument incorporates five functional scales (*physical, role, emotional, cognitive and social*); three symptom scales (*pain, fatigue and nausea/vomiting*); a *global health and QoL scale*; and single item symptom measures (*dyspnoea, sleep disturbances, appetite loss, constipation, diarrhoea*), and a question addressing the perceived *financial impacts* of disease, and covers experiences perceived during the last week. Symptoms are to be rated on a 4-point scale ranging from “Not at all” (1), “A little bit” (2), “Quite a bit” (3) and “Very much” (4) Two items in global health status range from “Very poor” (1) to “Excellent” (7). This instrument has been widely used and psychometrically tested and exhibits adequate levels of reliability and validity among different cancer populations (108-112). All subscales exhibit acceptable levels of internal consistency (113), with Chronbachs $\alpha > 0.70$ (114), except for *physical functioning* and *cognitive functioning*, see Table 3. In Paper I the total instrument was used. In paper IV, selected data from the instrument was used, i.e. *emotional functioning* and *fatigue* subscale, the single items of *insomnia* and QoL.

CR-10 (Papers II-IV)

The Borg Category Ratio scale (CR-10) (115) was used to assess overall fatigue. This unidimensional fatigue scale posed the question: “*How tired have you been feeling during the last few days?*” The scale is vertically arranged and ranges from 0 to 10, with one additional “maximum” point. There are verbal descriptors at 9 fixed points on the scale: 0 = *Not at all*, 0.5 = *barely perceptible*, 1 = *very mild*, 2 = *mild*, 3 = *moderate*, 5 = *strong*, 7 = *very strong* and 10 = *extremely strongly*, and also the point of *maximum*. The CR-10 has been used to measure fatigue both among healthy individuals (116) and in cancer patients (69, 117). The CR-10 scale has been found to be more sensitive in measuring general fatigue than a Visual Analogue Scale (VAS) or a Lickert scale (116).

MFI-20 (Papers II-IV)

Different aspects of fatigue were assessed by the Swedish version (69) of the Multidimensional Fatigue Inventory (MFI-20) (118, 119). This self-reporting instrument has been developed from patient experiences of fatigue through interviews. To avoid contamination of fatigue by somatic symptoms (e.g. headache) it does not

include specific somatic items. It includes five aspects of fatigue: *general fatigue* - general remarks on a person's functioning, e.g. "I feel rested"; *physical fatigue* - relates to feelings of tiredness; *reduced activity* - consequences of fatigue; *mental fatigue* - relates to cognitive symptoms of fatigue; *reduced motivation* - a feeling of lack of motivation to start any activity (118). The person is asked to specify the extent to which the particular statement relates to them on a five-point Lickert scale, ranging from *Yes, that is true* to *No, that is not true*. All items in the separate subscales are quantified to numbers between 1 and 5, and summarized to a subscale score ranging between 4-20, with a high level representing a higher level of fatigue. MFI-20 has been used among: cancer patients (69, 120, 121); in patients with chronic heart failure (122); systemic lupus erythematosus (123), rheumatoid arthritis (47); and in a general population (124). The original version of the MFI-20, translated to Swedish was used in paper II. After the psychometric tests (Paper II), one item (item 19) was removed from the instrument, resulting in a 19-item Swedish version. This version was used in Paper III and IV, and exhibits adequate levels of internal consistency for the included sample, with Cronbach's α ranging 0.72-94, see Table 2.

HADS (Paper III)

The Swedish version of the Hospital Anxiety and Depression Scale (HADS) (125) was used to assess anxiety and depression. This 14-item self-reported screening tool was developed to identify anxiety disorders and depression in medically ill patients by excluding items related to somatic symptoms. Responses concern feelings during the past week. Anxiety and/or depression disorders are measured on two 7-item subscales, and Bjelland et al (126) argued that the scale is suitable for screening anxiety disorders and depression in patients with somatic and psychiatric disorders as well as primary care patients and the general population. Each of the items in HADS is rated on a 0 - 3 point scale, with the total score for each scale ranging between 0 and 21 points. Zigmond and Snait (125) define 0-7 points as a "noncase", 8-10 points as a "doubtful" or "possible" case, and 11-21 points as a "definite" case of anxiety and/or depression. For the sample participated in Paper III, adequate levels of internal consistency was shown with Chronbach's α ranging 0.82-0.89, see Table 3.

SOFI (Paper IV)

Multidimensional aspects of fatigue were assessed with the Swedish Occupational Fatigue Inventory (SOFI) in Paper IV. This instrument has been developed for measuring perceived fatigue in working life. The SOFI was constructed with a multi-methodological approach, including interviews, literature search and a questionnaire survey (127), and has been evaluated in laboratory experiments(128, 129). The instrument consists of five aspects of fatigue; a general dimension (*lack of energy*), two physical dimensions (*physical exertion* and *physical discomfort*), one mental dimension (*lack of motivation*) and one dimension for sleepiness (*sleepiness*). The questions concerned how the person had been feeling during the last few days. The respondent is asked to specify the extent to which the 20 verbal expressions relate to them on a seven-grade Lickert scale with the two extreme values verbally defined, 0="not at all" and 6="to a very high degree". All items in the separate subscales are quantified to numbers between 0 and 6, and a mean from the including 4 item ratings are to be calculated, giving a mean score between 0-6, with a high level representing a higher level of fatigue. This instrument exhibits adequate levels of internal consistency, for 3 of the subscales, Cronbach's α ranging 0.69-0.85, see Table 3

Study-specific questionnaire (paper V)

A study-specific semi-structured questionnaire was constructed and used in study V. The questionnaire consisted of six topic areas covering experience in using systematic assessments of symptoms, and other QoL aspects in advanced cancer patients on admission to palliative care. The questions asked were: What positive experiences do you have of using the QoL questionnaire? What negative experiences do you have of using the QoL questionnaire? How do you feel that it (the QoL questionnaire) influenced your nursing care? How do you feel that it influenced the patients' situation? In situations when you did not hand out the questionnaire, why did you choose not to? What other thoughts, concerns and reflections do you have about using this QoL questionnaire? The answers were to be written by the respondents.

Table 3. Internal consistency (Cronbach's alpha) of summated subscales in measurements used in this thesis

Measurement	Paper	Subscale	Internal consistency of scales	
			PC	RT
EORTC QLQ C-30	I, IV	Physical Functioning	0.65	Not used
		Role Functioning	0.84	
		Emotional Functioning	0.85	
		Cognitive Functioning	0.59	
		Social Functioning	0.72	
		Fatigue	0.83	
		Pain	0.85	
		Nausea Vomiting	0.84	
Global Health Status/QoL	0.86			
MFI-20	II-IV	General Fatigue	0.76	0.89
		Physical Fatigue	0.76	0.87
		Reduced Activity	0.72	0.94
		Mental Fatigue	0.68/0.73*	0.85/0.87*
		Reduced Motivation	0.74	0.85
HADS	III	Anxiety	0.88	0.89
		Depression	0.82	0.86
SOFI	IV	Lack of energy	0.76	Not used
		Physical exertion	0.69	
		Physical discomfort	0.69	
		Lack of motivation	0.85	
		Sleepiness	0.78	

Abbreviations: EORTC QLQ C-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; MFI-20 = Multidimensional Fatigue Inventory; HADS = Hospital Anxiety and Depression Scale, SOFI=Swedish Occupational Fatigue Inventory. *represents the mental fatigue subscale including 3 items in the Swedish version

DATA COLLECTION

Recruitment

For recruitments of patients, three care settings were included: 1) a specialised palliative care facility comprising two inpatients wards and one home care team

(paper I-IV); 2) a oncology radiation clinic (paper II and III); 3) a medical out-patients clinic (paper II). Only adult individuals, with an age over 18 years, and Swedish speaking were considered eligible. For recruitment of healthy individuals, health care staff at a hospital and nursing home was included (paper II), and for recruiting registered nurses in palliative care, a specialised palliative care facility was used (paper V).

DATA COLLECTION I (Paper I)

Data from clinically answered EORTC QLQ C-30 by pts. with advanced cancer when admitted for specialized palliative care.

743 pts. were admitted during the study period

465 pts. did not participate

DATA COLLECTION II & III

Parallel data collection from a palliative care facility (II) and a oncology radiation clinic (III) Multidimensional Fatigue Inventory (MFI -20), Swedish Occupational Fatigue Inventory (SOFI) Borgs Category Ratio (CR-10), Hospital Anxiety and Depression Scale (HADS)

349 pts. with advanced cancer in palliative care were eligible (EORTC QLQ C-30 for pt. in palliative care were collected from clinical data)

120 pts. did not participate: 65 declined; 37 were cognitively impaired or dying; 18 due to administrative reasons

145 pts. visiting the medical out-patient clinic were eligible

31 pts. declined participation

220 health care staff were eligible

58 declined participation

100 pts. receiving radiotherapy were eligible

19 pts. declined participation

DATA COLLECTION IV

Registered nurses within a specialised palliative care facility were asked to answer a study specific questionnaire about their experiences of systematic assessment using a quality of life questionnaire.

36 nurses were eligible

10 nurses declined participation

Figure 1. Description of the data collection, including eligible participants and those who declined participation.

Procedure

The five studies included in this thesis derive from four different data collection occasions (see Figure 2). Oral and written information about the studies (including purpose of the study and contact details to the research team) were given to all eligible participants, and an informed consent through their participation. For the patients in palliative care information about the patient's participation was given to the responsible nurse at the time to facilitate contact if necessary, as this group could be in special need of this. No reminder contacts were taken with non-respondents. The specific procedures for each paper are presented below.

Paper I

The EORTC QLQ C-30 was used at the specialised palliative care facility to support nurse-patient communication, and to form a basis for individual nursing and medical care. In order to investigate symptoms and other QoL aspects in patients with advanced cancer at admission for palliative care, a patient group was identified in which all patients met the following criteria: The patients had a diagnosis of advanced cancer, a stated need for symptom relief, psychosocial support and other pronounced palliative care needs. The clinically responsible nurse presented the questionnaire to all consecutive patients with a cancer diagnosis, provided that the patient understood the Swedish language, and asked the patient to answer it. A nurse or a relative could assist the patients in reading or filling in the questionnaire if necessary. Although, only questionnaires answered by patients were included, proxy ratings were not included. Individual patient characteristics were recorded, including age, gender, and marital status, and cancer diagnosis, time of care and time of survival.

Paper II - IV

To be able to investigate fatigue, a set of four fatigue related measurements was used, including both unidimensional (CR-10) and multidimensional fatigue specific measurements (MFI-20 and SOFI), as well as an instrument for measuring anxiety and depression (HADS). Patients with advanced cancer, who on admission for specialized palliative care had fulfilled the clinical routine by answering the EORTC QLQ C-30, were identified by the health care staff and considered eligible. Patients with a cancer diagnosis receiving radiation therapy intended to be curative, and patients at a medical outpatient clinic, and a group of healthy individuals (a convenience sample of health care staff), were all considered eligible. Patients in palliative care were asked by a research nurse to participate, and the research nurse assisted if necessary in reading and/or writing when filling in the measurement. The group of patients receiving radiotherapy was taken from a longitudinal study and for the purposes of this thesis data was selected from the end of radiotherapy (week 3-5), a time-point chosen in order to capture the highest levels of fatigue. A more detailed procedure for data collection of this group is presented elsewhere (69). Patients at the medical outpatient clinic met their regular nurse (one nurse) at the clinic and were able to fill out the assessment instrument in the waiting room or at home and mail it to the research team. All patients were recruited consecutively, and the health care staff groups were contacted by one of the research nurses at a training event for each unit. There were no repeat contacts or reminders to any of the eligible participants. Data were collected for the patients in palliative care between 1997 – 2000, for patients during radiotherapy between 1997 and 1998, for patients at the medical outpatient clinic in 2000 - 2001 and for the HS group

in 1999. Individual participant's characteristics were recorded, including age, gender, marital status, and diagnosis, time of care and time of survival were appropriate. For the group of patients with advanced cancer patient's completed EORTC QLQ C-30 were collected.

Paper V

The semi-structured study specific questionnaire was introduced to registered nurses who had used the EORTC QLQ C-30 in their daily work at the specialised palliative care service, at a separate training event for each unit. The nurses were informed that their participation was voluntary and would be anonymous.

Sample

The samples from the different settings are described in Figure 1, including eligible participants and those who did not participate. Numbers of participants included in the different Papers, together with basic participants' characteristics are presented in Table 4. The participants from the specialised palliative care service included in Paper I were significantly younger ($p<0.05$), and the time period of care was longer ($p<0.001$) compared with those that did not participate. Sample size was calculated differently: In Paper II the patients that expressively declined were included in the calculation. In Papers III and IV, all patients including those who started but did not manage to fulfil participation, and those for whom their physical condition deteriorated rapidly after admittance and were therefore not to be asked to participate were included in the sample size calculation. Also non participants due to administrative reasons were included in Papers III and IV.

Table 4. Characteristics of participants in the five included studies, the five groups are: PC – patients with advanced cancer admitted for palliative care; RT – patients receiving radiotherapy; OP – patients attending an outpatient clinic; HS – Healthy individuals (hospital staff); and PCN – palliative care nurses

STUDY SAMPLE	PC		PC		RT		OP		HS		PCN	
	(I)		(II,III,IV)		(II,III)		(II)		(II)		(V)	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	278		229		81		114		160		26	
Female	171	61	138	60	73	90	43	28	146	80	23	88
Male	107	39	91	40	8	10	71	62	14	20	3	12
Age (years)												
Median	67		69		59		73		37			
Mean	66		68		59		71		38		41*	
Min - Max	24 - 91		30 - 92		26 - 76		41 - 97		19 - 62		23 - 61*	
Diagnosis												
Gastro-intestinal	90	32	71	31								
Gynecology	50	18	40	18	18	22						
Lung	34	12	33	14								
Urological	25	9	23	10	6	7						
Breast	22	8	13	6	53	66						
Blood/lymp	23	8	20	9	3	4						
CNS			12	5	1	1						
Head-Neck			9	4								
Unknown			8	3								
Heart							31	27				
Heart + other diseases*							68	60				
Parkinson							7	6				
Other	34	12					8	7				
Time of employment												
month											32	
Min - max											1 month - 8 years	

* represents the mean and range in years for all nurses at the unit at the time of study

Data analyses

In all papers descriptive statistics were used to describe sample characteristics. Statistically significance was established at the 5% significance level. For further analyses in specific paper please see below. For all quantitative analyses the Statistical Package for Social Science (SPSS), version 13.0 (papers I and II) and 15.0 (papers III and IV)

Analyses paper I

Descriptive statistics were used to describe the occurrence of symptoms, functions and global health status. The raw scores for all scales and single items in the EORTC QLQ C-30 were converted linearly to 0-100 scales in accordance with to the instrument

manual (130). A high score on the symptom subscales/single item represented a high level of symptomatology, whereas a high level in the functioning subscales and global health status represented a better level of functioning and higher Quality of Life. Analyses of subgroups according to age, gender, marital status and times of survival was performed. For group comparisons two-tailed independent Student's t-test or one-way analysis of variance (ANOVA) was used. To identify differences between subgroups, post hoc multiple comparisons with Bonferroni adjustment was used. Tests for linear trends were used for factors with ordered categories. A multivariate analysis was carried out with entered linear regression.

Analyses paper II

The items in each subscale in the MFI-20 were handled and summed according to the manual. Cronbach's alpha (114) and alpha if item deleted was used to test the internal consistency of subscales (113), and a level of >0.70 was considered satisfactory. Pearson's correlation coefficient was used for inter-item correlations calculation to determine the reliability of the MFI subscales, producing correlation coefficients between the items. Each item was also correlated with the other subscales on the instrument. Analyses for gender differences were performed for the palliative care group and the group of patients from the medical out-patient clinic, and mean inter-item correlations was used for presenting this gender comparisons. In this thesis the aspect of convergent validity was found to be appropriate, investigating the convergence of CR-10 and MFI,

Analyses paper III

For group comparisons two-tailed independent Student's t-test was used, and for multiple comparisons between groups one way analysis of variance (ANOVA) was used. To identify differences between subgroups, post hoc multiple comparisons with Bonferroni adjustment was used. The relationships between fatigue and putative factors (such as age, gender, diagnosis, and sample group) were analysed using multivariate logistic regression models. Responses to the CR-10 were dichotomised to: no or mild fatigue as non-cases of fatigue, and moderate to severe fatigue as cases of fatigue. Responses to MFI-20 were dichotomised for each subscale; score 4 - <16 as non cases and 16-20 as cases. In the first step a univariate logistic regression was performed, and in the next step adjustments for age and gender was conducted. The results are presented with odds ratio (OR) and 95% Confidence Interval (CI). To compare the individual patients' rating of anxiety and depression in the HADS a paired-sample t-test was used. Pearson's correlation coefficients were calculated between the CR-10 and HADS subscales.

Analyses paper IV

All included questionnaires (MFI-20, SOFI and the EORTC QLQ C-30) were analyzed according to their manuals. The *emotional functioning* subscale and the *fatigue* subscale together with the single items of *insomnia* and QoL from the EORTC QLQ C-30 were included in the analysis. The fatigue experience was investigated in relation to age, gender, cancer diagnosis, and time of survival. For group comparisons two-tailed independent Student's t-test was used, and for multiple comparisons between groups one way analysis of variance (ANOVA) was used. To identify differences between subgroups, post hoc multiple comparisons with Bonferroni adjustment was used and tests for linear trends were used for factors with ordered categories. Pearson's

correlation coefficients were used for analysing the association between fatigue variables and *emotional functioning* and fatigue and *quality of life*.

Analysis paper V

The written answers on the study specific questionnaire were analysed inspired by Thorn et al's (131) interpretive description, which has the primary aim of generating clinically relevant data. The specific strategy for the analysis was as follows: each individual's responses to all questions were first read through by the first (CLH) and second (YW) authors. In the next step all responses to each of the six questions were examined. The third step involved decontextualizing the data from both individuals and questions, and thereafter recontextualizing the data into groups based on similar manifest content (132). These groups of comments were then studied for commonalities and differences and findings formulated.

Credibility (Paper V)

Credibility is an important aspect of trustworthiness (104), and refers to confidence in the truth of the data and the interpretations of them. To demonstrate the credibility of the qualitative study (Paper V) the first and second authors jointly conducted the data analysis, and similarities and differences were discussed until consensus was reached. Authors CT and CJF then validated the analysis by reviewing the process from raw data through interpretation.

Missing data

In the EORTC QLQ C-30, each of the subscales are possible to calculate if at least half of the items are completed by ignoring any items with missed value, according the manual (133). In all other instruments a subscale was not included in the analysis, since we did not use techniques' of imputation because of the importance of participant's self-reports and of the low number of missed items.

ETHICAL CONSIDERATIONS

When considering ethical aspects of the studies in this thesis, there are some general aspects that were considered, such as the aspects of participant's autonomy; to respond to this aspect the research nurse made sure that the individual participant was capable of controlling his or her choice to participate. Hospitalised patients may feel pressure to participate in studies due to obligations to health care staff; in this thesis a research nurse not included in the clinical work performed the study procedure. All participants were given verbal and written information of the study, information about confidentiality and names of the researchers and who to contact were stated in the study information. Participants were informed about the right to discontinue participation at any time without giving reasons and that refraining should not influence their individual care. All participants gave informed consent. In addition, the possibility of generating harm was considered. For this thesis aspects of causing physical harm, primarily as a result of the energy demands placed by answering the different questionnaires and thus causing fatigue, were considered. Concerns about this aspect were handled by offering the patients with advanced cancer help with reading and writing. Risks of causing psychological harm through the questions were addressed, and a nurse specialised in palliative care (CLH) and familiar with the questionnaires gave information to the patients with advanced cancer and gave them time for debriefing sessions after data was collected. For the patients in palliative care the patient's responsible nurse was informed about the patient's participation to ensure that they could get help by contacting the research nurse or the research team in the event of questions. The Research Ethics Committee at Karolinska Institutet granted ethical approval (Reference Number: 97-191).

RESULTS

PAPER I (EORTC QLQ C-30)

A total of 278 patients with advanced cancer completed the EORTC QLQ C-30, within the first days after admittance for palliative care, sample characteristics is presented in Table 4. The result showed high levels of symptoms, with *fatigue* (mean 80), *appetite loss* (mean 59), and *dyspnoea* (mean 51) as most prominent. All of the patients reporting some degree of *fatigue*, and 40% of the patients reported the highest score of *appetite loss*, and 39% for *fatigue*, *dyspnoea* 26%, *constipation* 17% and *pain* 14%. Additionally 66% reported the lowest score in *role functioning* and 32% in *physical functioning* and 25% in *social function*. *Global health status/QoL* was scored at the lowest score for 18% of the patients.

Older patients reported significantly higher scores in the *role*, *emotional*, and *social functioning* scales than younger ones. Older patients also scored significantly higher in *global health status/QoL*, than younger patients. Younger patients reported statistically higher score in *pain* and more *financial impact* than older patients. Women reported significantly more *nausea/vomiting* and *diarrhoea* than men. Married or cohabiting patients reported significantly more *fatigue* and *constipation*, and lower *emotional*, *cognitive* and *social functioning* than single patients. Problems with *fatigue* and *dyspnoea* increased in relation to time of survival, and *physical*, *role*, *cognitive functioning* as well as *Global Health Status/QoL* decrease in relation to time of survival. Patients closest to death did not differ significantly from those with a longer time to live in relation to *social functioning*, and no impact of diagnosis on the QoL parameters was found. It was shown that 45% of participating patients were able to fill in the questionnaire themselves without any assistance. Patients who died within 30 days (49%) and 2 weeks (43%) after completing the questionnaire were able to participate, although most of these patients received some assistance.

A large number of patients (n=465) who were admitted to the palliative care service had not filled out the EORTC questionnaire. The non-participating patients spent a significantly shorter time at the unit, most often due to a shorter survival time.

PAPER II (MFI-20, CR-10)

A total of 584 participants were included and comprised four different groups; patients with advanced cancer (n=229); patients with cancer at the end of radiation therapy (n=81); patients visiting a medical out-patient clinic (n=114); and healthy volunteers (included 160 health care staff), sample characteristics are presented in Table 4. The participants completed MFI-20 and CR-10 measurements and aspects of reliability and validity were tested for the fatigue specific instrument MFI-20. The inter-item correlation coefficients ranged between 0.21 and 0.90, with lower values for patients with advanced cancer. All subscales of the MFI-20 were correlated; the inter-item correlation coefficients were all relatively high with almost all correlation coefficients exceeding 0.30. This shows that the individual items of a subscale were related to the other items in the same subscale, indicating that the instrument measured the same constructs (fatigue). All MFI subscales were also correlated with the CR-10 score ($p \leq 0.001$), reflecting convergent validity. The *general fatigue* subscale showed the highest correlation with the CR-10 scale ranging between 0.60 and 0.74. Cronbach's α test showed that all but two of the different subscales reached satisfactory levels of reliability, ranging from 0.67 to 0.94. The two exceptions were *mental fatigue* for patients with advanced cancer (0.68) and *reduced motivation* for the Hospital Staff

group (0.67). The analysis showed that if item 2, 3, 9, 13 or 19 were omitted an increase in α was evident: *physical fatigue* (item 2) for patients with advanced cancer and patients receiving radiotherapy, *reduced activity* (item 3) for all groups, *reduced motivation* (item 9) for the outpatients, *mental fatigue* (item 13) for the Hospital Staff, and *mental fatigue* (item 19) for the patients receiving radiotherapy and patients with advanced cancer. The level of non-response was low (less than 1.2%) and there was no pattern of the items omitted.

PAPER III (MFI-20, CR-10, HADS)

This study included a total of 309 participants' divided in two groups: patients with advanced cancer (n=228) and patients with cancer receiving curative radiotherapy (n=81), for patients characteristics please see Table 4. Patients completed CR-10, MFI-20 and HADS were included. It was hypothesised that patients with advanced cancer would report the highest levels in all investigated aspects of fatigue. These patients showed the highest mean scores of overall fatigue intensity (tiredness) rated by the global CR-10 ($p<0.01$), and for all the MFI-20 subscales ($p<0.05$), with the exception of *reduced motivation*. Higher scores (ranging between 13.1 and 17.8) were found for the global and physical aspects of fatigue (*general fatigue*, *physical fatigue*, *reduced activity*) and lower scores (ranging between 9.7 and 11.1) for the mentally related aspects (*mental fatigue* and *reduced motivation*) in both groups of patients. For patients with advanced disease, the ratings of *fatigue*, *anxiety* or *depression* were not related to type of cancer. For patients in the radiotherapy group, with the single patient with the CNS tumour excluded, significant differences were shown between diagnostic groups in *reduced activity* ($p<0.05$) and for *depression* (HADS) ($p\leq 0.001$). Patients with gynaecological cancers scored significantly higher in *reduced activity* than patients with urological cancers (mean 15.4 and 7.2 respectively) ($p<0.01$). For *depression*, patients with gynaecological cancers (mean 6.8) and blood/lymph cancers (mean 8.3) scored significantly higher in *depression* ($p<0.01$ and 0.05 respectively) than patients with urological cancers (mean 1.0). The univariate logistic regression showed that the patients with advanced disease had a statistically significant increased probability to experience all aspects of fatigue as compared to those undergoing radiation, excluding *mental fatigue*, the OR ranged from 7.9 (CI 4.5 – 14.0) for *physical fatigue* to 2.1 (CI 1.0 – 4.4) for *reduced motivation*. After adjustment for age and gender, the probability of experiencing overall, general and physical aspects of fatigue increased further for patients with advanced disease as compared to those undergoing radiation, Table 5. After these adjustments, a statistically significant increased probability for patients with advanced cancer to experience *mental fatigue* was shown. However, the significant probability to experience *reduced motivation* did not remain after these adjustments.

Table 5. Logistic regression analysis with odds ratio (OR) adjusted for age^a and sex, and Confidence Interval (CI) for the CR-10 and MFI-20 subscales

Participant groups	PC	RT
total	n=228	n=81
Tiredness (CR-10)		
Cases/no cases	197/31	55/25
Unadjusted OR for cases of tiredness ref RT (CI)	2.9 (1.6-5.3)*	0
Adjusted ^b OR for cases of tiredness ref RT (CI)	5.2 (2.4-11.2)*	0
MFI-20 subscales		
General Fatigue (GF)		
Cases/no cases	160/66	35/45
unadjusted OR for cases of GF ref RT (CI)	3.1 (1.8-5.3)*	0
Adjusted ^b OR for cases of GF ref RT (CI)	5.0 (2.7-9.3)*	0
Physical Fatigue (PF)		
Cases/no cases	182/45	27/53
Unadjusted OR for cases of PF ref RT (CI)	7.9 (4.5-14.0)*	0
Adjusted ^b OR for cases of PF ref RT (CI)	11.5 (5.8-22.7)*	0
Reduced activity (RM)		
Cases/no cases	165/63	30/49
Unadjusted OR for cases of RA ref RT (CI)	4.3 (2.5-7.3)*	0
Adjusted ^b OR for cases of RA ref RT (CI)	5.8 (3.1-10.7)*	0
Mental Fatigue* (MF)		
Cases/no cases	44/184	11/70
Unadjusted OR for cases of MF ref RT (CI)	1.5 (0.7-3.1)	0
Adjusted ^b OR for cases of MF ref RT (CI)	2.7 (1.1-6.5)*	0
Reduced motivation (RM)		
Cases/no cases	53/173	10/69
Unadjusted OR for cases of RM ref RT (CI)	2.1 (1.0-4.4)*	0
Adjusted ^b OR for cases of RM ref RT (CI)	2.1 (0.9-4.5)	0

^aAge divided in 5 age groups as follows: <50, 50-59, 60-69, 70-79, and ≥80 years. ^bAdjusted for age and sex. PC=Patients with advanced cancer in palliative care, and RT=cancer patients receiving radiotherapy. CR-10 = Category Ratio 10, MFI-20 = Multidimensional Fatigue Inventory, MF* = the Swedish version of the mental fatigue subscale has one item removed from the scale. Response scale for the CR-10 0–11, MFI – 20 scales 4–20. *= showed statistical significance of p<0.05.

It was hypothesised that the participants would report higher scores of *depression* than *anxiety*, with patients with advanced cancer reporting the highest levels. Initial analysis did not support this hypothesis since there was no difference in *anxiety* and *depression* ratings for the total group of patients receiving radiotherapy. When investigating the ratings of *anxiety* and *depression* at the different levels of fatigue, the results showed that these patients did report higher scores in *depression* than *anxiety*, when strongly fatigued (p<0.05). The patients with advanced cancer also reported significantly higher scores of *depression* than *anxiety* at the highest level of fatigue (p<0.001), Table 6. At this fatigue level 23% of all patients classified as anxious and 39% as depressed, with 25% of patients with advanced cancer classified as anxious and 44% as depressed and the 14% as anxious and 17% as depressed in the group of patients receiving radiotherapy.

PAPER IV (CR-10, MFI-20, SOFI, EORTC QLQ C-30)

A total of 228 patients with advanced cancer admitted for specialised palliative care were included in this study, for sample characteristics see Table 4. Patients completed CR-10, MFI-20, SOFI and EORTC QLQ C-30 measurements. Regarding time of survival the study cohort was followed until death for all but 3 patients, still alive in January 2008, when follow up ended and a last date was set to 1.1.2008. The median length of survival from the time for data collection was 63 days. Twenty-eight of the included patients survived for less than 2 weeks after answering the questionnaires. Overall, the patients reported *strong* fatigue (mean 4.9) on the CR-10 scale, and aspects of *physical fatigue*, *reduced activity* and *general fatigue* as most prominent on the MFI-20. The SOFI subscales; *lack of energy*, *sleepiness* and *lack of motivation* were most salient. On the selected EORTC subscales patients reported high scores for *fatigue* (mean 75.2) and low ratings for QoL (mean 37.3). Women reported a significantly higher intensity in *general fatigue* (MFI) than men (mean 17.2 and 16.2 respectively, $p < 0.05$). Married or cohabiting patients reported significantly higher intensity of fatigue than single patients ($p < 0.05$) in: overall fatigue (CR-10); *general fatigue*, *reduced activity*, *mental fatigue*, and *reduced motivation* (MFI); in *lack of energy*, *lack of motivation* and *sleepiness* (SOFI). According to age (the sample was divided in five age groups), the one way ANOVA showed a significant difference between groups in overall fatigue ($p < 0.01$), the post hoc test showed that all groups 79 years or younger rated their overall fatigue higher than patients 80 years or older ($p < 0.01$). When analysing the relation between fatigue and cancer diagnosis, results showed no significant differences in overall fatigue. Patients with breast cancer reported the highest ratings of *physical discomfort* ($p < 0.01$) (SOFI), while lung cancer patients rated the significantly highest levels of *physical exertion* ($p < 0.05$) (SOFI). The sample was divided into six groups regarding time from answering the questionnaires to death: ≤ 15 days; 16-30 days; 31-60 days; 61-91 days; 91-120 days and > 120 days. All aspects of fatigue increased for patients getting closer to death. The patients with a short survival (≤ 15 days) rated their overall fatigue significantly higher than the patients with a long survival (> 120 days). The correlations between fatigue and *emotional functioning*, and with *QoL* showed statistical significance for the majority of investigated aspect of fatigue for the groups who lived longer. This was not evident for the patients with short time of survival, indicating that fatigue was less associated with patients' experiences of *emotional functioning* and *QoL* closer to death. The analysis showed that the correlation between *fatigue* and *emotional functioning*, and *QoL*, was strongest for the groups of patients who lived between 61 to 120 days, Table 6.

Table 6. Correlation coefficients between fatigue related variables and emotional functioning (EF) and Quality of life (QoL) in relation to patient's time of survival.

Time of survival	≤15 days (n=28)		16-30 days (n=33)		31-60 days (n=49)		61-90 days (n=27)		91-120 days (n=18)		>120 days (n=73)	
	EF	QoL	EF	QoL	EF	QoL	EF	QoL	EF	QoL	EF	QoL
CR-10	-.14	-.24	-.002	-.06	-.10	-.35*	-.56*	-.66*	-.56*	-.41	-.44*	-.37*
MFI												
GF	-.25	-.07	-.24	-.18	-.06	-.32*	-.51*	-.66*	-.44	-.54*	-.36*	-.20
PF	-.29	.08	.01	-.16	-.08	-.46*	-.47*	-.58*	-.53*	-.71*	-.35*	-.27*
RA	.21	-.04	-.24	-.19	-.17	-.49*	-.27	-.50*	-.34	-.40	-.29*	-.38*
MF	-.19	-.15	-.33	-.04	-.46*	-.16	-.57*	-.30	-.12	-.01	-.28*	-.18
RM	-.01	-.27	-.21	-.12	.10	-.14	-.32	-.65*	-.13	-.58*	-.28*	-.38*
SOFI												
Lack of energy	-.24	-.20	-.40*	-.07	-.12	-.36*	-.56*	-.59*	-.53*	-.76*	-.31*	-.14
Physical exertion	-.11	-.14	-.30	-.19	-.23	-.26	-.45*	-.13	-.44	-.32	-.12	-.06
Physical discomfort	-.30	-.23	-.29	.04	-.27	-.26	-.68*	-.21	-.36	-.38	-.32*	-.06
Lack of motivation	.13	-.51*	-.52*	-.24	-.39*	-.16	-.61*	-.51*	-.67*	-.68*	-.27*	-.29*
Sleepiness	-.06	-.22	-.15	.07	-.21	-.28	-.70*	-.44*	-.24	-.56*	-.17	-.08
EORTC												
Fatigue	-.30	.18	-.44*	-.15	-.27	-.35*	-.48*	-.63*	-.62*	-.86*	-.38*	-.25*
Insomnia	-.47*	-.02	-.56*	-.24	-.16	-.02	-.29	-.47*	-.62*	-.38	-.40*	-.10

CR-10 = Category Ratio 10, MFI-20 = Multidimensional Fatigue Inventory, GF=general fatigue, PF=physical fatigue, RA=reduced activity, MF= mental fatigue the Swedish version of this scale has one item removed from the scale, RM=reduced motivation; and SOFI=Swedish Occupational Fatigue Inventory, EORTC= European Organization for Research and Treatment of Cancer QoL Questionnaire C-30, Response scale for the CR-10 0–11, for the MFI–20 scales 4–20 and SOFI scales 0-6 and EORTC 0-100. For the symptom scales and all other scales higher scores represents a higher symptomatology/problem. * represents a statistical significant correlation coefficient, p<0.05.

PAPER V (STUDY-SPECIFIC QUESTIONNAIRE)

Twenty-six of the 36 registered nurses working in palliative care eligible for this study completed the questionnaire as requested (response rate of 72%). The results showed that the nurses perceived both facilitators and barriers of using a quality of life questionnaire (EORTC QLQ C-30) for systematic assessments in clinical practice. These facilitators and barriers were described by the nurses both in relation to patients and in relation to themselves as professionals. Facilitators for using of the QoL instrument were expressed in terms noting that it was a comprehensive, but short instrument that took approximately 10 minutes to complete. Several nurses pointed to its value in identifying symptoms that might not naturally have been discussed without the systematic assessment. These aspects were that they were forced to make themselves be more structured and not forget important things needed to give good care, and also the opportunity for patients to write down problems they do not easily express verbally. The instrument was also described by some nurses as aiding a therapeutic process with patients. This included the chance for patients to describe their feelings about a wide array of problems, but was often emphasised as most useful if completed in conjunction with discussion. The instrument was also found useful in

clarifying differences in perspectives between the patient and the nurse. Using the instrument was described as leading to positive outcomes, which included better and faster symptom management, a deeper understanding of the patient's situation and quality of life, and aiding nurses in formulating better care plans more rapidly. Barriers in using the QoL instrument were described in terms of explicit criticism directed to the use of the questionnaire in this patient group; these problems ranged from practical issues such as layout not tailored to the needs of this patient group, i.e. small print and many pages, to issues about appropriateness of structured measures for people at the end-of-life expressed in terms of "too comprehensive for all patients to have the strength to complete". Barriers for using the instrument were also described in terms of "tired patients become more tired and irritable", and that questions were "too intimate" for some patients and "too intellectual" for others. Other criticisms were stated more indirectly responses to the question about when the instrument was not used were generally given when patients were perceived as "too sick and tired to answer questions". There were several comments indicating the nurse's own attitudes, rather than the patient's situation or desires clearly affected their use of the QoL instrument, e.g. "the questionnaire is too inflexible and not useful for me personally". Several nurses also commented that they could "forget" to hand out the instrument.

DISCUSSION

Identification and relief of symptoms are of major concern in palliative care. The aim of this thesis was therefore to describe and explore to what extent and in what ways patients with advanced cancer experience fatigue, and to investigate aspects of the assessment and measurement of fatigue for these specific patients.

Experience and perception of fatigue

Our results (Paper I, II, IV) indicate that fatigue is of major concern in patients with advanced cancer. This confirms earlier findings (52, 57, 134), however many studies have failed to show any relationship between stage of disease and fatigue (77, 135, 136). The results presented in this thesis demonstrated that patients with advanced cancer experienced fatigue more intensively than did patients earlier in the cancer trajectory, receiving curative cancer therapy (Paper III). The intensity of fatigue among patients with advanced cancer (Paper I, III, IV) is in line with reports from comparable groups presented by others (121, 137, 138). The results indicates further that it is the intensity of fatigue that seems to be related to the underlying exposure to radiation or to the level of disease burden rather than the different fatigue profiles, such as the relation between physical and mental aspects (Paper III).

The result of this thesis confirms the multidimensionality of fatigue in patients with cancer disease affecting both physical and mental senses. We have shown that patients at different stages of cancer mostly experienced fatigue as a bodily sensation: as an overall feeling of tiredness, tiring easily, not feeling fit or rested, and lack of energy (Paper III). Mental aspects of fatigue including ability to concentrate, making plans and do things had less of an impact. The patients with advanced cancer differed significantly from those undergoing treatment in the intensity of the physical aspects of fatigue (*general fatigue*, *physical fatigue* and *reduced motivation*), although the difference was not as clear between the two groups of patients as regards the mental aspects. Mental fatigue may increase after a cancer diagnosis. De Jong et al. (139) mean that worries or anxiety about the process of recovery and treatment leads to an increase in mental fatigue. This may have influenced *mental fatigue* in the patients receiving radiotherapy, while on the other hand patients with advanced cancer might have adapted to their situation leading to a lower impact of *mental fatigue*. This results may fit in the Fatigue Adaption Model presented by Olson et al. (61), where patients may change between tiredness, fatigue and exhaustion due to their ability to adapt to stressors related to disease processes. The physical differences may indicate an underlying physical aetiology in response to the disease progress (59).

Variables associated with fatigue

Age, gender, cancer diagnosis and marital status

It is indicated in the literature that aspects of age, gender, diagnosis and marital status may affect fatigue, although there is no general agreement on the relationships (78, 85, 86, 140). We did not find a systematic relationship between ages, although younger patients tended to report higher levels of fatigue.

Being married or cohabiting was found to be related to higher levels of reported fatigue (Paper I, IV). This contradicts earlier findings (141), although Kenefick (142) also found that patients living with a partner reported significantly more symptom

distress than did patients living alone. There may be several explanations of these findings which has been discussed in the different papers, such as the experience of symptom distress as being legitimised from supportive individuals (31) or that they are more used to sharing their experiences with others. It has been proposed that married couples may be restricted to their partner, while singles might have a larger supporting network with friends (142). The married patients were younger, which complicates the interpretation of the results. However, this may have important clinical implications, since patients may be treated differently depending on their social network.

Fatigue and anxiety and depression

Paper III demonstrates that cancer patients, both in palliative care and undergoing radiotherapy, reported more depression than anxiety as assessed by the HADS. These findings are in line with earlier reports from patients admitted for palliative care (143). For patients receiving radiotherapy, Ahlberg et al. (144) found that depression increased significantly during treatment, whilst anxiety decreased compared to the time prior to treatment. There was only a significant difference between the cancer patient's ratings of anxiety or depression at the highest fatigue level. Forty-four percent (51 pts.) of the patients with advanced cancer were classified as "cases" of depression, and about 17% (5 pts.) of the patients receiving radiotherapy. The relation between anxiety and/or depression with fatigue is still unclear (145, 146). The number of patients with depression and anxiety disorders in Paper III, shows the importance of screening for depression and anxiety in patients with cancer, particularly in patients with advanced cancer. The palliative care trajectory varies and both symptom assessment and management of depression and anxiety may be difficult, although Higginson and Costantini (1) put forward that there are simple screening methods for assessing psychological problems available that work well in patients with advanced cancer.

Fatigue correlated with time of survival, emotional functioning and quality of life

Our results indicate a relationship between increased fatigue and time of survival (Paper I, III, IV). In addition to this, it was demonstrated that fatigue, in all dimensions including *sleepiness* increased as patients got closer to death with a statistically significant difference shown when patients with less than two weeks to live were compared to those having more than four months to live (Paper IV). The experience of being sleepy increased approaching death, while on the other hand there were no statistical difference found for the experiences of sleep disturbance comparing patients with short time of survival with patients living longer. This could describe the patients with advanced cancer at the end of life as sleepy but not having trouble to sleep. From a clinical point of view it is not uncommon for patients at the end of life, and might support the empirical findings that fatigue is not alleviated by sleep and rest.

There is a common agreement that fatigue negatively influences quality of life. In Paper IV the results showed that relationship between fatigue and quality of life varies during the palliative care trajectory and the results indicate that the association between fatigue and quality of life decreases in the last month of life. This may reflect that other symptoms and aspects of life are more connected to quality of life when patients are getting closer to death. Also the relationship between fatigue and *emotional functioning* decreased closer to death, while this feeling of being tense, worrying, feeling irritable or depressed remained the same according to the statistical analyses. The correlation between fatigue and both *emotional functioning* and *quality of life* was strongest for the group of patients who lived between 61 to 120 days. These findings allow for the speculation that the fatigue experience may change at the end of life. It can be

hypothesized that in this time period there might be a change in the individuals condition and they experience more distress from fatigue, which could reflect a phase where the patients go from living with their disease to a situation where they might be more affected by fatigue. The decreased association that was seen in groups of patients living shorter may be due to the patients' change of internal standards, values or priorities or a change in the definition of fatigue, a *response shift*, i.e. a process of adaptation to the situation. Our findings support the proposals posed by the EAPC working group (147) on fatigue in palliative care; that fatigue in the final stage of life may serve as protection and relieves from suffering. This has also been explored by Wu and McSweeney (148) where the value of fatigue was discovered as having a positive meaning and could serve as a defence mechanism that protected the patient from psychological collapse. This also challenges the definition presented by the NCCN (45) described in the background section where fatigue in patients with cancer is defined as “*a distressing persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment*”.

Assessments and measurements of fatigue

The aspect of assessment and management of symptoms in patients with advanced cancer is of great concern to health care professionals. Patients suffer from several symptoms and are often in a very complex situation. Managing symptoms is one of the specific aims of palliative care, with inputs from the whole team. All the team members make their own specific assessments with their own expertise and skills. With so much information gathered by so many personnel, the risk of duplication is great and unnecessary stress can be caused to the patient. Subjecting an already fatigued patient to different assessments and information-sharing processes in the same area may not be justifiable. It has also been reported that the discourse space might be controlled by health care staff, and the structure of the conversation regarding topics and conversational frames driven by an expert-driven agenda in palliative care consultations (149). Fatigue is an issue that is not only difficult to manage, but also difficult to talk about with patients with advanced cancer (87). In the qualitative study (Paper V) several nurses pointed to the value of systematic assessment using a quality of life instrument. Symptoms might not naturally have been identified and discussed without the systematic assessment. It gives an opportunity for patients to write down problems they do not easily express verbally. This may be a way of bringing up fatigue as a clinically important symptom for nurses and other health care professionals to observe.

This thesis has focused on aspects of assessment and measurement of fatigue. We have shown clinical difficulties in making an assessment with a standardised measurement, as there were a large number of patients who did not answer the quality of life questionnaire. This was mainly due to shorter period of care, since many patients died within a short time after admission. This reflects the difficulties to perform these procedures both clinically and for research purposes in palliative care. However, this thesis also demonstrates that the patients were able to answer different instruments even very close to death (Paper I - IV). Barriers from the nurses' view in using the QoL instrument were described (Paper V) in terms of explicit criticism directed to the use of the questionnaire in this patient group; these problems ranged from practical issues such as layout not tailored to the needs of this patient group, i.e. small print and many pages, to issues about appropriateness of structured measures for people at the end-of-

life expressed in terms of “too comprehensive for all patients to have the strength to complete”. Other criticisms were stated more indirectly for example “too sick and tired to answer questions”. There were several comments indicating the nurse’s own attitudes, rather than the patient’s situation or desires e.g. “the questionnaire is too inflexible and not useful for me personally”. Several nurses also commented that they could “forget” to hand out the instrument. The various aspects of barriers and facilitators expressed by the nurses, both for themselves and for the patients, may indicate a need to look at the aspects of education for nurses, as well as other health care professionals, in the use of systematic assessments, and also the need for support and organisation in the service that may be needed. The nurses comprised in this thesis, explored difficulties in using the EORTC QoL instrument clinically. Today a specific shortened module is available for palliative care (150, 151). A report by Nicklasson and Bergman (152), demonstrated good compliance by patients in palliative care, in line with findings in the present thesis, and pointed out that the problems with reliability, especially with the cognitive functioning subscale, still exist. Since the nurses described many difficulties in using a measurement instrument clinically, it may be assumed that it can be difficult to use different symptom-specific measurements in palliative care. Focus should instead be on screening of symptoms on admission, including aspects of distress and problems that are of most importance to the individual patients, which should also be included in follow up assessments. The concept of *symptom distress* has been proposed as a separate part of the symptom experience (153, 154), representing a difference between symptom intensity and the distress the symptom causes the patient, and may be advantaged to use since it had demonstrated that fatigue may have different meaning during the palliative care trajectory, although reported as an intensive feeling.

Fatigue-specific instruments may be most appropriate for research purposes. In this thesis the use of multidimensional fatigue instruments gave the opportunity to investigate the fatigue experience in more depth, and to look at differences among the participants. The outcomes of most of these multidimensional instruments have to be aggregated on different subscales. When aspects concerning validity and reliability were tested or discussed, most of the instruments reached satisfactory levels in measuring patients on group levels (adequate level 0.70)(104).

The systematic review presented in the background section demonstrates that several instruments are available for assessment of fatigue among patients with cancer in Sweden. These instruments are not broadly used or tested, which is a factor that has to be considered when choosing an instrument for research or for deepened assessments in clinic. In their controversial book, Randall and Downie (15) question whether “the assessments, questionnaires, counselling, and measurement scales, which have become so typical of the palliative care approach, can also be seen as a kind of harassment at the end-of-life” (Randall & Downie 2006 p. viii). Their perspective, emphasising a return to basic humanistic values and focus on symptom relief in end-of-life care is in contrast to much of the general discourse in Swedish health care on measurable outcomes and evidence-based practice. It is further brought forward by WHO (13) that an “*identification and impeccable assessment*” has to be made about problems in physical, psychosocial and spiritual areas. This is a general approach, however from the experiences of nurses in palliative care this goal might be difficult to reach, and in ways of how nurses learn of new problematic situations described by Hawthorn and Dluhy (97). It was explored that nurses and also patients sometimes had difficulties in communicate about different areas, which further challenge the assessment procedure.

In this thesis the complexity of fatigue in palliative care and both facilitators and barriers of using measurement tools in clinical practice demonstrates that this approach of an assessment procedure might not be used as a separate method but can facilitate the interaction between the nurse and patient (97). These further explore the need for research in the field of palliative care, and were the symptom specific instruments used in this thesis can be useful.

Fatigue in palliative care

A major finding in this thesis is the difference in fatigue experience both during the cancer continuum, but foremost in the palliative care trajectory. It has been demonstrated that although the intensity of fatigue increases the association to *emotional functioning* and *quality of life* decreased for patients approaching death. Management of fatigue in patients with advanced cancer with extensive physical fatigue may in fact benefit from other interventions than exercise such as distraction or engagement in creative activities, such as pottery, woodworking, gardening, and painting (155). The time of survival presented from completion of the questionnaire to death was between two days and almost 10 years. This demonstrated the diverse in time comprised in palliative care. Early and late phase are to be included as well as end of life care. End of life care as defined by ESO (14) comprise the last hours, days or weeks of life, which is in line with findings of a change in experience of fatigue in Paper IV. As described in the background section we assume that the term *palliative care* share the same terminology and purpose, when used. But there is not a consensus about definitions and terminology used. The absence of a consensus about terminology of palliative care and definitions about fatigue may prevent research about fatigue in patients with advanced cancer. Graham and Clark (156) present the challenge for palliative care in the 21st century as to “develop models and coverage appropriate to those in need whatever their diagnosis, income or setting without losing the original principles of the hospice movement” (Graham and Clark 2007, p.64). In this circumstances nurses needs to take on new knowledge and approaches and be reflective within their work, as well as palliative care research needs to be performed.

METHODOLOGICAL CONSIDERATIONS

Some areas important to consider in evaluating the extent to which generalisation of the results may be made are discussed here:

Internal validity

Internal validity refers to systematic errors within studies.

Selection bias

This refers to systematic errors in selecting participants for the study (157). The main focus was to investigate fatigue in patients with advanced cancer. Patients admitted to specialised palliative care are by definition frail and experience complex symptom, and the rather large group of non participating patients as reported in Paper I might reflect this. This non participating group had a significantly shorter time of care at the unit, most often due to shorter survival. When part of a cohort of the population is missing, there is a risk of missing important information. Categories of patients and all dimensions of a concept, in this case fatigue might not be covered. However, this study reflects the normal circumstances in palliative care, and we lack further information about the patients very close to death or with very short time of care and cannot say anything about their level of fatigue. The results therefore may reflect an underestimation of fatigue intensity. There are known problems with patient recruitment in palliative care, due to short time of survival, fatigue, cognitive impairment and ethical considerations (158).

Information bias

This refers to problems of misclassification. Studying a subjective symptom such as fatigue the focus is on the patient's experiences. The present thesis focused on generating knowledge about fatigue in patients with advanced cancer using standardised questionnaires to minimise the risk of misclassification. The measurement used: EORTC QLQ C-30, was already in use at the clinic, and was appropriate to use to explore symptoms and other quality of life aspects in this thesis. The MFI-20 was developed based on patient experiences (67), which is an advantage capturing the patient's view on fatigue. The CR-10 scale is not extensively used among patients with cancer, although this is a known form of measurement for assessment of physical exertion (159). For these study purposes this uni-dimensional measurement was found to be appropriate in giving the opportunity to divide the fatigue experience at different intensity levels, as actually reported by patients and not an estimated cut-off level. SOFI was developed for measuring perceived fatigue in working life. This instrument has been developed for Swedish populations which were seen as an advantage. All instruments have been tested for internal consistency and found acceptable for group comparison, except *physical functioning*, and *cognitive functioning* (EORTC QLQ C-30) and *physical exertion* and *physical discomfort* (SOFI), for the patients with advanced cancer. This indicates that the different items comprised in these separate subscales do not entirely measure the same concept in this sample of patients which has to be considered when interpreting the results. In this thesis two concepts of quality of life has been used: in Paper I health related quality of life was used comprised in the EORTC QLQ C-30, in Paper IV the single item "How would you rate your overall

quality of life during the past week?" was used. The approach used in Paper IV was in an attempt to let the patient themselves involve what they comprise in the quality of life concept.

Recall bias

Refers to the way a respondent answers a question, not just by the correct answer, but also by the respondent's memory. All instruments that were used ask for a retrospective assessment of symptom experience. The time frames for individual patients reports vary but these variations are difficult to control for and are not considered a bias in interpreting the results.

Statistical considerations

Data obtained from the rating scales were ordered as categorical responses designated as numerals, where a non-parametric test is often recommended. However, since the aggregated scales used in the present thesis transform the categorical data to a scale with a wider range based on mean values, parametric tests was used, in accordance with the developers of the specific instrument. Further, Glass and Hopkins (160) mean that *t*-test is a robust test with respect to failure to meet the normal assumptions, and that robustness studies have confirmed that the *t*-test findings are generalized to ANOVA, which are both used in this thesis. To adjust for multiple significance tests Bonferroni correction was used.

External validity

This refers to the ability to generalize the findings to other populations than the one investigated. Small sample size is threats to external validity. In Paper I data originated from the clinic, and since there is a large number of participants, aspects of sample size are taken into consideration, and the requirement was found to be met. For an item analysis (Paper II) a sample size of about 100-200 respondents is appropriate (113), and these data were also used in papers III and IV. As aspects of internal validity and precision in assessments were considered the results would be representative for patients with advanced cancer in specialised palliative care.

CONCLUSIONS

Fatigue is of major concern in patients with advanced cancer. These patients experienced fatigue more intensively than did cancer patients receiving curative radiotherapy. The results presented in this thesis demonstrates that fatigue is a multidimensional sensation, affecting both body and mind, although with mainly physical affection, while the ability to concentrate, make plans and do things is less affected. The patients with advanced cancer differed significantly from those undergoing treatment in the intensity of the physical aspects of fatigue (*general fatigue*, *physical fatigue* and *reduced motivation*), although this difference was not as clear between the two groups of patients as regards the mental aspects. The results indicate a relationship between increased fatigue and stage of cancer, showing a linear increase in fatigue intensity in relation to time of survival, although the association between fatigue and *emotional functioning* and with *quality of life* decreased approaching death. Patients with approximately 60-120 days to live showed a higher association between these variables. These findings allow for the speculation that the meaning of fatigue experience may change at the end of life. These results also point to the variety of fatigue experiences in the palliative care trajectory. We did not find a relationship between age, gender or cancer diagnosis and fatigue. Marital status seemed to affect the experience of fatigue, hence being married or cohabiting was found to be related to higher levels of reported fatigue. It was also demonstrated that all patients with advanced cancer experience some degree of fatigue. Patients with advanced cancer suffer from several other symptoms: *fatigue* and *appetite loss* were the two highest rated symptoms, followed by *dyspnoea*, *pain* and *depression*. The results also demonstrates that cancer patients, both in palliative care and during radiotherapy, reported more depression than anxiety on the HADS, when having *strong* fatigue. We have tested and adjusted the translated fatigue instrument (MFI-20) to respond to adequate levels of reliability and validity for assessment of fatigue. We have demonstrated clinical difficulties in making a QoL assessment with a standardised measurement. Difficulties were partly due to short time of care, with many patients dying within a short time after admission. Further nurses reported several barriers for both themselves and the patients. The nurses also experienced and saw advantages in using systematic assessment clinically. To conclude, for research purposes we were able to investigate the fatigue experience in more depth using multidimensional fatigue instruments.

CLINICAL IMPLICATIONS

The results from this thesis add to existing knowledge about the high occurrence of fatigue among patients with advanced cancer (146, 147), and its multidimensional manifestation (121, 137). Patients at different stages of cancer, experienced most of all fatigue as a bodily sensation: as an overall feeling of tiredness, tiring easily, not feeling fit or rested, and lack of energy. Aspects of fatigue such as a mental sensation including ability to concentrate, making plans and do things had less of an impact. It was also demonstrated that although fatigue intensity increased approaching death, the association between fatigue and emotional functioning and quality of life decreased. While fatigue was significantly correlated with both emotional and quality of life when having longer time of survival, higher correlation coefficients were found for patients having between 60-120 days to live. This reflects the discrepancy in fatigue experiences among patients with advanced cancer in palliative care. This has to be considered in the assessment and management of fatigue, comprising assessment of both severity and distress of fatigue.

Systematic assessment of symptoms and other health-related quality of life aspects is a main issue in palliative care. The essence in palliative nursing and a base to perform these assessments lies in the nurse-patient relationship. Using a measurement tool can be beneficent in creating a base for good patient-nurse relationship. However, we have pointed to the need for education and support in how to use such instruments that has to be considered for clinical use. By a reflective use and communication about its outcomes instruments could facilitate a more patient-driven agenda in the patient-nurse relationship. It has been demonstrated that measurements can be used for screening and assessment of fatigue among patients with advanced cancer, although multidimensional instrument might be for research or special evaluating processes.

RECOMMENDATIONS FOR FUTURE RESEARCH

We have been able to contribute new knowledge about fatigue in patients with cancer, but there is still much to be known. Further research has to be performed within this population of frail patients at the end of life.

There is also a need for:

- Further efforts to improve palliative care research by larger research groups established both nationally and internationally, as a respond to the limits of research about fatigue in patients with advanced cancer including small sample size and lack of control groups.
- Collaborating about consensus regarding definitions about the terminology used in palliative care and also about the definition of fatigue and on how to measure symptoms such as fatigue in palliative care research.
- Factors underlying fatigue aetiology needs to be further addressed as well as intervention research including nursing interventions that may reduce fatigue.
- Further research about the meaning of fatigue in patients with advanced cancer, comprising physical, psychological, social and existential aspects. These aspects have to be investigated during the palliative care continuum, including distress from fatigue or fatigue as a relief from psychological affects.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Fatigue hos patienter med en avancerad cancer sjukdom, aspekter av att bedöma och att mäta

Bakgrund

Att känna sig trött, kraftlös och utan energi är vanligt förekommande besvär som vi alla känner emellanåt. Denna vanliga trötthet kan vi oftast bota genom att vila och sova ordentligt någon natt. Människor med cancer upplever ofta en ovanlig och extrem trötthet, som inte går att sova bort. I andra språk som i engelska och franska finns ett samlingsbegrepp för denna upplevelse, vilket är *fatigue*. Fatigue har kommit att används bland hälso- och sjukvårdspersonal som term för denna upplevelse, men vid samtal med patienter används ordet trötthet. Fatigue är vanligt förekommande bland människor som drabbats av cancersjukdom, men förekommer också hos människor med Kronisk Obstruktiv Lungsjukdom, Reumatoid artrit (reumatism) och vid hjärtsjukdom. Studier har visat att fatigue är det vanligaste och mest besvärande symtomet som en följd av cancer, dess behandling och när sjukdomen inte går att bota (avancerad cancer). Även om flertalet studier påvisat detta uppmärksammas det inte alltid i möten med patienterna. Omkring 50.000 personer drabbas av cancer varje år, och i slutet av 2005 fanns i Sverige cirka 365.000 personer som har eller har haft cancer, så många människor har drabbats eller kan drabbas av fatigue. Orsaken till fatigue är fortfarande inte klarlagd. Olika faktorer har använts som förklaring bakom upplevelsen av fatigue, såsom sjukdomen i sig och konsekvenser av sjukdomen som blodbrist, avmagring, infektioner och rubbningar i kroppens ämnesomsättning. Ängest, depression, och stress relaterat till situationen anges också som förklaring. De flesta studier som genomförts har rört patienter som får cancerbehandling, exv. kirurgiska ingrepp, strålbehandling och cellgiftsbehandling (cytostatika). Ofta beskrivs fatigue som en kroppslig upplevelse (fysisk) men även som mental. Det finns ingen samlad kunskap om upplevelsen av fatigue skiljer sig mellan olika grupper av patienter med cancer och få studier har genomförts för att öka kunskapen om fatigue hos patienter där cancersjukdomen inte går att bota.

Syfte

Syftet med avhandlingen var att utveckla den befintliga kunskapen om fatigue hos patienter med en cancersjukdom som inte går att bota. Detta har skett genom att beskriva och utforska i vilken omfattning och på vilka sätt dessa patienter upplever fatigue, inom denna grupp och i jämförelse med patienter som får strålbehandling som bot för sin cancersjukdom. Vidare att undersöka hur man kan bedöma och mäta fatigue hos dessa patienter samt relationen mellan fatigue och ångest, depression, emotionell funktion och livskvalitet.

Metod

Olika typer av frågeformulär har använts, dessa har analyserats genom statistiska metoder (kvantitativ metod) samt analys av skriven text (kvalitativ metod). Totalt har fem olika delstudier genomförts, där deltagarna besvarat de olika frågeformulären vid ett tillfälle.

Resultat

Den första studien visade att alla patienter (278 st) med avancerad cancer upplevde någon grad av fatigue. Även andra symtom var vanligt förekommande, och 40 % skattade det högsta möjliga värdet av besvär med aptitlöshet, 39 % skattade det högsta möjliga värdet av besvär med fatigue, 26 % med andnöd, 17 % med förstoppning och 14 % det högsta möjliga värdet av besvär med smärta. Problem med fatigue och andnöd ökade i livets slut, och fysisk funktion, rollfunktion, kognitiv funktion och övergripande upplevelse av hälsorelaterad livskvalitet försämrades i livets slut. Resultaten visade att 45 % av patienterna klarade av att själva fylla i frågeformuläret utan hjälp, patienterna som bara levde i ytterligare två veckor besvara formuläret med lite hjälp.

Delstudie II undersökte hur väl ett frågeformulär (från början utvecklat av holländska forskare, men översatt till svenska för att mäta fatigue hos patienter som får strålbehandling), mäter fatigue hos patienter med avancerad cancer. Instrumentet är uppbyggt av 20 frågor som mäter fem olika aspekter av fatigue. Genom olika statistiska metoder säkerställdes att man verkligen mäter fatigue (validitet) och att det mäts på ett tillförlitligt sätt (reliabilitet) hos just denna grupp av patienter. Vi fann att en fråga inte fungerade och den togs bort från instrumentet, som sedan fungerade väl för mätning av fatigue. Denna delstudie omfattade också patienter som fick strålbehandling och en grupp patienter som inte hade cancer utan behandlades på en medicinsk öppenvårdsmottagning, samt en grupp friska individer (frivillig hälso- och sjukvårdspersonal) och instrumentet fungerade väl också för dessa grupper.

I delstudie III undersöktes totalt 309 patienter, en grupp med avancerad cancersjukdom och en grupp med patienter som hade en cancersjukdom där bot var möjlig genom strålbehandling. Patienterna med avancerad cancer skattade de högsta medelvärdena i alla delskalor, utom skalan som mäter minskad motivation. Alla patienter uppgav att känslan av fatigue var mer fysisk än mental. Efter att justerat för påverkan av ålder och kön hos deltagarna, visade resultaten att oddset för patienter med avancerad cancer är mellan 2 och 8 gånger högre att drabbas av fatigue än för patienter som får strålbehandling. Studien visade också att patienterna skattar mer depression än ångest när de har stark fatigue.

Delstudie IV omfattade 228 patienter med avancerad cancer, med en överlevnadstid på i genomsnitt 63 dagar. Resultatet visade att fatigue ökade ju närmare döden individen var, både i övergripande mätning men också vid mätning av olika aspekter av fatigue samt en upplevelse av att vara sömning. Sambandet mellan fatigue och en känsla av att vara spänd, orolig, irriterad och deprimerad minskade ju närmare livets slut individen var. Detta gällde också relationen mellan fatigue och livskvalitet. För människor med mellan 60 och 120 dagar kvar att leva var sambandet kraftigare.

I de olika kvantitativa delarbetena (delstudie I-IV) har påverkande faktorer som ålder, kön, cancerdiagnos (typ av cancer) och civilstånd undersökts i relation till fatigue, och där yngre, kvinnor, patienter med lungcancer, samt gifta tenderar att skatta högre värden av fatigue än äldre, män, andra diagnosgrupper och ensamstående. Dessa resultat visar inga tydliga systematiska samband.

I delstudie V, undersöktes sjuksköterskors erfarenheter av att använda ett frågeformulär för systematisk bedömning av symtom och andra livskvalitetsaspekter i dagligt arbete i palliativ vård. Trettiosex sjuksköterskor besvarade skriftligt ett studiespecifikt instrument, som sedan analyserades utifrån innehållet i vad de skrivit.

Sjuksköterskorna beskrev positiva erfarenheter relaterat till hur det var ett stöd i deras professionella roll, underlättade kontakten med patienten, samt omfattningen av information de fick. Sjuksköterskorna beskrev också svårigheter med att införliva formuläret i den traditionella bedömningen de gjorde, här beskrevs problem med instrumentet och situationer i vården där det inte passade att använda. Sjuksköterskornas egna attityder och bekvämlighet i att använda formuläret spelade in.

Diskussion

Avhandlingen belyser symtomet fatigue, som är av stor betydelse för patienter med avancerad cancer. Resultaten från avhandlingen bekräftar befintlig kunskap samt ger ny kunskap genom beskrivningen av fatigue, påverkande faktorer och relationen till emotionell funktion och livskvalitet. Dessa patienter upplever fatigue mer intensivt än patienter med cancer under botande strålbehandling. Resultaten visar att fatigue är en upplevelse främst i kroppen som en generell trötthet, fysiskt upplevd och med en minskad motivation, medan aspekter av att kunna koncentrera sig, ha planer och att göra saker rapporterades till en lägre del. Resultaten indicerar en relation mellan intensitet av fatigue och tid kvar att leva, medan relationen mellan fatigue och känslan av att vara spänd, orolig, irriterad och deprimerad samt med livskvalitet minskade ju närmare livets slut individen var. Detta kan påvisa att betydelsen av fatigue minskar i livets slutskede. Här kan vi bara spekulera om denna intensiva känsla blir ett skönt skydd för påfrestningen det innebär att närma sig döden. Resultaten visar också att dessa relationer ser ut på ett annat sätt för personer med längre tid kvar att leva, där man kan spekulera om att upplevelsen istället är mer påfrestande och besvärande. Det har visat sig vara svårt att använda ett frågeformulär för bedömning av symptom och andra livskvalitetsaspekter i palliativ omvårdnad, och där det kan diskuteras vara en fråga om utbildning i dess användande och stöd för att införliva en sådan procedur i kliniskt arbete. Fortsatta studier behövs för att ytterligare öka kunskapen om fatigue hos människor med avancerad cancer, för att finna sätt att hjälpa dessa personer att hantera upplevelsen och dess konsekvenser.

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REFERENCES

1. Higginson IJ, Costantini M. Dying with cancer, living well with advanced cancer. *Eur J Cancer*. 2008 Mar 13.
2. Tsai JS, Wu CH, Chiu TY, Hu WY, Chen CY. Symptom patterns of advanced cancer patients in a palliative care unit. *Palliat Med*. 2006 Sep;20(6):617-22.
3. Solano JP, Gomes B, Higginson IJ. A comparison of symptom prevalence in far advanced cancer, AIDS, heart disease, chronic obstructive pulmonary disease and renal disease. *J Pain Symptom Manage*. 2006;31(1):58-69.
4. Feyer P, Kleeberg UR, Steingraber M, Gunther W, Behrens M. Frequency of side effects in outpatient cancer care and their influence on patient satisfaction-a prospective survey using the PASQOC(R) questionnaire. *Support Care Cancer*. 2008 Mar 6.
5. The Swedish National Board of Health and Welfare. *Cancer Incidence in Sweden 2006*. Stockholm; 2007.
6. The Swedish National Board of Health and Welfare. *Dödsorsaker 2004; 2007*
7. National Cancer Institute, Dictionary of Cancer Terms. [cited 2008 31-3]; Available from:http://www.cancer.gov/Templates/db_alpha.aspx?CdrID=478743.
8. National Comprehensive Cancer Network. *Advanced Cancer and Palliative Care Treatment Guidelines – Version I*. 2003 [cited 2008-3- 31]; Available from: http://www.nccn.org/patients/patient_gls/english/palliative/1_introduction.asp.
9. Clark D. From margins to centre: a review of the history of palliative care in cancer. *Lancet Oncol*. 2007 May;8(5):430-8.
10. Copp G. A review of current theories of death and dying. *J Adv Nurs*. 1998 Aug;28(2):382-90.
11. Lughton J, Kindlen M, eds. *Palliative Care. The Nursing Role*. Edinburgh: Churchill Livingstone; 1999.
12. Stratford M. Palliative nursing. In: Monroe B, Oliviere D, eds. *Patient participation in palliative care A voice for the voiceless*. Oxford: Oxford university Press; 2003. p. 135-50.
13. Sepulveda C, Marlin A, Yoshida T, Ullrich A. Palliative Care: the World Health Organization's global perspective. *J Pain Symptom Manage*. 2002 Aug;24(2):91-6.
14. Ahmedzai SH, Costa A, Blengini C, Bosch A, Sanz-Ortiz J, Ventafridda V, et al. A new international framework for palliative care. *Eur J Cancer*. 2004;40(15):2192-200.
15. Randall F, Downie RS. *The Philosophy of Palliative Care. Critique and Reconstruction*. Oxford: Oxford University Press; 2006.
16. Tishelman C. Advances in contemporary palliative and supportive care. *Contemp Nurse*. 2007 Dec;27(1):3-6.
17. Blackford J. Back to our roots: Palliative care in the clinical setting. *Contemp Nurse*. 2007 Dec;27(2):7-9.
18. European Association for Palliative Care. Definition of palliative care [cited 2008 4-3]; Available from: <http://www.eapcnet.org/about/definition.html>.
19. The Swedish National Board of Health and Welfare. *Vård i livets slutskede. Socialstyrelsens bedömning av utvecklingen i landsting och kommuner*; 2006.
20. The Swedish National Board of Health and Welfare. *Döden angår oss alla; Värdig vård vid livets slut*. Stockholm; 2001. Report No: 2001:6
21. Bowling A. Current state of the art in quality of life measurement. In: Carr AJ, Higginson IJ, Robinson PG, eds. *Quality of Life*. London: BMJ Books; 2003.
22. Kaasa S, Loge JH. Quality of life in palliative medicine-principles and practice. In: Doyle D, Hanks G, Cherny N, Calman K, eds. *Oxford Textbook of Palliative Medicine*. Oxford: Oxford university press; 2004. p. 196-210.
23. Jocham HR, Dassen T, Widdershoven G, Halfens R. Quality of life in palliative care cancer patients: a literature review. *J Clin Nurs*. 2006 Sep;15(9):1188-95.
24. World Health Organization Quality of Life Group Working Group. Programme on mental health; WHQOL Measuring Quality of life. 1997 [updated 1997; cited 2008-3-30]; Available from: http://www.who.int/mental_health/media/68.pdf.
25. Calman KC. Quality of life in cancer patients-an hypothesis. *J Med Ethics*. 1984

- Sep;10(3):124-7.
26. World Health Organization, Chatterji S, Ustün BL, Sadana R, Salomon JA, Mathers CD, et al. The conceptual basis for measuring and reporting on health. The World Health Organisation; 2002 [updated 2002; cited 2008-3-30]; Available from: <http://www.who.int/healthinfo/paper45.pdf>.
 27. Fayers P, Machin D. *Quality of Life: Assessment, Analysis and Interpretation*. Chichester: John Wiley & Sons Ltd; 2001.
 28. Walsh D, Rybicki L, Nelson KA, Donnelly S. Symptoms and prognosis in advanced cancer. *Support Care Cancer*. 2002;10(5):385-8.
 29. Miaskowski C, Cooper BA, Paul SM, Dodd M, Lee K, Aouizerat BE, et al. Subgroups of patients with cancer with different symptom experiences and quality-of-life outcomes: a cluster analysis. *Oncol Nurs Forum* 2006;33(5):E79-89.
 30. Arnes J, Krishnasamy M, Higginson I. *Fatigue in cancer*. New York: Oxford University Press Inc.; 2004.
 31. Tishelman C, Taube A, Sachs L. Self-reported symptom distress in cancer patients: reflections of disease, illness or sickness? *Soc Sci Med*. 1991;33(11):1229-40.
 32. Dodd M, Janson S, Facione N, Faucett J, Froelicher ES, Humphreys J, et al. Advancing the science of symptom management. *J Adv Nurs*. 2001;33(5):668-76.
 33. Barsevick AM, Whitmer K, Nail LM, Beck SL, Dudley WN. Symptom cluster research: conceptual, design, measurement, and analysis issues. *J Pain Symptom Manage*. 2006;31(1):85-95.
 34. Lenz ER, Pugh LC, Milligan RA, Gift A, Suppe F. The middle-range theory of unpleasant symptoms: an update. *Adv Nurs Science*. 1997;19(3):14-27.
 35. Finlayson TL, Moyer CA, Sonnad SS. Assessing symptoms, disease severity, and quality of life in the clinical context: a theoretical framework. *American J Managed Care*. 2004;10(5):336-44.
 36. Dalal S, Del Fabbro E, Bruera E. Symptom control in palliative care-Part I: oncology as a paradigmatic example. *J Palliat Med*. 2006;9(2):391-408.
 37. Armstrong TS. Symptoms experience: a concept analysis. *Oncol Nurs Forum*. 2003;30(4):601-6.
 38. Hoekstra J, Vernooij-Dassen MJ, de Vos R, Bindels PJ. The added value of assessing the 'most troublesome' symptom among patients with cancer in the palliative phase. *Patient Educ Couns*. 2007 Feb;65(2):223-9.
 39. David A, Pelosi A, McDonald E, Stephens D, Ledger D, Rathbone R, et al. Tired, weak, or in need of rest: fatigue among general practice attenders. *BMJ*. 1990;301(6762):1199-202.
 40. Magnusson K. Definition, diagnostic criteria and algorithms of patients evaluation. In: Marty M, Pecorelli, S, eds. *Fatigue and Cancer Scientific updates*, 5: Elsevier; 2001.
 41. Prue G, Rankin J, Allen J, Gracey J, Cramp F. Cancer-related fatigue: A critical appraisal. *Eur J Cancer*. 2006 May;42(7):846-63.
 42. Aistars J. Fatigue in the cancer patient: a conceptual approach to a clinical problem. *Oncol Nurs Forum*. 1987;14(6):25-30.
 43. Piper BF, Lindsey AM, Dodd MJ. Fatigue mechanisms in cancer patients: developing nursing theory. *Oncol Nurs Forum*. 1987;14(6):17-23.
 44. Ream E, Richardson A. Fatigue: a concept analysis. *Int J Nurs Stud*. 1996;33(5):519-29.
 45. Mock V, Abernethy A, Atkinson A, Barsevick A, Berger AM, Cella D, et al. *NCCN Clinical Practice Guidelines in Oncology TM Cancer-Related fatigue*. 2007 [cited 2008-3-31]; Available from: http://www.nccn.org/professionals/physician_gls/PDF/fatigue.pdf
 46. Breukink SO, Strijbos JH, Koorn M, Koeter GH, Breslin EH, van der Schans CP. Relationship between subjective fatigue and physiological variables in patients with chronic obstructive pulmonary disease. *Resp Med*. 1998;92 (4): 676-82.
 47. Rupp I, Boshuizen HC, Jacobi CE, Dinant HJ, van den Bos GA. Impact of fatigue on health-related quality of life in rheumatoid arthritis. *Arthritis Rheum*. 2004 Aug 15;51(4):578-85.

48. Theander K, Unosson M. Fatigue in patients with chronic obstructive pulmonary disease. *J Adv Nurs*. 2004;45(2):172-7.
49. Forlenza MJ, Hall P, Lichtenstein P, Evengard B, Sullivan PF. Epidemiology of cancer-related fatigue in the Swedish twin registry. *Cancer*. 2005;104(9):2022-31.
50. LeGrand SB. Cancer fatigue-more data, less information? *Curr Oncol Rep*. 2002 Jul;4(4):275-9.
51. Visovsky C, Schneider SM. Cancer-related fatigue. *Online J Issues Nursing*. 2003;8(3):8.
52. Sood A, Moynihan TJ. Cancer-related fatigue: an update. *Curr Oncol Reports*. 2005;7(4):277-82.
53. Barsevick AM, Whitmer K, Walker L. In their own words: using the common sense model to analyze patient descriptions of cancer-related fatigue. *Oncol NursForum*. 2001;28(9):1363-9.
54. Ahlberg K, Ekman T, Gaston-Johansson F, Mock V. Assessment and management of cancer-related fatigue in adults. *Lancet*. 2003;362(9384):640-50.
55. Lawrence DP, Kupelnick B, Miller K, Devine D, Lau J. Evidence report on the occurrence, assessment, and treatment of fatigue in cancer patients. *J National Cancer Inst Monogr*. 2004(32):40-50.
56. Del Fabbro E, Dalal S, Bruera E. Symptom control in palliative care -Part II: cachexia/anorexia and fatigue. *J Palliat Med*. 2006;9(2):409-21.
57. Barnes EA, Bruera E. Fatigue in patients with advanced cancer: a review. *Internat J Gynecol Cancer*. 2002;12(5):424-8.
58. Miaskowski CA, Portenoy RK. Assessment and management of cancer-related fatigue. In: Berger AM, Portenoy R K, & Weissman DE, eds. *Principles & Practice of Palliative Care & Supportive Oncology*. second ed. Philadelphia: Lippincott Williams & Wilkins; 2002.
59. Gutstein HB. The biologic basis of fatigue. *Cancer*. 2001 Sep 15;92(6 Suppl):1678-83.
60. Olson K. A new way of thinking about fatigue: a reconceptualization. *Oncol Nurs Forum*. 2007 Jan;34(1):93-9.
61. Olson K, Turner AR, Courneya KS, Field C, Man G, Cree M, et al. Possible links between behavioral and physiological indices of tiredness, fatigue, and exhaustion in advanced cancer. *Support Care Cancer*. 2008 Mar;16(3):241-9.
62. Ryan JL, Carroll JK, Ryan EP, Mustian KM, Fiscella K, Morrow GR. Mechanisms of cancer-related fatigue. *Oncologist*. 2007;12 Suppl 1:22-34.
63. Yennurajalingam S, Bruera E. Palliative management of fatigue at the close of life: "it feels like my body is just worn out". *JAMA*. 2007;297(3):295-304.
64. Visser MR, van Lanschot JJ, van der Velden J, Kloek JJ, Gouma DJ, Sprangers MA. Quality of life in newly diagnosed cancer patients waiting for surgery is seriously impaired. *J Surg Oncol*. 2006;93(7):571-7.
65. Jonsson A, Aus G, Bertero C. Men's perception of fatigue when newly diagnosed with localized prostate cancer. *Scand J Urolog Nephrolog*. 2007;41(1):20-5.
66. Haylock PJ, Hart LK. Fatigue in patients receiving localized radiation. *Cancer Nurs*. 1979;2(6):461-7.
67. Smets EMA. *Fatigue in cancer patients undergoing radiotherapy*. Amsterdam: University of Amsterdam; 1997.
68. Smets EM, Visser MR, Garssen B, Frijda NH, Oosterveld P, de Haes JC. Understanding the level of fatigue in cancer patients undergoing radiotherapy. *J Psychosom Res*. 1998;45(3):277-93.
69. Furst CJ, Ahsberg E. Dimensions of fatigue during radiotherapy. An application of the Multidimensional Fatigue Inventory. *Support Care Cancer*. 2001 Jul;9(5): 355-60.
70. Pickett M, Mock V, Ropka ME, Cameron L, Coleman M, Podewils L. Adherence to moderate-intensity exercise during breast cancer therapy. *Cancer Practice*. 2002;10(6):284-92.
71. Bennett B, Goldstein D, Lloyd A, Davenport T, Hickie I. Fatigue and psychological distress--exploring the relationship in women treated for breast cancer. *Eur J Cancer*. 2004;40(11):1689-95.

72. Can G, Durna Z, Aydinler A. Assessment of fatigue in and care needs of Turkish women with breast cancer. *Cancer Nursing*. 2004 Mar-Apr;27(2):153-61.
73. Hartvig P, Aulin, J., Hugerth, M., Wallenberg, S & Wagenius, G. Fatigue in cancer patients treated with cytotoxic drugs. *J Oncol Pharm Practice*. 2006;12(3):155-64.
74. Servaes P, van der Werf S, Prins J, Verhagen S, Bleijenberg G. Fatigue in disease-free cancer patients compared with fatigue in patients with chronic fatigue syndrome. *Support Care Cancer*. 2001;9(1):11-7.
75. Hjermstad MJ, Fossa SD, Oldervoll L, Holte H, Jacobsen AB, Loge JH. Fatigue in long-term Hodgkin's Disease survivors: a follow-up study. *J Clin Oncol*. 2005; 23(27):6587-95.
76. Hjermstad MJ, Oldervoll L, Fossa SD, Holte H, Jacobsen AB, Loge JH. Quality of life in long-term Hodgkin's disease survivors with chronic fatigue. *Eur J Cancer*. 2006;42(3):327-33.
77. Stone P, Hardy J, Broadley K, Tookman AJ, Kurowska A, A'Hern R. Fatigue in advanced cancer: a prospective controlled cross-sectional study. *Br J Cancer*. 1999 Mar;79(9-10):1479-86.
78. Jordhoy MS, Fayers P, Loge JH, Saltnes T, Ahlner-Elmqvist M, Kaasa S. Quality of life in advanced cancer patients: the impact of sociodemographic and medical characteristics. *Br J Cancer*. 2001 Nov 16;85(10):1478-85.
79. Peters L, Sellick K. Quality of life of cancer patients receiving inpatient and home-based palliative care. *J Adv Nurs*. 2006 Mar;53(5):524-33.
80. Stasi R, Abriani L, Beccaglia P, Terzoli E, Amadori S. Cancer-related fatigue: evolving concepts in evaluation and treatment. *Cancer*. 2003 Nov 1;98(9):1786-801.
81. Piper B, Lindsay A, Dodd M, Ferketich S, Paul S, Weller S. The development of an instrument to measure the subjective dimension of fatigue. In: Funk S, Tornquist E, Campagne M, Archer Gopp L, Wiese R, eds. *Key aspects of comfort*. New York: Springer Publishing Company; 1989. p. 199-209.
82. Smets E, Garsen B, Schuster-Uitterhoeve A, de Haes J. Fatigue in cancer patients. *Br J Cancer*. 1993;68:220-4.
83. Curt GA, Breitbart W, Cella D, Groopman JE, Horning SJ, Itri LM, et al. Impact of cancer-related fatigue on the lives of patients: new findings from the Fatigue Coalition. *Oncologist*. 2000;5(5):353-60.
84. Östlund U, Wennman-Larsen A, Gustavsson P, Wengström Y. What symptom and functional dimensions can be predictors for global ratings of overall quality of life in lung cancer patients. *Support Care Cancer*. 2007;15(10):1199-205.
85. Teunissen SC, de Haes HC, Voest EE, de Graeff A. Does age matter in palliative care? *Crit Rev Oncol Hematol*. 2006 Nov;60(2):152-8.
86. Hussain A, Stewart K, Arseneault R, Moineddin R, Cellarius V, Lawrence Librach S, Dudgeon D. Women Experience Higher Levels of Fatigue Than Men at the End of Life: A Longitudinal Home Palliative Care Study. *J Pain Symptom Manage*. 2007;33(4):389-97.
87. Lindqvist O, Widmark A, Rasmussen BH. Meanings of the phenomenon of fatigue as narrated by 4 patients with cancer in palliative care. *Cancer Nurs*. 2004 May-Jun;27(3):237-43.
88. Dean GA, P. Fatigue. In: Ferrell B, Coyle, N, eds. *Textbook of Palliative Nursing*. New York: Oxford University Press, INC; 2001.
89. Mock V. Fatigue management: evidence and guidelines for practice. *Cancer*. 2001;92(6 Suppl):1699-707.
90. Lundström S. *Corticosteroids in advanced cancer: epidemiology, symptom relief and patients experiences [Thesis for doctoral degree]*. Stockholm: Karolinska Institutet; 2007.
91. Ream E. Fatigue in patients receiving palliative care. *Nurs Stand*. 2007 Mar 21-27;21(28):49-58.
92. Oldervoll LM, Loge JH, Paltiel H, Asp MB, Vidvei U, Hjermstad MJ, et al. Are palliative cancer patients willing and able to participate in a physical exercise program? *Palliat Support Care*. 2005 Dec;3(4):281-7.
93. Ferrell B, Coyle, N, eds. *Textbook of Palliative Nursing*. New York: Oxford University Press, Inc; 2001.

94. Muir CJ, McDonagh, A., Gooding, N. Assessment issues. Multidimensional patient assessment. In: Berger AM, Portenoy RK, Weissman DE, eds. *Principles & Practice of Palliative Care & Supportive Oncology*. Second ed. Philadelphia: Lippincott Williams & Wilkins; 2002.
95. Ferris FD, Balfour HM, Bowen K, Farley J, Hardwick M, Lamontagne C, et al. A model to guide patient and family care: based on nationally accepted principles and norms of practice. *J Pain Symptom Manage*. 2002; 24 (2):106-23.
96. Stromgren AS, Groenvold M, Sorensen A, Andersen L. Symptom recognition in advanced cancer. A comparison of nursing records against patient self-rating. *Acta Anaesth Scand*. 2001b;45(9):1080-5.
97. Haworth SK, Dluhy NM. Holistic symptom management: modelling the interaction phase. *J Adv Nurs*. 2001 Oct;36(2):302-10.
98. Polit DF, Beck CT. *Nursing Research In Principles and methods*. seventh ed. Philadelphia: Lippincott, Williams & Wilkins; 2004.
99. de Haes H, Teunissen S. Communication in palliative care: a review of recent literature. *Curr Opin Oncol*. 2005 Jul;17(4):345-50.
100. Magnusson K, Karlsson E, Palmblad C, Leitner C, Paulson A. Swedish nurses' estimation of fatigue as a symptom in cancer patients-report of a questionnaire. *Eur J Cancer Care (Engl)*. 1997 Sep;6(3):186-91.
101. Knowles G, Borthwick D, McNamara S, Miller M, Leggot L. Survey of nurses' assessment of cancer-related fatigue. *Eur J Cancer Care*. 2000;9(2):105-13.
102. Hammick M, Stone P, Cancer Fatigue Forum; Cancer fatigue and its impact on patients: knowledge within the cancer care team. *J of Interprofessional Care*. 2003;17(2):183-92.
103. Miller MK, N. Nurses' knowledge and attitudes towards cancer-related fatigue. *Eur J Oncol Nurs*. 2001;5(4):208-17.
104. Polit DF, Beck CT. *Assessing Data Quality*. In *Nursing Research Principles and Methods*. seventh ed. Philadelphia: Lippincott Williams and Wilkins; 2004. p.758.
105. Stone P, Richards M, Hardy J. Fatigue in patients with cancer. *Eur J Cancer*. 1998 Oct;34(11):1670-6.
106. Bottomley A. Assessment of Fatigue in Cancer Patients. In: *Fatigue and Cancer*. Amsterdam: Elsevier Science B.V; 2001. p. 218.
107. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *J Clin Epidemiol*. 1993;46(12):1417-32.
108. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The EORTC QLQ-C30: a quality of life instrument for use in international clinical trials in oncology. *J of National Cancer Institute*.1993; 85 (5): 365-76.
109. Bergman B, Sullivan M, Sorenson S. Quality of life during chemotherapy for small cell lung cancer. II. A longitudinal study of the EORTC Core Quality of Life Questionnaire and comparison with the Sickness Impact Profile. *Acta Oncologica*. 1992;31(1):19-28.
110. Sigurdardottir V, Bolund C, Brandberg Y, Sullivan M. The impact of generalized malignant melanoma on quality of life evaluated by the EORTC questionnaire technique. *Qual Life Res*. 1993 Jun;2(3):193-203.
111. Kaasa S, Bjordal K, Aaronson N, Moum T, Wist E, Hagen S, et al. The EORTC core quality of life questionnaire (QLQ-C30): validity and reliability when analysed with patients treated with palliative radiotherapy. *Eur J of Cancer*.1995 Dec;31A(13-14):2260-3.
112. Osoba D, Aaronson N, Zee B, Sprangers M, te Velde A. Modification of the EORTC QLQ-C30 (version 2.0) based on content validity and reliability testing in large samples of patients with cancer. The Study Group on Quality of Life of the EORTC and the Symptom Control and Quality of Life Committees of the NCI of Canada Clinical Trials Group. *Quality of Life Research*. 1997;6(2):103-8.
113. Spector. *Summated rating scale construction - An introduction*. Newsbury Park, California: Sage Publications,INC; 1992.
114. Cronbach L, J. Coefficient alpha and the internal structure of tests.

- Psychometrika. 1951(16):297-334.
115. Borg G. A category scale with ratio properties for intermodal and interindividual comparisons. In: Geissler H-G, Petzold P, eds. Psychophysical judgment and the process of perception. Berlin: VEB Deutscher Verlag der Wissenschaften; 1982.
 116. Grant S, Aitchison T, Henderson E, Christie J, Zare S, McMurray J, et al. A comparison of the reproducibility and the sensitivity to change of visual analogue scales, Borg scales, and Likert scales in normal subjects during submaximal exercise. *Chest*. 1999;116(5):1208-17.
 117. Åhsberg E, Furst CJ. Dimensions of fatigue during radiotherapy--an application of the Swedish Occupational Fatigue Inventory (SOFI) on cancer patients. *Acta Oncologica*. 2001;40(1):37-43.
 118. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res*. 1995;39(3):315-25.
 119. Smets EM, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer*. 1996;73(2):241-5.
 120. Ahlberg K. Cancer-related Fatigue - Experience and Outcomes. Göteborg: The Sahlgrenska Academy at Göteborg University; 2004.
 121. Munch TN, Stromgren AS, Pedersen L, Petersen MA, Hoermann L, Groenvold M. Multidimensional measurement of fatigue in advanced cancer patients in palliative care: an application of the multidimensional fatigue inventory. *J Pain Symptom Manage*. 2006 Jun;31(6):533-41.
 122. Falk K, Swedberg K, Gaston-Johansson F, Ekman I. Fatigue and anaemia in patients with chronic heart failure. *Eur J Heart Fail*. 2006 May 9.
 123. Da Costa D, Dritsa M, Bernatsky S, Pineau C, Menard HA, Dasgupta K, et al. Dimensions of fatigue in systemic lupus erythematosus: relationship to disease status and behavioural and psychosocial factors. *J Rheumatol*. 2006 Jul;33(7):1282-8.
 124. Schwarz R, Krauss O, Hinz A. Fatigue in the general population. *Onkologie*. 2003 Apr;26(2):140-4.
 125. Zigmond A, Snaith R. The Hospital Anxiety and Depression Scale. *Acta psychiatr scand*. 1983;67:361-70.
 126. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale. An updated literature review. *J Psychosom Res*. 2002 Feb;52(2):69-77.
 127. Åhsberg E, Gamberale F, Kjellberg A. Perceived quality of fatigue during different occupational tasks. Development of a questionnaire. *Int J Ind Ergon*. 1997;20:121-35.
 128. Åhsberg E, Gamberale F. Perceived fatigue during physical work: An experimental evaluation of a fatigue inventory. *Int J Ind Ergon*. 1998;21:117 - 31.
 129. Åhsberg E, Gamberale F, Gustafsson K. Perceived fatigue after mental work: an experimental evaluation of a fatigue inventory. *Ergonomics*. 2000 Feb;43(2):252-68.
 130. Fayers P, Aaronson N, Bjordal K, Curran D, Groenvold M. EORTC QLQ-C30, Scoring Manual. Brussels; 1999.
 131. Thorn S, Reimer Kirkland S, O'Flynn-Magee K. The analytic challenge in interpretive description. *Int J of Qualit Methods*. 2004;3(1):1-21.
 132. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Edu Today*. 2004 Feb;24(2):105-12.
 133. Fayers P, Aaronson N, Bjordal K, Sullivan M. EORTC QLQ-C30, Scoring Manual. Brussels: Quality of Life Unit, EORTC Data Center, EORTC Quality of Life Study Group; 1995.
 134. Wagner LI, Cella D. Fatigue and cancer: causes, prevalence and treatment approaches. *Br J Cancer*. 2004 Aug 31;91(5):822-8.
 135. Hann DM, Garovoy N, Finkelstein B, Jacobsen PB, Azzarello LM, Fields KK. Fatigue and quality of life in breast cancer patients undergoing autologous stem cell transplantation: a longitudinal comparative study. *J Pain Symptom Manage*.

- 1999;17(5):311-9.
136. Irvine D, Vincent L, Graydon JE, Bubela N, Thompson L. The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with the fatigue experienced by healthy individuals. *Cancer Nurs*. 1994;17(5):367-78.
 137. Echteld MA, Passchier J, Teunissen S, Claessen S, de Wit R, van der Rijt CC. Multidimensional fatigue and its correlates in hospitalised advanced cancer patients. *Eur J Cancer*. 2007 Apr;43(6):1030-6.
 138. Ahlner-Elmqvist M, Jordhoy MS, Bjordal K, Jannert M, Kaasa S. Characteristics and Quality of Life of Patients Who Choose Home Care at the End of Life. *J Pain Symptom Manage*. 2008 Apr 7.
 139. de Jong N, Candel MJ, Schouten HC, Abu-Saad HH, Courtens AM. Course of mental fatigue and motivation in breast cancer patients receiving adjuvant chemotherapy. *Ann Oncol*. 2005 Mar;16(3):372-82.
 140. Miaskowski C. Gender differences in pain, fatigue, and depression in patients with cancer. *J Natl Cancer Inst Monogr*. 2004(32):139-43.
 141. de Graeff A, de Leeuw JR, Ros WJ, Hordijk GJ, Blijham GH, Winnubst JA. Sociodemographic factors and quality of life as prognostic indicators in head and neck cancer. *Eur J Cancer*. 2001 Feb;37(3):332-9.
 142. Kenefick AL. Patterns of symptom distress in older women after surgical treatment for breast cancer. *Oncol Nurs Forum*. 2006 Mar;33(2):327-35.
 143. Stromgren AS, Goldschmidt D, Groenvold M, Petersen MA, Jensen PT, Pedersen L, et al. Self-assessment in cancer patients referred to palliative care: a study of feasibility and symptom epidemiology. *Cancer*. 2002 Jan 15;94(2):512-20.
 144. Ahlberg K, Ekman T, Gaston-Johansson F. Fatigue, psychological distress, coping resources, and functional status during radiotherapy for uterine cancer. *Oncol Nurs Forum*. 2005;32(3):633-40.
 145. Valentine AD, Meyers CA. Cognitive and mood disturbance as causes and symptoms of fatigue in cancer patients. *Cancer*. 2001;92(6 Suppl):1694-8.
 146. Stone PC, Minton O. Cancer-related fatigue. *Eur J Cancer*. 2008 Mar 30.
 147. Radbruch L, Strasser F, Elsner F, Goncalves JF, Loge J, Kaasa S, et al. Fatigue in palliative care patients - an EAPC approach. *Palliat Med*. 2008 Jan;22(1):13-32.
 148. Wu HS, McSweeney M. Cancer-related fatigue: "It's so much more than just being tired". *Eur J Oncol Nurs*. 2007 Apr;11(2):117-25.
 149. Ohlen J, Elofsson LC, Hyden LC, Friberg F. Exploration of communicative patterns of consultations in palliative cancer care. *Eur J Oncol Nurs*. 2008 Feb;12(1):44-52.
 150. Groenvold M, Petersen MA, Aaronson NK, Arraras JI, Blazeby JM, Bottomley A, et al. The development of the EORTC QLQ-C15-PAL: a shortened questionnaire for cancer patients in palliative care. *European Journal of Cancer*. 2006;42(1):55-64.
 151. Petersen MA, Groenvold M, Aaronson N, Blazeby J, Brandberg Y, de Graeff A, et al. Item response theory was used to shorten EORTC QLQ-C30 scales for use in palliative care. *Journal of Clinical Epidemiology*. 2006;59(1):36-44.
 152. Nicklasson M, Bergman B. Validity, reliability and clinical relevance of EORTC QLQ-C30 and LC13 in patients with chest malignancies in a palliative setting. *Qual Life Res*. 2007 May 4.
 153. Tishelman C, Degner LF, Mueller B. Measuring symptom distress in patients with lung cancer. A pilot study of experienced intensity and importance of symptoms. *Cancer Nurs*. 2000;23(2):82-90.
 154. Goodell TT, Nail LM. Operationalizing symptom distress in adults with cancer: a literature synthesis. *Oncol Nurs Forum Online*. 2005;32(2):E42-7.
 155. la Cour K, Josephsson S, Tishelman C, Nygard L. Experiences of engagement in creative activity at a palliative care facility. *Palliat Support Care*. 2007 Sep;5(3):241-50.
 156. Graham F, Clark D. The changing model of palliative care. *Medicine* 2007;36(2):64-6.
 157. Kazdin AE. *Research design in Clinical Psychology*. Third ed. Allyn and Bacon; 1998.

158. Jordhoy MS, Kaasa S, Fayers P, Ovreness T, Underland G, Ahlner-Elmqvist M. Challenges in palliative care research; recruitment, attrition and compliance: experience from a randomized controlled trial. *Palliat Med.* 1999;13(4):299-310.
159. Borg GA. Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise.* 1982;14(5):377-81.
160. Glass G, Hopkins K. *Statistical Methods.* In *Education and Psychology.* third ed. Allyn and Bacon; 1996.

APPENDIX

CR10

Hur trött har Du känt Dig under de senaste dagarna?

Börja med att titta på orden, ringa sedan in den siffra som bäst motsvarar hur trött Du känt Dig. Maximalt, där det är en punkt i stället för en siffra, innebär att Du varit tröttare än Du någonsin tidigare varit.

0	Ingen alls	
0,5	Extremt svag	(Knappt kännbar)
1	Mycket svag	
2	Svag	(Lätt)
3	Måttlig	
4		
5	Stark	(kraftigt)
6		
7	Mycket stark	
8		
9		
10	Extremt stark	
•	”Maximal”	

Items and subscales in the Multidimensional Fatigue Inventory (MFI-20)

MFI dimension	Item no.	Item list
General Fatigue	1	I feel fit
	5	I feel tired
	12	I am rested
	16	I tire easily
Physical Fatigue	2	Physically I feel only able to do a little
	8	Physically I can take on a lot
	14	Physically I feel I am in a bad condition
	20	Physically I feel I am in an excellent condition
Mental Fatigue	7	When I am doing something, I can keep my thoughts on it
	11	I can concentrate well
	13	It takes a lot of effort to concentrate on things
	19	My thoughts easily wander
Reduced Activity	3	I feel very active
	6	I think I do a lot in a day
	10	I think I do very little in a day

Items and subscales in the Swedish Occupational Fatigue inventory (SOFI)

SOFI dimension	Item no.	Item list
Lack of energy	3	Worn out
	8	Spent
	15	Drained
	17	Overworked
Physical exertion	1	Palpitations
	7	Sweaty
	13	Out of breath
	19	Breathing heavily
Physical discomfort	4	Tense muscles
	6	Numbness
	11	Stiff joints
	18	Aching
Lack of motivation	2	Lack of concern
	10	Passive
	12	Indifferent
	20	Uninterested
Sleepiness	5	Falling asleep
	9	Drowsy
	14	Yawning
	16	Sleepy