

**Stress, Social Support, General Self-efficacy and  
Health Related Quality of Life in Patients with  
Neuroendocrine Tumors**

A cross-sectional and pilot study

*Trude Haugland*

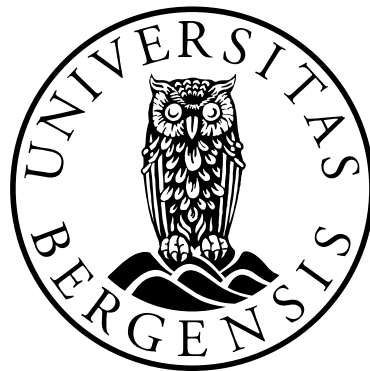
Dissertation for the degree philosophiae doctor (PhD)  
at the University of Bergen, Norway

2013



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## **Acknowledgements**

The present work has been carried out at the National Competence Center for Neuroendocrine Tumor and the Medical Department of Oslo University Hospital HF, Rikshospitalet, and was financed by the National Competence Center for Neuroendocrine Tumor. Thank you to the Norwegian Association for Patients with Neuroendocrine Tumor, the Norway America Association and The Norwegian Association of Nurses, who have provided grants for the project.

I would like to express my deepest gratitude to those who have supported me through this work. Primarily, I am grateful to all the patients who willingly took part in the study and taught me a lot about living with a serious disease. In addition, I want to thank the nursing staff for their assistance and for sharing their broad knowledge about patients with neuroendocrine tumor. A special thank you goes to Kari Lise Hansen, Vera Dahle, Elisabeth Mortensen, Yvonne Hareid, Bente Paulsen and, and Marie Paulsen who willingly guided the patients through the intervention in this study. Furthermore, I wish to acknowledge the effort those who initiated this study; the head nurse of the gastroenterological part of the Medical department at Rikshospitalet, Kjerstin Mordal, the former head nurse of Medical Department at Rikshospitalet Ellen Beccer Brandvold and the former Head of Medical Department at Rikshospitalet, Jappe Blomhoff. Also thank you to Espen Thiis Evensen for sharing your knowledge of NET with me and for keeping me ongoing with your warm humor and, to Kristian Holm for your helpfulness during the data-collection period. I am grateful to my fellow researcher Deidi Bergestuen for the partnership and for sharing her experiences during our little pep talks.

Throughout the study, I collaborated with all the regional centers for neuroendocrine tumors. I would like to extend a special thank you to August Bakke, Helge Aarstad, John Florholmen, Jon Arne Søreide. Also thank you to Torill Ensrud at the Rehabilitation Center at Mesnalia. Visiting University of California San Francisco (UCSF) as a scholar was a part of my PhD study. I want to thank my mentor Sally Rankin for her helpfulness and supervision during my stay. Thanks also to my office mate Teri Lindgren for willingly sharing her research knowledge. I deeply thank my research fellow Holly DeVon for the wonderful and valuable support, thoughtful critique you have given me and for editing my manuscripts. Throughout my dissertation, I have been a part of a research and support group at the University of Bergen. I am grateful for the continual support from all my fellow doctoral students.



I would like to express my gratitude to the supportive members of the EANS group. A particular thank you to Lisbeth Gravdal Kvarme for always being humoristic and supportive. I appreciate being a part of the University of Oslo, Institute of Nursing Science and Health research, and I am very thankful to Nina Vøllestad and Marit Kirkevold and, all the ASVfaculties and students for being a supporting team to me.

I would like to express my deepest gratitude to my supervisors who supported me throughout this work. I appreciate tremendously the bright knowledge, the thorough support, encouragement and help from Astrid Klopstad Wahl. The broad wisdom she has shared and her never-ending enthusiasm has motivated me to complete this work. Gerd Karin Natvig provided valuable support throughout the planning of the study. Also thank you to Marijke Veenstra, for sharing her statistical knowledge and her endless patience with me. Furthermore, thank you Morten Vatn for sharing your research experience and bright knowledge of NET with me.

Many thanks to the most important elements of my life; my friends and family. Marit Dahl Mikkelsen, thank you for always believing in me. In addition, many thanks to my female marathon-group for taking me out running every week.

I owe a debt of gratitude to my mother who has always believed in me and, to my late mother-in-law who put me up during the doctoral program in Bergen. Special thanks to Lars and my daughter Linn who are a highly beloved source of joy and encouragement, and to my lovely grandchild Ada, who makes me experience the feeling of real happiness of life.

Finally, many, many thanks to my beloved husband Thor-Atle who is always there for me. Your love, encouragement, and endless patience have helped me to make this work possible. I love you.

## **Abstract**

**Background:** Neuroendocrine tumor (NET) is a chronic irreversible disease after metastases occur which has to be managed rather than cured. Getting an irreversible, slow growing cancer disease may be perceived as a health threat and cause stress. A balance between evaluation of individual disability and need for palliative treatment with the risk of adverse reactions may be a challenge in managing the disease. Interventions enabling patients to cope with stress and improve health related quality of life (HRQoL) may be a complementary treatment option. Personal resources such as social support and general self-efficacy have demonstrated to be associated with better HRQoL. An intervention based on the principles of self-efficacy to cope with stress and improve health outcomes in patients with NET is necessary and timely. However, the literature is sparse on issues of stress, general self-efficacy, social support and HRQoL in patients with NET.

**Aim:** The objective of this thesis aims to 1) expand knowledge of HRQoL in patients with NET; 2) evaluate the association between stress, general self-efficacy, social support and HRQoL and 3) evaluate the importance of a patient education intervention based on the principles of self-efficacy.

**Methods:** A cross sectional descriptive, survey design and an explorative, longitudinal design of three points in time were used. Recruitment of two different samples was collected in order to perform the studies. In June 2007, data were collected at all NET centers nationwide for the cross sectional study and 196 patients returned the questionnaires. From September 2005 to December 2007, 37 patients from three of five NET centers completed the intervention data were collected for the exploratory, study. The questionnaires covered socio-demographic and self-reported HRQoL (SF-36), stress (Impact of Event Scale), social support (Interpersonal Social Evaluation List) and general self-efficacy (General Self-efficacy).

**Results:** Chi-square statistics and Analysis of variance demonstrated that lower age, part-time or full-time employment, higher education and higher income levels were associated better HRQoL. Bonferroni correction was used to adjust the level of significance. T-tests demonstrated that patients with NET had poorer HRQoL than the

general Norwegian population on all subscales of the SF-36 except for bodily pain. The largest difference demonstrated by effect sizes was general health, role limitations physical and vitality (Paper I). Multiple linear regressions demonstrated that having symptoms and co-morbid conditions predicted poorer HRQoL. In addition, higher stress was significantly associated with poorer mental and physical HRQoL and higher levels of social support and general self-efficacy were significantly associated with better mental HRQoL. Furthermore, higher levels of general self-efficacy were significantly associated with better physical HRQoL. Finally, social support and general self-efficacy partly mediated the relationship between stress-and mental HRQoL (Paper II). Mixed effect models showed that stress, general self-efficacy and physical HRQoL changed significantly following a 6- month patient educational intervention. Symptoms and co-morbidity were inversely associated with physical HRQoL(Paper III).

**Conclusion:** Patients with NET demonstrated poorer HRQoL than the general Norwegian population on all subscales of SF-36, except bodily pain. Stress related negatively to poorer HRQoL and those with more social support and higher levels of general self-efficacy had better HRQoL than those with less social support and lower levels of general self-efficacy. In addition, social support and general self-efficacy had a partly mediating relationship with the stress-HRQoL association. The exploratory study demonstrated that stress was reduced and general self-efficacy and physical HRQoL were improved following the intervention. The intervention needs to be replicated in a RTC with appropriate sampling.

## **List of Original Papers**

### **Paper I**

Haugland T, Vatn MH, Veenstra M, Wahl AK, Natvig GK. Health Related Quality of Life in Patients with Neuroendocrine Tumors compared with the General Norwegian Population.

*Quality of Life Research*, 2009, 18;719-726.

### **Paper II**

Haugland T, Veenstra M, Vatn MH, Natvig GK, Wahl AK. Stress Health Related Quality of Life in Patients with Neuroendocrine. The Significance of Social Support and General Self-efficacy as Mediators? *Acta Oncologica* Submitted Dec 2012.

### **Paper III**

Haugland T, Veenstra M, Vatn MH, Wahl AK. Patient Education to Reduce Stress and Improve General Self-efficacy and Health Related Quality of Life in Patients with Neuroendocrine Tumors – a Pilot Study. *Nursing Research and Practice*, Submitted Feb 2013

## List of Abbreviations

NET	Neuroendocrine tumors
GI	Gastrointestinal
HRQoL	Health related quality of life
NE	Neuroendocrin
GEP-NETs	Gastro-entero-pancreatic neuroendocrine tumors
SI-NET	Small intestine-Neuroendocrine Tumor
CgA	Chromogranin A
PP	Pancreatic Peptide
HCG	Human chorionic gonadotrophin
ZES	Zollinger Ellison Syndrome
MEN 1	Multiple endocrine neoplasia1
Ki-67	Antigen (protein)
U-5HIAA	Urinary-5 hydroxyindoleacetic
CT	Computer tomography
MRI	Magnet Resonance Imaging
HIV	Human immunodeficiency virus
WHOQL-Bref	World Health Organization Quality of Life-Bref questionnaire
FACT-G	Functional Assessment of Cancer Therapy-General
RCT	Randomized controlled trial
T1	Test point 1
T2	Test point 2
T3	Test point 3
NOK	Norwegian kroner
IES	Impact of Event Scale
GSE	General Perceived Self-Efficacy Scale
ISEL	Interpersonal Support Evaluation List
PCS	Physical component scores
MCS	Mental component scores
ANOVA	Analysis of Variance
ES	Effect size
MH	Mental health
SF	Social functioning
DRG	Diagnosis related group
EORTC QOQ-C30	Euroepan Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cancer30

## 1. Introduction

Neuroendocrine tumors (NET) or *carcinoids* are relatively slow growing and rare types of cancer. The incidence of NET is (5.25/100 000) and the prevalence is 35/100000 [1;2]. The cause of NET is unknown. NET most commonly arise from the gastrointestinal (GI) tract and tend to metastasize [3]. However, improved treatment strategies have contributed to better symptom control and possibly prolonged survival as patients may live many years with the disease [3;4]. The therapeutic challenge requires a balance between evaluation of individual disability and need for palliative treatment with the risk of adverse reactions. Diarrhea, fatigue, pain, flushing, and dyspnea commonly put restrictions on daily life, in the form of reduced physical and social activity [5;6]. Consequently, disability may lead to reduced quality of life [7] [5;6;8-13]. Quality of life may be an important outcome when cure is not possible [14] because standard treatment may result in symptoms and adverse effects from all types of tumors. Prior research has focused on NET screening and detection practices, symptom control by medication [15-20] and survival rates [21-24].

Getting a cancer diagnosis and experiencing symptoms and adverse effects may be perceived as a health threat and cause stress. Several authors have addressed stress issues negatively associated with health related quality of life (HRQoL) in cancer populations [8-11;25]. However, there are several studies that have suggested that personal resources are positively related to on HRQoL. Studies have shown a significant positive relationship between social support and HRQoL in men treated for prostate cancer [26] patients with breast cancer [27], spouses of men with prostate cancer [28] individuals at risk of hereditary cancer [8], and patients with long term survival following cardiac transplant [29]. General self-efficacy has also been reported as a personal resources; research demonstrated that individuals at risk for hereditary cancer reporting higher levels of general self-efficacy demonstrated better mental HRQoL [8]. In addition, research has shown that social support and self-efficacy may act as a mediator in the relationship of stressful life events on HRQoL. Consequently the impact of stressful life events on HRQoL may be reduced by social support and self-efficacy [30-33].

Thus, interventions enabling patients to cope with stress and improve HRQoL might be a complimentary treatment option. Core components of such interventions could be based on the

principles of self-efficacy in order to motivate the patients to take part in their self-development, adaptation and acquisition of new skills and competences. Different types of patient education interventions (e.g knowledge, patient and family education, provision of emotional and psychosocial support, self-efficacy, coping skills, and relaxation training) have been shown to be effective in reducing stress and improve HRQoL across settings and diseases [34-37]. In particular, patient education interventions based on the principles of self-efficacy have shown to enhance self-efficacy [38-41], and reduce stress [25;40;42], therefore enhancing HRQoL [43]. Improved HRQoL may yield beneficial effects by improving coping processes [34-36;44;45]. Consequently, the belief in patients' own self-efficacy may affect their success in coping with their disease. On this basis, an intervention based on the principles of self-efficacy to improve health outcomes in patients with NET is necessary and timely.

The literature is sparse on issues of stress, self-efficacy, social support and HRQoL in patients with NET. For example, some studies have reported on reduced HRQoL [46-48], but no studies have looked into psychosocial aspects of HRQoL nor different types of psychosocial interventions in patients with NET. The goal of health care is to prevent illness or deterioration and promote health. Health promotion means actively supporting the physical, social and mental well-being of the individual [49] (p. 95-98). In order to do so, the present thesis study aims to evaluate stress, social support and general self-efficacy in association with HRQoL in patients with NET.

## **2. Aims of the thesis**

The objective of this thesis was to expand knowledge of HRQoL in patients with NET, evaluate the association between stress, general self-efficacy, social support and HRQoL, and evaluate the importance of a patient education intervention based on the principles of self-efficacy.

The main objectives of the papers comprising the thesis were to:

- Describe HRQoL in a nationwide sample of patients with NET compared with a general Norwegian population (Paper I).
- Evaluate associations between stress, general self-efficacy, social support and HRQoL (Paper II).
- Evaluate changes in stress, general self-efficacy and HRQoL among patients with NET

following a patient education intervention (Paper III).

### **3. Background; the clinical case of neuroendocrine tumors**

#### **3.1 Definition and classification, epidemiology and etiology**

Neuroendocrine (NE) cells exist in most of the solid organs of the body and develop mainly from the nervous system. The two main functions of the NE cells are synthesizing peptide hormones and amino acids, which are saved within secretion granula and directly secreted into the circulatory system (endocrine function) or to the intercellular space (paracrin function). NE secretion granula are specific to the NE cells. The physiological functions of NET are production of insulin, glucagon, somatostatin and gastrin. NE cells are represented in both the central and peripheral nervous system. First and foremost NE cells are present in the mucous membranes of the body and the skin [50]. Gastro-entero-pancreatic neuroendocrine tumors (GEP-NETs) are rare tumors of the gastrointestinal tract arising from the cells of the NE system [50]. In 1907, Oberndorfer first used the term “karzinoide”, a carcinoma-like neoplasm, to describe tumors in the intestinal tract, which appeared to have a more benign course than adenocarcinomas.

The average age at time of diagnosis is 55 years although the disease has been seen in people in their twenties [51]. The most general GI-carcinoids are gastric carcinoids, small intestinal carcinoids, appendix carcinoids, colonic and rectum carcinoids. Carcinoid tumors are characterized by the production of high amounts of hormonally active substances including serotonin, bradykinins, and tachykinins. Chromogranin A (CgA) is a secretory protein that is presented in all NE cells and is a tumor marker. In all the tumor subgroups high levels of CgA, PP and human chorionic gonadotrophin (HCG)  $\alpha$  and  $\beta$  may be found. They are responsible for the carcinoid syndrome that is manifested by flushing, diarrhea, carcinoid heart disease and, less commonly, wheezing [51].

The pathology of NET is assessed and classified by specialized histochemical methods and electronical microscopy. Most gastric endocrine tumors arise in the mucosa and hyperplasia of endocrine cells and formation of extra-epithelial clusters that produce histamine may occur. Also gastric gastrin producing tumors have been described associated with Zollinger Ellison Syndrome (ZES) or Gastrinoma Syndrome [50]. The most common tumor of the duodenum is



the gastrin producing tumor of the small intestine; argentaffin (EC-cell, serotonin producing). Glucagon-glicentin is the predominant tumor component of the large bowel and is less commonly malignant [4;50]. Carcinoid tumors are often multiple. Genetic predisposition has been demonstrated for duodenal gastrinoma in multiple endocrine neoplasia (MEN1)[1]. The World Health Organisation (WHO) defines the entire group of tumors as neuroendocrine neoplasms and divides the tumors into NET G1, NET G2 and poorly differentiated neuroendocrine carcinoma; NEC G3. The European Neuroendocrine Tumor Society has proposed a tumor – node – metastasis staging and grading system for various types of GEP-NET based on levels of Ki-67 [2]. Ki-67 is a protein associated with cellular proliferation and is a cellular marker. Levels of Ki-67 reflect the differentiation of the tumor cells. Aggressiveness is related with tumors with liver and lymph node metastases and high proliferation by Ki-67 and levels of hydroxyindoleacetic (U-5-HIAA), neuropeptide K and CgA in plasma [23;50]. In summary, NET is a rare, slow growing disease that tends to metastasize. The production of neuroendocrine tumor hormones give rise to symptoms that vary widely and surgical treatment may be the only cure if performed prior to metastases.

### 3.2 Survival and prognosis

Survival depends on a number of factors such as original tumor site and aggressiveness [1]. Length of survival is directly related to both the extent of the disease and the time of diagnosis and the degree of differentiation of the tumor [1]. Nevertheless, data show that the 5-year survival of all patients with NET regardless of primary site and degree of spread did not change between 1973 and 2002 and remained at 60 – 65 % [1]. Current research predicts the 5- and 10-year survival rates in a Norwegian sample to be 78% and 53 % respectively [51]. Reports in the literature vary regarding primary tumor size and the presence of distant metastases at diagnosis. The size of carcinoid tumor may be used as a prognostic indicator; larger than 2 cm in diameter is considered malignant and metastasis is likely to have occurred [1;2;50]. A poorer prognosis in NETs and distant metastases were associated with elevated levels of U-5HIAA and CgA ratio  $\geq 6.2$ , and Ki-67 values  $\geq 5\%$ , age  $\geq 64$ , male gender and the presence of carcinoid heart disease [51]. The overall 5-year survival for patients with no metastases at diagnosis was 94%, for those with regional disease 85%, for those with liver

metastases 63%, and for patients with distant metastases without liver involvement, 75%. Survival was significantly decreased in patients with distant metastases compared to the group with local or regional disease. Five-year survival for primary tumors  $\leq 1$  cm was 85%,  $>1-2$  cm 77%, and  $>2$  cm 78% [51]. A significant difference in survival based on primary tumor size among the patients with SI-NET was not found in the Norwegian sample [51]. The results emphasize an important clinical feature of NETs where even small primary tumors may be associated with metastases and decreased survival [51]. Distant liver metastases at time of diagnosis, elevated CgA-levels and advanced age were significant predictors of survival [51]. NET represents a complex group of tumors with remarkable variation in the course of the disease. The level of specializing of the team in managing the NETs vary on survival rates [1]. Thus, multidisciplinary teams at referral centers should give guidance on the definitive management of patients with all varieties of NET.

### 3.3 Course of disease

Disease refers to a condition that is viewed from a patho-physiologic model, such as an alteration in structure and function [52] (p 4). NET is such an alteration.

Illness is the human experience of symptoms and suffering, and refers to how the disease is perceived, lived with, and responded to by individuals and their families [52] (p 4).

Understanding the illness experience is essential in providing holistic care [52] (p 4).

Chronic disease is considered an irreversible presence, accumulation, or latency of disease status or impairments that involve the total human environment for supportive care and self-care, maintenance of function, and prevention of further disability [52] (p 6). NET may be regarded chronically as the patients may live for a long time and the symptoms are relieved with adequate medical treatment [51;53]. There is no single onset pattern of chronicity, hence, a chronic disease can appear suddenly or through insidious process, have episodic flare-up or exacerbations or remain in remission with absence. Consequently, balancing treatment regimens while focusing on quality of life consists of maintaining wellness or keeping symptoms in remission [52] (p 5).

The majority of patients with NET are facing progression disease at the time of diagnosis due to lack of initial symptoms. In earlier stages, radical surgery may be possible. Resection of the

primary lesion should always be considered in metastatic disease, due to risk of local complications over time. Because of the relatively slow progression of the disease, the disease trajectory resembles that of the chronically ill patient [54]. The illness trajectory consists of regressive steps in the course of the illness, with stable and downward phases [1;4;55]. A common challenge in NETs is often the variable period of non-specific symptoms before diagnosis, with a range of two weeks to 21 years of symptoms before diagnosis [1;51]. The most common presenting symptoms are diarrhea, weight loss, fatigue, flushing, nutrition intolerance, restlessness, fluctuating mood and other non specific symptoms and pain [4;50;51;56]. The symptoms may affect many dimensions of the patients life, and does not only reduce the patient's activity and physical capacity, but may also cause discomfort, anxiety about the progress of the disease, and depression. If right heart valves are involved, right heart failure may occur and cause breathlessness [57;58].

### 3.4 Standards of clinical management

For the purpose of this thesis, clinical management includes medical treatment of the disease trajectory and care for symptoms and prevention of deterioration of the illness. The European Neuroendocrine Tumor Society (ENETS) consensus conferences have produced guidelines on the pharmacological management and medical control of NET [59]. No guidelines exist for patients with NET or for patient education. However, Norwegian legislation regulates the patients' rights for information and education [60]. Additionally, evidence should be the basis for information and patient education in coping with the disease [61]. Pharmacological management consist of biological agents such as somatostatin analogues, interferon- $\alpha$  [1;1;2]. Embolization, debulking or radio-isotope are options for treatment of liver metastases, and valve replacement by open heart surgery if the valves are affected [1;1;2]. Optimal management can stabilize and delay disease development [62]. Regular, annual medical visits for 10-15 years is preferred, initially at six months intervals and some times more frequently, because relapse may occur [1;2;62]. When the disease appears to be stable, the intervals between visits may be less frequent, the "follow up" visits consist of clinical blood status, CgA in serum, x-ray, CT scanning and MR.

Patients diagnosed with and treated for NET may have a risk of side effects of treatment and

progression of the disease [1;2]. Psychosocial consequences due to the uncertainty of the changes in disease trajectory may lead to stress reactions. In some cases, the symptoms such as diarrhea and fatigue may limit social activities and thus, social isolation may occur [56]. Side effects of medical treatment may influence daily activities mentally, physically and socially, and consequently, impact HRQoL. The aim of the treatment is to keep the patient disease and symptom-free for as long as possible and to maintain a good quality of life. In order to achieve optimum health and HRQoL and to prevent subsequent events and improve secondary prevention efforts, patient information and education should be emphasized [63]. Patient education may be understood as “*any set of planned, educational activities designed to improve patients’ health behaviors, health status or both*” [36]. The purpose of patient education is “*to maintain health and, in some cases, to slow deterioration. These purposes are met through changes in behaviors, mental attitudes, or both*” [64]. Patient education and secondary prevention strategies in daily practice are still inadequate in Norway and there exists no standard guidelines, providing patients with health information and education. In addition, providing patients with information and education may enable them to take an active part and be responsible for their own health and social functioning [61;65]. Through a patient education program the patients may better cope with their disease, prevent complications, problem solve, make appropriate decisions, increase confidence, and place patients and health professionals in a partnership relationship [61;64;65].

A patient educational program that is *relevant* and tailored to the patients needs and interests is desirable. Furthermore, a program that is action based specifically to help patients make the necessary changes in their lives; may provide patients the opportunity to self-monitoring their own progress and reward and encourage patients when they succeed. Finally, the patients can determine their progress in dialog with their health care personnel [66] (p 65 - 76)

In order to improve the problem of lack of knowledge and information, and experience of stress due to the uncertainty of the disease trajectory, treatment and symptoms, it is likely that patients receive follow- up service in the period after diagnosis. However, the period should start when the patient feel comfortable and be in the phase of new orientation soon after diagnosis [67].

Results from studies in chronic disease populations revealed that program content, timing, providers, approaches, and settings have been provided as a single intervention, in combination

with, or as a supplement to standardized care. The interventions have included the following approaches; consultations at hospitals, educational sessions, group sessions, support groups and telephone follow up. The timing has varied from two weeks to 12 months [34-36].

To consider whether educational goals have been achieved at the individual level the following issues should be assessed; are psychosocial problems present and, has the patients' HRQoL improved? Research indicated that group sessions were an intervention that showed promise, and was used to plan follow-up interventions for this study [37]. Timing for the intervention was based on recommendations [68] and followed a guide especially performed for patients with NET. However, improving the patients' knowledge, sessions with teaching and telephone follow-ups were also warranted.

## **4. The main concepts**

### **4.1 Health related quality of life**

Quality of life has been an important objective of research in recent decades. This is explained by the increasing focus on the importance of patient reported outcomes in determining the efficacy and impact of care across settings and disease contexts [69;70]. Quality of life is an important parameter for evaluating the quality and outcome of health [71;72].

Quality of life represents the range of human experience, and usually refers to overall well-being or life satisfaction [71;73;74]. The concept of quality of life is separate from health, but is related to it [43;72] and refers to a broader construct encompassing HRQoL. Thus, quality of life seems to be an umbrella term that includes various concepts such as functional status perception, life conditions, behavior, lifestyle and symptoms. Spilker (1996) has illustrated quality of life as a pyramid of three different levels; i) overall satisfaction with life; ii) the generic level such as the individual's satisfaction with different life domains (physical, psychological, economic, spiritual and social); and iii) disease specific symptoms or disability [75]. Quality of life is often used as a general construct to describe subjective and psychosocial variables [76]. WHO has defined quality of life as:

“ Individuals perception of their position in life in the context of the culture and value-systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the individual's

physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to salient features of their environment” (p 1405).

The definition of quality of life reflects an individual subjective appraisal of health status and well being that is influenced in complex ways by a broad array of factors. Health related quality of life has been strongly influenced by the definition from the HWO in 1948; “*Health is the state of complete physical, mental and social well-being and not merely the absence of disease and infirmity*” [77]. HRQoL reflects current levels of health status and well-being and is not age, disease or treatment specific [78]. In addition, the parts of the construct affect each other and their overall summation. The dynamic nature of HRQoL poses measurement challenges.

HRQoL is composed of both positive and negative experiences and affects. Self-perceptions of life may change over time in response to life and health events, as well as experiences.

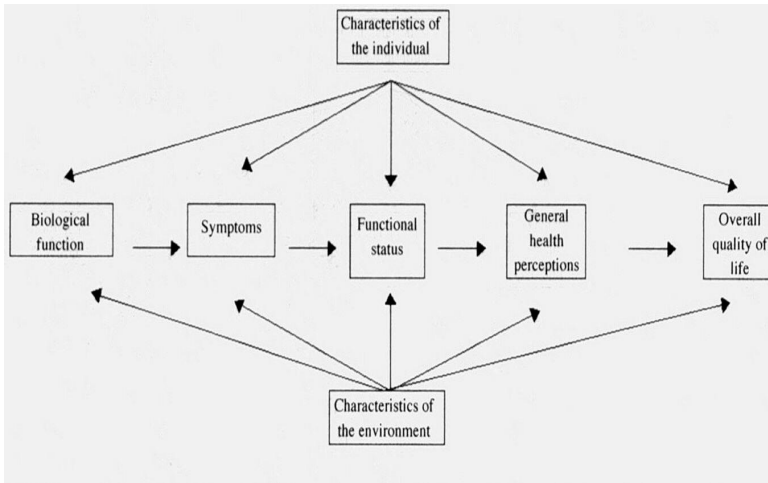
Consciously or unconsciously, individuals may accommodate, adapt or adjust to deteriorating circumstances, either in relation to health or other factors. To feel as good as possible about oneself, one may do this. Thus, the experience of HRQoL may be understood as a dynamic process. In the present study HRQoL is used and defined as a subjective and multidimensional concept including physical functioning, social functioning, role functioning, pain, vitality, general health perceptions and mental health [79].

Based on the Wilson & Cleary model, Ferrans et al (2005) have suggested a modified theoretical model for a subjective perception of quality of life related to how satisfied an individual is with of her life as a whole (see Figure 1) (83). The purpose of the model is to distinguish between conceptual measures of quality of life and to suggest their dominant causal associations. Polit & Beck (2008) claim that a conceptual model guides the relationship among the concepts as well as a basis for generation of research hypotheses [80]. In this thesis, Ferrans’ model (Figure 1) is used to understand the difference between constructs relevant for the theoretical and methodological framework and how clinical variables are linked with HRQoL. The model is not grounded in a specific quality of life definition and consists of a combination of the biological and sociological approach. It is likely that patients with NET experience biological, physiological and psychosocial changes when diagnosed. These changes justify the use of a conceptual model that combines these paradigms in HRQoL research in patients with NET. Wilson and Cleary’s model has been used frequently in nursing research [81;82].

According to, Ferrans et al (2005), overall quality of life and general health perceptions exist on a continuum of increasing ideal biological function on one end and more complex and integrated measures of health perception and overall quality of life on the other end. The first level includes biological-physiological variables and traditional clinical variables, as well as physiological examinations. The second level is the perception of an abnormal physical, emotional or cognitive state is considered to be an important determinant of functioning. The third level, functional status is the ability to perform particular defined tasks. The fourth level refers to subjective health that integrates all of the preceding concepts representing an integration of symptom status, functional status and the biological variables. The fifth level, quality of life, is considered as the rating of the perception of satisfaction with life as a whole. Each of the levels in the model is influenced by individual and environmental characteristics [83]. Although the arrows in the model are shown in only one main direction Wilson & Cleary point out that the relationships may be bi-directional [74]. Therefore, all the variables may serve as mediators to overall quality of or vice versa. In this thesis, we included the variables of medical diagnosis, stress, disease related symptoms, co-morbidity and, social support and general self-efficacy. This thesis is focused on the generic level of HRQoL as an outcome and is elaborated in paper I, II and III.

In summary, the definition of HRQoL and the conceptual model developed by Wilson and Cleary and adapted by Ferrans consider HRQoL to be a subjective phenomenon as well as a multidimensional concept of core elements. The model can be used as a conceptual model linking concepts together with HRQoL.

**Figure 1.** The Conceptual model for health related quality of life by Ferrans, C. E., Zerwic J. J., Wilbur J. E., and Larson, J. L., 2005. The model is used with the permission of Dr. Ferrans et al and Journal of Nursing Scholarship (Ferrans CE. et al, Model for health-related quality of life. 2005, 37(4), 336-342. Copyright © Journal of Nursing Scholarship 2005).



## 4.2 Stress

Receiving a cancer diagnosis represents a stressful experience [9-11;84]. Stress may be understood as the response to a threatening event [85] which is complex and based on the perception of the individual’s experience and self-report [86;87]. In the present study stress is used and defined as intrusive thoughts and avoidance related to a specific event in line with Horowitz’ understanding of these concepts:

*“Intrusion is characterized by unbidden thoughts and images, troubled dreams, strong pangs or waves of feelings, and repetitive behavior. Avoidance responses included ideational constriction, denial of the meanings and consequences of the event, blunted sensation, behavioral inhibition or counter-phobic activity, and awareness of emotional numbness” [88] (p. 210).*

Intrusive and repetitious symptoms are common after exposure of extreme stress, whereas avoidance symptoms are less common. Living with a cancer diagnosis involve the uncertainty about the disease trajectory and if or when the disease would cause the death. Consequently, according to Horowitz (1979) [88] living with NET may represent an overwhelming, stressful experience that may release responses such as intrusive thoughts and avoidance of the specific event that releases the intrusive thoughts. An overwhelming sense is often experienced with feelings of fear combined with matching physiological reactions such as sweat, increased heart rate and restlessness. Avoidance behaviors arise from attempts to block unpleasant feelings and



thoughts and usually follows the overwhelming effort of reducing the disturbing event [89]. Consequently, HRQoL may be influenced by stress responses. This study includes stress as a symptom, which potentially relates directly to health outcomes as well as influences HRQoL. This is specifically elaborated on in papers II and III.

### 4.3 General self-efficacy

Bandura based the social cognitive theory on the concept of *self-efficacy* elaborating on the understanding that humans are direct agents in shaping and responding to environmental conditions, and that human motivations and actions are regulated by forethoughts [90]. Self-efficacy is the belief in one's competence to take on difficult or novel tasks, and to cope with adversity arising from specific demanding situations [91] and makes a difference in how people feel, think and act [90]. This may reflect the persons' ability to problem-solve in general. Thus, improving the patients' self-efficacy may act as a basis for problem-solving strategies. Self-efficacy influences the choice of activities and motivational level, thus, beliefs of personal efficacy make an important contribution to the acquisition of the knowledge on which skills are founded. The person's belief in his own ability to cope with different challenges and to exert some control over environmental events is the central mechanism [92]. In this study self-efficacy is defined as "*beliefs in one's capabilities to organize and execute the course action required producing given attainments*" [90] (p 3). Furthermore, "*the effect of self-efficacy influences the course of action chosen by the individual, how much effort they put into it and how long they will persist if they first fail, and how much stress and depression they experience in coping environmental demands and level of accomplishments they realize*" [90] (p 3). Therefore, self-efficacy plays an important role, as well as knowledge and skills, in health promoting behaviors [32;33;90]. For example, in patients with NET self-efficacy may be reflected in the individual's belief in their ability to manage symptoms and produce desired effects in a given activity, problem or unexpected challenge which, includes problem solving. The beliefs influence whether the patient is pessimistic or optimistic in performing different tasks. Self-efficacy may be reflected in the patients' beliefs in their ability to deal with stressful situations and thus, their ability to solve problems related to the stress. Hence, perceived self-efficacy may be an important resource in performing different tasks and in determining activities or situations to perform or avoid.

Self-efficacy may depend on the initial sense of self-efficacy and beliefs in the positive outcome to the new challenge [90]. However, initial beliefs about competencies may increase as, the patient is able to cope and adjust their behavior [93-95]. Self-efficacy is influenced by the interaction of personality, social environment and behavior. The dynamic process of how personality, social environment and behavior influences a person's personal agency may be viewed as the basis for developing a person's self-efficacy. Realization of personal agency requires self-observation of the outcomes that flow from actions. By repeatedly observing actions following environmental events, individuals learn that actions produce effects. Hence, internal and external feedback lead to individually self-evaluation and self-regulation toward a desired result. The self-regulation usually occurs through modification of behavior and perception of control. In this process the individual develops self-efficacy and provides the basis for behavior. Perceived self-efficacy is defined and measured independently of performance [90]. In order to complete an action, important predictors of motivation are a combination of perceived self-efficacy and outcomes expectation and knowledge as well as perceived control. Therefore, if people believe that their actions can make a difference, then they have much incentive to act. Contrastingly, low confidence in performing activities implies low self-efficacy and makes it less likely that an individual will act [90].

Efficacy beliefs are patterned differently in different individuals in levels, generality and strength. The beliefs are patterned in one level if they refer to a simple demand, and to another level if they refer to difficult demands of performing within a particular domain or function. The range of perceived capability for a given person is measured against levels of task demands that represent varying degrees of challenge or impediment to successful performance. When patients engage in a particular situation and experience unknown symptoms, self-efficacy can be improved by learning about NET related symptoms, for example. Hence, the extent of applicability of a generalized domain to a new situation is of importance. Patients with NET may feel successful when performing exercise unsupervised after a successful supervised exercise. Strength refers to the confidence people feel they have in accomplishing the particular task [90]. To perceive self-efficacy, four sources of skills are necessary: enactive mastery experience, vicarious experience, verbal persuasion and strengthening physical and affective state [90]. *Mastery experience* serve as an indicator of capability in that the individual's experience of

success in being able to perform a desired action or engage in a particular cognition may act as an incentive for behavioral change. Mastery experience is the most influential source of efficacy information because it provides authentic evidence of whether one can master whatever it takes to succeed. A resilient sense of efficacy requires experience in overcoming obstacles through perseverant effort [90] (s. 80). *Vicarious experience* influences efficacy appraisals through modeled attainment in that the sharing of experiences and learning from other patients or individuals who succeed in valued activities promote a sense of personal capacity. *Verbal persuasion* is trying to encourage other persons to believe in their own capacity to reach their goals. *Strengthen physiological and affective state* is strengthening the individual's knowledge in human physical and mental reactions by internal and external influence. Hence, the individuals exercise control over functioning [90]. Based on the abovementioned, self-efficacy may be an important characteristic in how patients cope with NET. The four sources of skills to perceive self-efficacy might be seen as useful tools in problem solving strategies. Though Bandura indicates that self-efficacy is context specific and that assessment methods must be tailored to an event or research setting, some researchers prefer the concept of general self-efficacy [96]. The idea of the universal construct is that the concept of general self-efficacy may be of a general character. General self-efficacy refers to a global confidence in one's coping ability across a wide range of demanding and novel or stressful situations. The levels and amount of exposure to challenges and demanding situations through the lifespan vary between individuals. It is likely that challenges and demanding situations of general character may influence a persons' daily life. Consequently, the person's ability to cope with situations in general may influence the person's levels of stress and HRQoL. Thus, it is important to evaluate not only how the individual copes with disease, but also with general situations influencing the individual's life. In this study, the concept of general self-efficacy will be used. General self-efficacy is specifically elaborated on papers II and III.

#### 4.4 Social support

Social support refers to a variety of phenomena that characterize an individual's social environment. Social support is a multidimensional construct and refers to the degree to which individuals are socially embedded and have sense of belonging, obligation and intimacy, and

reflects the function and quality of social relationships. Social support may be resources provided by others, such as coping assistance, an exchange of social resources [97], or more formalized support such as health care services [98]. Thus, social support occurs through an interactive process that provide information, advice, and feedback [8;97]. Seeking social support seems to be one of the most successful coping strategies that lead to favorable health outcomes [97;98]. There are two types of social support; structural and functional [99]. Structural social support refers to the presence of social relationships. Functional support, or perceived support, refers to an individual's perceptions of the resources available in the social network that are perceived as supportive. Social environment includes family, friends and healthcare providers who have influence over when and where health care is sought and whether treatment is adhered to. Many of the constructs of social environment may have implications for health [100]. Cohen (2004) assumes that social support protects a person against the pathologic effects of stressful situations, but is relatively unimportant for the person's health and well-being in non-stressful situation [100]. Consequently, social support is activated when needed and social connections benefit health by providing psychological and material resources that are needed in coping with stress. Cohen (2004) also claims that social support and personal characteristics such as general self-efficacy are least partly independent of one another, and there are few studies addressing the overlap [100].

The literature on social relationships and physical HRQoL is relatively small. In the current study, social support is defined in five ways; support for self-esteem or the extent to which people feel accepted; emotional closeness or the extent to which people feel emotional confidence and; tangible aid or the provision of materiel resources such as money or service; group belonging or spending time with others; and appraisal support or assistance defining and understanding difficult events [101]. The concept of social support is addressed in paper II.

#### 4.5 Patient education

We hypothesized that patient education, informed by Bandura's social cognitive theory, and strategies in enhancing self-efficacy [90] may improve HRQoL in patients with NET. Strategies for enhancing self-efficacy incorporate mastery experiences, vicarious experiences, social persuasion, and strengthening physical and psychological state [32;90].

*Mastery experience* may be integrated into a patient education intervention by writing individual goals. Mastery experience develops when people become convinced that they have what it takes to succeed; they persevere in the face of adversity, and rebound from setbacks. Mastery may result from experiencing hard times, in which the patient may emerge stronger and more able to perform tasks. However, appraisal of personal efficacy also depends on preconceptions of the individual's capability, the amount of effort they expend, the perceived difficulty of the tasks, the amount of external aid they receive and under which circumstances they perform. Further, the temporal pattern of their successes and failures, and the way these experiences are cognitively organized and reconstructed in memory are important. One of the main mechanisms is internal motivation [90]; the patient must want to achieve change. Motivation is related to the patient's will [90]. For example, the patient may want to achieve better physical conditioning but has fatigue and thinks that he/she is unable to perform physical activities. However, the patient may be willing to perform an action to achieve a reward. A relevant question from the nurse will be to ask the patient to suggest an alternative to resting. When the patient answers what he/she might do, the following response from the nurse might be; how are you going to do it and/or how often do you want to do it? Every answer the patient gives, comes from him self, from the internal motivation of wanting or not wanting to do something. In addition, the suggestion from the patient is likely to be realistic and workable for him/her. The final question is to ask the patient how realistic the suggestions are on a scale of 0 -10. If the assessment is below 7, the nurse should ask the patient to reconsider and formulate a new plan that is achievable. It is important that the patient achieve their goal and experience success in order to be motivated to continue working toward their goals. If the patient assesses the achievability of their goal to be 7 or more, then the plan is realistic and the nurse should support and recognize the patient's performance. *Vicarious experience* depends on processes governing the impact of modeling self-efficacy such as modes of modeling, performance similarity, attribute similarity, multiplicity and diversity, coping versus mastery and competence of modeling. The group sessions integrated shared positive experiences as a means of support and to role model for each other. *Verbal persuasion* includes giving feedback, which highlights the person's capabilities and in turn may raise efficacy beliefs. The last strategy, *physiological and affective state*, is strengthened by managing NET specific symptoms and identifying malignant changes in

physical state due to NET disease. When patients learn to identify symptoms, they become more convinced of their ability to solve problems and discomfort such as diarrhea and fatigue and, stress. Lorig's (2001) research results demonstrate improved self-efficacy and improved health outcomes following a patient educational program [41;102-107]. Patient education is addressed in paper III.

## **5. Prior research**

### **5.1 Health Related Quality of Life in patients with Neuroendocrine Tumors compared with the General Norwegian Population**

Age, co-morbidity, and lower annual income are independently related to lower levels of all HRQoL subscores among men with prostate cancer [108] contrary to patients with pancreatic neuroendocrine tumors (n = 44) where there was no relationship between age, gender, disease duration, marital status and disease duration and HRQoL [7]. Results from a study of mostly men (71%), mean age 59 years, diagnosed with non-small cell lung cancer, show that older people could not function as well as younger people [109]. In a comparative study a sample of long-term survivors of testicular cancer (n = 1409), mean age 44 years, demonstrated more bodily pain, less vitality and poorer social functioning but better mental HRQoL than a sample of the general population [10]. The testicular cancer surveillance study also reports lower mental component scores, compared with the general norm population. The physical component score, however, did not differ from the general norm sample.

Another prospective study reporting HRQoL in 141 Japanese patients with prostate cancer, shows that the mental health subscale was the only subscale that differed significantly from Japanese population norms [110]. Larsson (2010) demonstrates that a sample of women with breast cancer (n = 85) experiences significantly poorer HRQoL on all sub-scales except general health compared to a sample of the female general population. The results may be confounded by age since groups varied significantly by age (breast cancer patients ranged from 30-80 years vs. controls ranged from 55-64 years). The patients received adjuvant treatment such as chemotherapy, radiotherapy and hormones, separately or in combination, or no therapy [111]. Moreover, a cross sectional study of individuals at risk of hereditary cancer (n = 121) demonstrates similar mental component scores and higher levels of physical component score

compared with a sample of the general population [8]. Age was negatively associated with physical component HRQoL while level of education was positively associated with physical component scores of HRQoL.

In a cohort study, Berglund et al [47] compared HRQoL among 29 Swedish patients with multiple endocrine neoplasia type 1 (MEN1), with matched population-based norm values. The age of the MEN1 sample ranged from 28 to 77 years, the distribution of gender was similar and the disease duration ranged from < 1 year to 30 years. The authors found that patients with MEN1 have significantly lower levels of general health and social functioning. In addition, a longitudinal study of 24 patients with NET scored 10 points or more below expected scores for two function scales and symptom scales at baseline measured by a cancer specific quality of life questionnaire. The results demonstrate significantly poorer physical and social function, global health, nausea/vomiting and diarrhea measured by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QoL-C30) at 12 months following diagnosis, compared with Swedish population-based norm values [56]. In a longitudinal, prospective, and comparative study, another sample of 59 patients with NET demonstrate poorer cancer related HRQoL measured by EORTC QoL-C30 on all subscales than the Swedish norm population at baseline as well as 12 months post diagnosis. The mean age was 60 years and 81 % was on sick leave or old age pensioner. Seventy percent had developed metastases [112]. Patients with pancreatic neuroendocrine tumors (n = 44) demonstrated significantly poorer MCS measured by SF-12 and General Health Quality-12 than the Italian general population [7]. A retrospective, comparative study of Beaumont et al (2012) shows that patients with NET (n = 663) have statistically significant poorer HRQoL SF-36 than the general US population [13]. Effect sizes were large for physical functioning, role limitation-physical, general health and vitality indicating that these factors may have clinical importance for patients with NET. In summary, studies demonstrate that age, gender, co-morbidity and treatment are related to HRQoL. However, few studies have evaluated individual characteristics in association with HRQoL. Prior research of HRQoL in patients with cancer compared with general norm populations shows inconsistent results across settings and disease contexts. Generally, it appears that patients with cancer have a lower HRQoL compared to healthy populations. No studies have evaluated multivariate relationships between socio-demographic characteristics of the

individuals and HRQoL in patients with NET. In addition, no studies have compared the health related quality of life of the Norwegian NET population with a population- based norm.

## 5.2 Associations between Stress, General Self-efficacy, Social Support and Health Related Quality of Life

### 5.2.1 The relationship between stress and health related quality of life

Researchers have been seeking to discover the influence of stress on health related quality of life for decades [27;86;113-116]. Several authors have addressed symptoms of stress that are negatively association with disease related HRQoL in patients with cancer [26;42;114;117-119]. A follow up prospective study by van deWiel et al (2008) demonstrates that intrusive thoughts and feelings were significantly negatively associated with the MOS-36 Short Form Health Survey subscores of mental health and general health as well as the mental and physical component scores in women following breast cancer surgery (n = 83) [11]. Furthermore, avoidance-subscore measured by the Impact of Event Score tool relates significantly with the bodily pain sub-scale. In Mykletun's study (2005), stress is strongly negatively related to both physical and mental health in long term survivors (n = 1409) after treatment for testicular cancer [10]. In addition, results of a study of individuals at risk for hereditary cancer, attending genetic counseling, demonstrate significant negative associations between stress and mental health [8]. In a sample consisting of patients with breast cancer, stress does not predict negative mental health on the SF-36 [120].

In summary, a preponderance of research demonstrates negative associations between stress as measured by intrusion and avoidance, and mental and physical HRQoL in patients with cancer. Although Larsson (2003) [121] show a negative association between distress and cancer specific HRQoL in patients with NET, no studies have measured stress with the Impact of Event Scale modified to be NET specific. Identifying stress influenced by NET may be important information for health personnel when planning strategies in order to help the patients in the coping process.



### 5.2.2 The relationship between general self-efficacy and health related quality of life

Self-efficacy has been a consistent predictor of quality of life in patients across chronic illness conditions [34-36;39;44;45;122-127]. Research has focused on associations between disease-related self-efficacy and disease-specific quality of life [104;126;128-130]. In addition, general self-efficacy may be associated with a broader spectrum of quality of life [131]. However, there has been little emphasis on the associations between general self-efficacy and HRQoL in patients with cancer. Higher levels of general self-efficacy are related to better HRQoL in individuals attending counseling at risk for hereditary cancer [8] and for patients with rheumatoid arthritis [132]. In addition, results from a cross sectional study demonstrate a direct positive relationship between general self-efficacy and physical functioning assessed by a MOS-20 questionnaire in 104 patients with HIV [125].

In summary, general self-efficacy has been a positive predictor of HRQoL. Although several authors have suggested that self-efficacy were associated with less stress [133-135], no studies have evaluated the association between general self-efficacy and HRQoL, nor the mediation role of general self-efficacy on the association between stress and HRQoL in patients with NET. Improved general self-efficacy may enable patients to better solve problems which may be useful in coping with stressful situations. Thus, they may take part in their self-development. Based on their beliefs in succeeding in coping with the disease, HRQoL may be enhanced,

### 5.2.3 The association between social support and HRQoL

Cohen [87] claimed that there is an association between social support and HRQoL in that, those with more social support have better HRQoL than those with lower social support. In addition, the benefit of social connections exists irrespective of whether one is under stress [100]. This may be explained by the suggestion that individuals who participate in a social network are subject to social controls and peer pressures. Social controls and peer pressures may influence normative health behaviors related to exercise, diet, or smoking. Social interaction may result in feelings of responsibility for others and resulting in better self-care, thus, it may influence individual's HRQoL. A retrospective survey by Sirri et al (2011) found that social support is

positively related to physical and social dimensions of HRQoL measured by World Health Organization Quality of Life-Bref (WHOQL-BREF) in long term survivors of 66 cardiac transplant [29]. In addition, the descriptive cross sectional surveys demonstrate that social support measured by the Social Support Questionnaire is an important factor affecting a general cancer specific HRQoL in patients with cholangio carcinoma (n = 260) [136] and gastrointestinal cancer (n = 146) [137]. A comparative study demonstrate that social support measured by The Enhancing Recovery in Coronary Heart Disease Patients Social Support Instrument has a significant relationship with cancer specific HRQoL in 175 men treated with localized prostate cancer [138]. Luszczynska et al (2007) found that social support is significantly associated with physical functioning as measured by the SF-20 (physical component) in 104 patients infected with HIV [125]. A descriptive study of 118 patients infected with HIV report significantly positive relationships between social support and all subscales of HRQoL except bodily pain and tangible support [139]. Patients with breast cancer demonstrate positive relationship between social support and HRQoL [84]. Furthermore, a cross sectional study of Carlsson found that a sample of individuals at risk for hereditary cancer attending genetic counseling has significantly positive association between social support and mental component scores [8].

Research has shown that social support is associated with less stress [133-135] and social support appears to have a positive effect on adjustment following treatment [87]. Social support influences the cognitive appraisal of stressful encounters by helping to mitigate the effect of stressful events and HRQoL. Coping then, is a result of the cognitive appraisal of tangible support availability [97]. The subscores appraisal and self-esteem by Interpersonal Social Evaluation List, were related to better emotional HRQoL in patients attending genetic counseling for hereditary cancer, [8] and in patients with breast cancer [84], indicating a moderating effect of social support on mental HRQoL. As stress, measured by The Perceived Stress Scale, mediates the effect of Enhancing Recovery in Coronary Heart Disease Patients Social Support on HRQoL (measured by The Functional Assessment of Cancer Therapy-General, FACT-G) in men treated for prostate cancer [138], it is likely that social support may mediate stressful life events [86]. In summary, some studies have shown that social support is positively related to HRQoL across disease settings. However, no studies have evaluated the

association between social support and HRQoL in patients with NET. Feedback from patients, friends or family highlights the person's capabilities, thus, social support may be an important part of the individual's resources in the coping process.

#### 5.2.4 The associations between stress, general self-efficacy, social support and health related quality of life.

Researchers have evaluated associations between stress, self-efficacy, social support and HRQoL and found that stress associated negatively with HRQoL. In addition, those with more social support and self-efficacy had better HRQoL. A study of women with breast cancer and low levels of social support measured by Appraisal support, there was a significant negative relationship between cancer-related intrusive thoughts and HRQoL. However, for those with high levels of social support, the cancer-related intrusive thoughts were not significantly related to HRQoL. Furthermore, social support acted as a buffer to stressful life events in women with breast cancer (n = 179) in a descriptive study [140]. In a descriptive cross sectional study of 260 patients with gynecological cancer, social support appeared to protect patients from traumatic stress symptoms associated with poor physical HRQoL [141]. These results suggest that appraisal social support can mitigate traumatic life events in patients with cancer [84]. However, while emotional support did not protect against stressful life events as measured by a mental health inventory in patients with breast cancer, tangible support did [140].

Self-efficacy may act as a self-regulating process by reducing the discrepancies between stress and mental HRQoL [86;142]. Carlsson (2004) found that stress, social support and general self-efficacy had a direct negative relationship with mental HRQoL in individuals at risk for hereditary cancer (n =121). In addition, general self-efficacy and social support (by appraisal and self-esteem) seemed to moderate the association between stress and mental HRQoL analyzed with multiple linear regression [8]. No mediation effect was investigated thus; mediation was evaluated in this study.

In summary, there is evidence that general self-efficacy and social support have a positive relationship with HRQoL while stress has a negative impact on HRQoL. However, the results are inconsistent and no studies have investigated the association between general self-efficacy, social support, stress and HRQoL in patients with NET. In addition, no studies have evaluated

the mediation effect of general self-efficacy and social support on the association of stress and HRQoL.

### 5.3 Patient education to improve stress, general self-efficacy and health related quality of life

Stress is regarded as a symptom in response to a specific stressor [88] and may influence the patients' adaptation to disease and thus their HRQoL [5;8-11]. Consequently, stress might influence the patients' physical and mental functioning. Interventions aimed at increasing patients' ability to cope with stress may be a complimentary treatment option. A randomized controlled trial (RCT) of patients with gynecological cancer (n = 179) demonstrated reduced stress and improved HRQoL following an individual support intervention led by nurses and psychologists [143]. The intervention was based on the principles of cognitive restructuring techniques as applied to cancer related issues, identifying support, coping with effect of treatment [143]. In addition, a RCT aimed to reduce stress among women (n = 353) with gynecological cancers demonstrated significant reduction over time [144]. The intervention considered seven hour-long individual and one telephone booster session that took place 1 week after the sixth session. The sessions focused on enhancing coping and support-solicitation skills and identifying and dealing with emotional reactions to cancer. Techniques were drawn from cognitive-behavioral interventions.

Previous RTCs have found moderate, positive impact on chronicity-specific self-efficacy in chronically ill patients [145]. An educational program aimed at delivering support for self-care by developing peoples self-care skills, confidence and motivation to take more effective control over their long-term conditions improved self-efficacy. A caveat was that the educational program appealed most to white, middle class people with long-term conditions who already viewed themselves as effective self-managers [145]. A waiting list RCT reported statistically significantly improved chronicity specific self-efficacy in 154 chronically ill Vietnamese and Chinese patients but was not helpful in Greek and Italian populations [146]. The intervention consisted of six weekly sessions of 2.5 hours duration using the Chronic Disease Self-Management Workshop Leaders manual. The patients were taught symptom management, problem solving, dealing with the emotions of chronicity, exercise and relaxation, use of

medication, healthy eating, and communication skills. The intervention was based on the four principles of self-efficacy; mastery experience, vicarious experience, verbal persuasion, and strengthened physical and affective state [146]. In another RCT, Buszewicz [38] significant differences were noted for the pain subscore of the arthritis self-efficacy scale and self-efficacy for other aspects of management after 12 months in 812 patients with arthritis, following an intervention based on the principles of self-efficacy. The intervention consisted of an education booklet, and an invitation to participate in a local “challenging arthritis” course. The booklet was not described, but was designed for the study and incorporated information available to the public from the Arthritis Care and the Arthritis Research Campaign.

Interventions including self-management often results in improved health outcomes for patients with chronic conditions [147] and cancer [148]. Several studies have reported on HRQoL outcomes, assessed by a variety of domain specific measurements following an intervention based on social cognitive theory principles [35;44;145;146;149-151]. A review of studies of patients with cancer undergoing an intervention based on the principles of self-efficacy found positive changes in domain specific quality of life [36]. Rehse and Pukrop (2003) reviewed the effect of psychosocial interventions on quality of life in adult cancer patients. Twelve percent of the studies referred include support groups which provided mutual help. The most important aspects of the intervention were emotional support and coping skills training. Fifty-four percent of the studies used cognitive behavioral or behavioral methods to modify cognitions of specific coping skills. In addition, minimal differences in HRQoL could be observed when an intervention lasted for at least 12 weeks [37]. A meta analysis of RCTs among cancer patients demonstrate improvements in physical function and global quality of life following psychosocial interventions [36] based on Bandura’s social cognitive theory. McCorcle found improvements in mental and physical components of HRQoL (SF-12) following a 6 months RTC to improve self-management skills in women with 123 gynecological cancers [149]. The primary aim of the intervention was to assist patients in developing and maintain self-management skills after surgery and to facilitate their active participation in decision-making with regard to treatment. The intervention included symptom management and monitoring, emotional support, patient education, coordination of resources, referrals and direct nursing care over 18 patient contacts. In a RCT evaluating mental and physical components of HRQoL in

patients with arthritis, Buszewicz [38] found no significant differences between the intervention group and the control group. The intervention aimed to evaluate clinical effectiveness of a self-management programme for patients in primary care with osteoarthritis consisted of an education booklet and an invitation to participate in a local arthritis course. The controls received only the education booklet. A controlled study including breast cancer patients (n = 65) attending support groups did not show significant improvements of social support measured by The Social Support Questionnaire and cancer specific HRQoL. The intervention included information on illness and treatment and relaxation. Patients met for 2 hours twice a week for four weeks [152].

In summary, lack of standardization of interventions, differences in disease trajectories, variations in chronic vs. acute conditions, and inconsistent prior findings on the relationship between stress and Quality of Life provide the rationale for this study.

## **6. The study**

### **6.1 Design, recruitment, participants and measurements**

A cross sectional descriptive, survey design was used for Phase I of the study (Papers I and II) and an explorative, longitudinal design of three points in time (T1 - T3) was used for Phase II (Paper III). Recruitment of two different samples was collected in order to perform the studies.

#### **6.1.1 Data collection**

A cross-sectional design using survey methodology with anonymous, self-reported questionnaires was employed in Phase I.

*Participants for the cross sectional, descriptive survey (Papers I & II)*

All NET centers nationwide (University Hospital Haukeland HF, University Hospital in the North of Norway HF, Oslo University Hospital HF, University Hospital Trondheim HF) identified and mailed information about the study and questionnaires. Inclusion criteria were:

- Undergoing medical treatment for NET
- Tumors restricted to the GI tract
- Ability to read, speak and write in Norwegian
- Age  $\geq$  18 years

Exclusion criteria were:

- Terminally ill
- History of radical surgery that may have been curative
- Diagnosed with cognitive or mental dysfunction

Of two hundred and sixty-one patients who were diagnosed and treated for NET , 236 patients were eligible in June 2007. Twenty-five patients met the exclusion criteria, which were assessed by their physicians. One hundred ninety-six (83%) patients returned the questionnaire after one reminder. Consent was assumed with return of the survey.

#### *General Population Sample*

The data from the Norwegian Survey of Living Conditions served as controls and were collected in 2002 and are available through *Statistics Norway* [153]. We collected demographic data and data from the Quality of life (SF-36) survey. The Norwegian Social Science Data Services mailed the survey to a random sample of individuals over 18 years of age [153]. Six thousand eight hundred and twenty-seven individuals (age range 15 – 103 years) answered the questionnaire (SF-36) during the period of October 2002 to February 2003, a response rate of 66 %. Respondents in the same age range as the patients with NET (23 – 85 years) were included (n =5152).

#### *Participants for the exploratory study (Paper III)*

The 26 week exploratory study was employed in Phase II and used a single-group pre- test post-test design at three different assessment points (T1-T3): two weeks before (T1), two weeks after (T2) and 6-months after (T3) enrollment in a patient education intervention.

The exploratory study took place at three of the five Norwegian regional University Hospital NET centers (Bergen, Trondheim and Oslo). The sample included NET-patients. Enrollment occurred at the clinic where the patients were referred. Additional inclusion criteria compared to the cross sectional survey was that the patients had to be diagnosed with NET within the last 24 months.

The patients were mailed information about the study and a questionnaire and a stamped envelope after informed consent was given to the NET centers. The patients were sent questionnaires by mail from the referral hospital with a stamped envelope to return documents. Those who did not return the questionnaire within 2 weeks received a reminder letter by mail.

The study was conducted from September 2005 to December 2007.

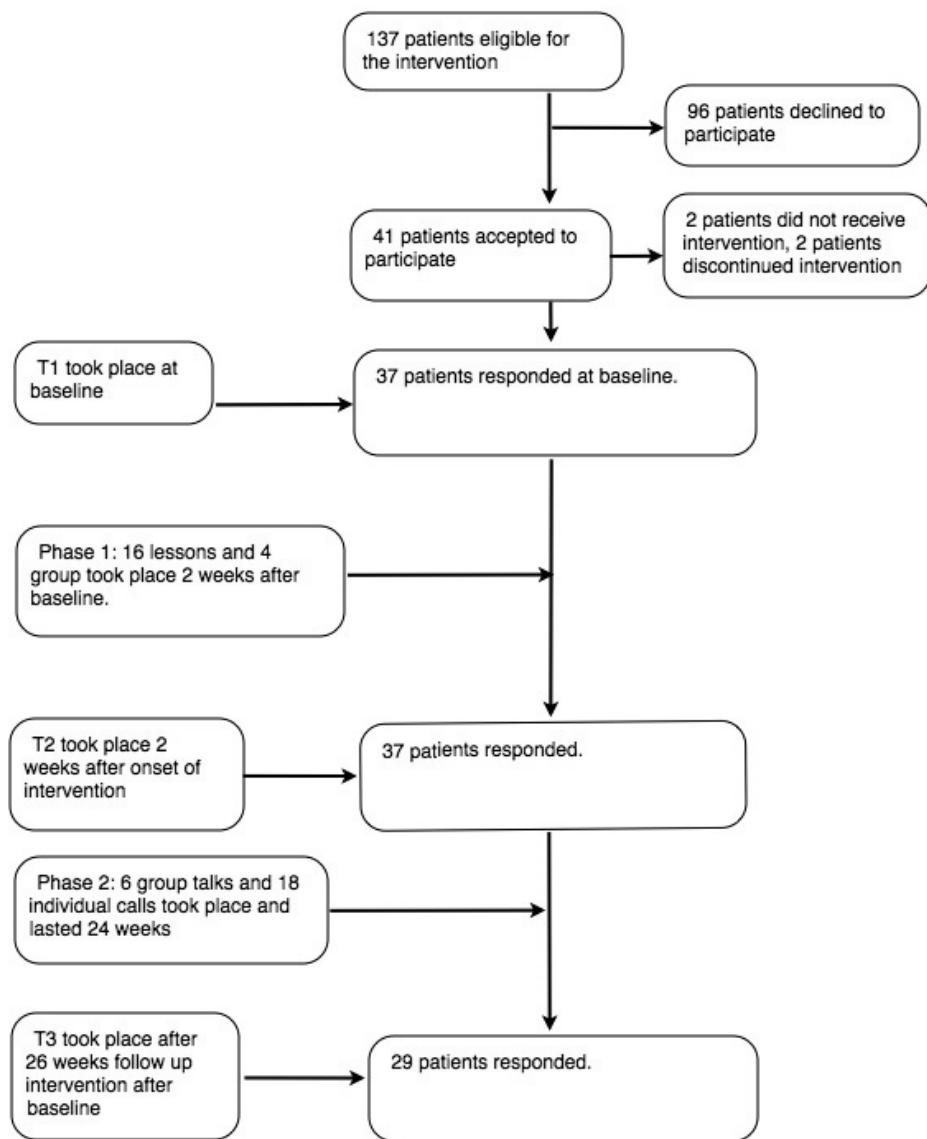
### *Participants*

One hundred-and-thirty-seven ( $n = 137$ ) subjects met inclusion criteria. Of these, 96 ( $n = 96$ , response rate 70%) declined to participate. No data were collected from those who declined to participate.

Forty-one patients with NET were enrolled ( $n = 41$ , response rate 30%, 51% male). Two patients dropped out and two died prior to T2. Measures were completed two weeks after start up of the intervention (T2). Thus, 37 patients completed the 26 weeks intervention. Twenty-nine patients ( $n = 29$ , response rate 71% of the enrolled patients) returned the questionnaire at six months following the patient education intervention start up (T3) due to lost to follow up (see Flow diagram).



Flow diagram for the participants of the intervention and the time of test points



## 6.2 Patient education intervention

### The 26 Week Intervention

The intervention was inspired by Bandura's Social Cognitive Theory focusing on self-efficacy [90]. Social cognitive theory is based on the assumption that patients are the principal agent in shaping and responding to environmental conditions, and consequently, are able to acquire new skills and competencies, take part in their self-development, and adapt as needed. Focusing on the patients' strengths and capacities to utilize supportive relationships and think critically may enable the patients to cope with cancer related-stress and thus improve HRQoL [61].

Strategies for enhancing self-efficacy incorporate 1) *Mastery experience* which includes considering and utilize previous successful performances; 2) *Vicarious experience*, or modeling others, involves watching someone else in a similar situation who has had success in performing activities; 3) *Verbal persuasion* is encouraging patients to believe that they have the ability to achieve their goals and; 4) *Strengthening physical and psychological state* includes teaching the patients about their disease and psychological reactions to severe illness [32;33].

The intervention consisted of 10 sessions over a period of 26 weeks. The intervention consisted of lectures, group discussions and individual telephone calls in two phases (Intervention Table). All group discussions and individualized telephone calls were facilitated by a total of six nurses specialized in patients with NET. The first phase took place over four consecutive days and included lectures and group discussions. All patients participated in a 45-minute orientation session to introduce them to study protocols, goals, and the principles of general self-efficacy. During the introductory session, patients received a booklet containing the intervention protocol. During the next four days, 45 minute didactic sessions were conducted in the morning followed by a 60 minute group discussion. The purpose of the morning sessions was to improve the patients' knowledge of NET, side effects of medication and treatment and what to expect in the follow visits. In the afternoon, the patients underwent motivational training and goal setting exercises. Motivational training included empathetic guidance in goal-setting, specific and constructive questioning on patient priorities and, supporting constructive alternatives if barriers were encountered in setting goals. Writing goals and discussing how to best achieve goals based on previous

experiences accomplished mastery. The participants were instructed on ways to break down larger goals into smaller, weekly action plans that were measurable, realistic and attainable. Vicarious learning was modeled on other patients' successful self-care activities. In addition, the patients were trained on how to encourage each other in self-efficacy thoughts. A strategy to strengthen physical and physiological state was accomplished through information about NET. Content of information included knowledge of the illness trajectory and how to respond on symptoms. This facilitated the implementation of appropriate actions when needed and avoided setbacks. In addition, patients learned when it was appropriate to contact their physician or oncology nurse.

The second phase lasted for 24 weeks and included 6 follow – up group discussions and 18 individual telephone calls. All group discussions and individualized telephone calls were facilitated by a total of six nurses specialized (nurse) in patients with NET. Patients met at the NET centers at their regional hospitals for 90 minutes group discussion every four weeks. Four to six individuals took part in each group discussion. Weekly telephone calls (45 minutes) were conducted between the group meetings. Motivation and training was led by the nurse who assisted patients in achieving their goals by giving positive feedback and focusing on their strengths and success. The nurse also encouraged patients to share previous successful experiences with each other as well as taking part in social activities in order to build supportive relationships.

To ensure adherence to the intervention, the principal investigator trained the nurses on how to apply the principles of self-efficacy during three 45-minutes sessions and in additional booster sessions. The nurses performed a critical self-evaluation after every group session by reflecting on how the four principles of self-efficacy had been discussed and supported and how they used the principles in clinical practice during the group sessions and individual talk. Reflections were then logged for follow-up discussion with the principal investigator. In addition, the principal investigator was available for counseling the nurses at any time if the nurses needed guidance. The nurses received a training booklet to refer as needed. The booklet contained information about the purpose with the group session, and how to prepare for the group session. The booklet also contained information about social cognitive theory, how to utilize the principles of self-efficacy, and offered suggestions for the group sessions. Finally, the booklet included action-

plans and how to use them.

The Intervention Table is included in the thesis to illustrate the main topics of the patient education intervention.

**Intervention Table.** Description of the phases, the content and the responsible persons in the 26-week patient education intervention

Phase	Content	Responsible Person	
<i>Phase 1</i> <i>Week 1</i>	Introduction (1 x 45 min)	<ul style="list-style-type: none"> <li>• Study protocol, information about goal setting and information about principles of self-efficacy. The patients received a booklet with the intervention protocol to take home.</li> </ul>	<ul style="list-style-type: none"> <li>• The principal investigator</li> </ul>
	Discussion (16 x 45 min)	<ul style="list-style-type: none"> <li>• Disease specific knowledge</li> <li>• Psychological reactions on severe illness</li> <li>• Social rights</li> <li>• Physical activity</li> <li>• Nutrition</li> </ul>	<ul style="list-style-type: none"> <li>• Physician</li> <li>• Psychologist</li> <li>• Social worker</li> <li>• Physiotherapist</li> <li>• Nutritionist</li> </ul>
	Group sessions (4 x 60 min)	<p><i>Discussions based on the principles of self-efficacy in order to enhance problem solving strategies:</i></p> <ul style="list-style-type: none"> <li>• <i>Mastery experiences:</i> Utilize previous, optimistic and positive experiences and evaluate their written goals</li> <li>• <i>Vicarious experiences:</i> Utilize significant other's optimistic and positive experiences in the coping process</li> <li>• <i>Verbal persuasion:</i> Encourage participants to believe they could achieve their goals, share experiences, and support each other's coping strategies</li> <li>• <i>Strengthen physical and psychological state:</i> Utilize disease specific knowledge and enable the patients to recognize disease specific symptoms and when to contact health care for assistance</li> </ul>	<ul style="list-style-type: none"> <li>• Nurse</li> </ul>
<i>Phase 2</i> <i>Week</i> <i>2 – 26</i>	Group sessions (6 x 90 min)	<p><i>Discussions based on the principles of self-efficacy in order to enhance problem solving strategies:</i></p>	<ul style="list-style-type: none"> <li>• Nurse</li> </ul>
	Individual telephone calls (18 x 30 min)	<ul style="list-style-type: none"> <li>• <i>Individual support based on the principles of self-efficacy:</i> follow up of weekly goals and reflective notes</li> </ul>	<ul style="list-style-type: none"> <li>• Nurse</li> </ul>

## 6.3 Measures

### 6.3.1 Demographic and disease related variables

The following demographic data were obtained by questionnaire: *age* (continuous variable in years), *gender*, *marital status*, *education* (primary: < 10 years, high school: 10-13 years, secondary education:> 13 years), working status (full-time, part-time, retired), income (continuous variable in Norwegian currency; NOK), time since diagnosis (continuous variable), symptom frequency (yes/no, diarrhea, fatigue, nutrition intolerance, flushing, restlessness, fluctuation in mood, and individually specified symptoms).

### 6.3.2 Short form 36 (SF-36)

The SF-36 was developed in the United States as part of the Medical Outcomes Study to assess satisfaction with medical care [78]. The questionnaires consist of 36 items scored on Likert type scales [78]. The instrument measures eight dimensions of health including: physical function, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitation, and mental health. Item scores are transformed into scales ranging from 0 to 100. Higher scores indicate better subjective health status. The eight scores may also be transformed into one mental and one physical component scores. The mental component scores of SF-36 are based on scores for vitality, social functioning, emotional role limitations and mental health. The physical component scores are based on the physical function, physical role limitations, bodily pain and general health subscores [78;154]. The questionnaire has shown satisfactory reliability, validity and responsiveness to changes in health status across a broad spectrum of cancer patients and other patient populations, including Norwegian populations [155]. The reliability of the scale estimated by Cronbach's alpha is shown in Table 3.

### 6.3.3 Impact of Event Scale

The impact of event scale (IES) is a questionnaire developed by Horowitz et al that assesses current subjective stress related to a specific event [88]. The measurement is sensitive to change over time and thereby useful in assessing progression of stress. A modified version of Impact of Event Scale was used to measure current subjective stress specifically related to NET. The IES consists

of 15 items, 7 of which measure intrusive symptoms (invasive thoughts, nightmares, invasive feelings and imaginary), 8 tap avoidance symptoms (numbing of responsiveness, avoidance of feelings, situations, ideas) and combined, provide a total subjective stress score [88].

Respondents are asked to rate the levels of stress on a six point Likert scale ranging from 0 (never) to 5 (often) according to how often each has occurred in the last week. The total score ranges from 0 to 75 and a higher score indicates a higher impact from stress. The IES has been translated into different languages, and has shown satisfactory reliability, validity, sensitivity and responsiveness [88], including in Norwegian cancer populations [8;10]. The reliability of the scale estimated by Cronbach's alpha is shown in Table 3.

#### 6.3.4 General self-efficacy

The General Perceived Self-Efficacy Scale (GSE) is a questionnaire developed by Schwarzer at the Freie Universität in Berlin [96]. The GSE Scale is a ten item scale in which people judge how able patients are [156]. Each item is scored from one (quite wrong) to four (quite right). The summary score ranges from 10 to 40, where the highest score indicates high self-efficacy. The scale has demonstrated validity and reliability across cultures [96;156]. The reliability of the scale estimated by Cronbach's alpha is shown in Table 3.

#### 6.3.5 Interpersonal Support Evaluation List

The Interpersonal Support Evaluation List (ISEL) was developed by Cohen & Hoberman [86] and was intended to be used with a general population sample. King and colleagues modified and used the measure in long-term recovery patients after coronary artery bypass surgery [157]. The questionnaire has five subscales; appraisal support, self-esteem support, group belonging, emotional closeness and tangible aid (Paper II). Also, an average total sum score may be used [86]. The items in the measure are scored from 1 (definitely true) to 4 (definitely false), where the highest score indicate high social support [86]. The reliability of the scale estimated by Cronbach's alpha is shown in Table 3.

### 6.4 Data analysis and statistical methods

Descriptive analyses (mean, median, percentages, SD, range) were performed to assess the characteristics of the respondents (Paper I, II, III) and outcome measures of stress, general self-

efficacy, PCS and MCS (Paper III). Chi-square tests were performed to examine for differences in categorical data and Analysis of Variance (ANOVA) were used to investigate differences in characteristics of the responders (Paper I and II). Post-hoc Bonferroni correction was performed in order to adjust the level of significance for the number of simultaneous comparisons of variables (Paper I). T-tests were performed in order to examine the differences in the means in the subscales of SF-36 across the samples. Effect size for differences in HRQoL between patients with NET and the general Norwegian population (Paper I) was calculated to assess the clinical relevance of the difference between the two samples. In addition, effect sizes for changes in stress, general self-efficacy and HRQoL (Paper III) was calculated to assess the clinical relevance of the changes of the variables. According to Cohen's classification for differences in means, a small effect size ranges from 0.2 to 0.49, a moderate from 0.5 to 0.79 and greater than 0.8 as a large [158]. Bivariate analyses (Pearson's  $r$ ) was used to investigate possible associations between continuous variables (Paper II) aiming to determine the strength and direction of the relationship between the variables; gender, age, marital status, education, disease duration, physical component scores, mental component scores, stress, social support and, general self-efficacy. Cohen guidelines suggest a small association to be  $r = 0.1$  to  $0.29$ , a moderate from  $r = 0.3$  to  $0.49$  and a large  $r = 0.50$  to  $1.0$  [159] (p. 79-81).

To be able to predict the value of the dependant variable HRQoL (mental and physical HRQoL) we described the relationship between a continuous, dependent variable and one or more (continuous or categorical) independent variable (predictors, explanatory variables or covariates) by performing multiple linear regression analyses (Paper II). The specified regression models were based on the assumption of associations identified by previous research. Selected demographic variables were used as possible confounders as well as social support, general perceived self-efficacy and stress. Mental and physical component scales of Health related quality of life was entered in the regression analysis as the two dependent variables.

Due to the small sample size, we constructed mixed effect models (individual growth models) to evaluate overall changes in stress, general self-efficacy and HRQoL from T1 to T3 (Paper III, Table 4). Mixed effect models integrate analysis of individual within-patient trajectories as well as differences across trajectories between patients [160]. This technique overcomes some of the limitations of traditional repeated measure analysis of variance (ANOVA), such as the



requirement of balanced data with all individual parameters measured at each of the three time points. The analysis does not require list-wise detection of missing data. These analyses enabled estimation of average within-patient change over time in our primary outcome measures of stress, general self-efficacy and HRQoL as well as the rate of change across patients. In all analyses, we accounted for age, gender, symptoms and co-morbidity. For each of the explanatory variables effects of interaction with time were evaluated separately. Gender, as well as baseline age and co-morbidity, were held constant across time and were considered fixed predictors in our models. The presence of one or more symptoms changed over the three points in time and was included as time variables. Given the small sample size, we used time (T1, T2, T3) as a linear variable. As average change in stress deviated from linearity, we also ran the model using time as a categorical variable, which led to the same conclusion.

Mixed-effect models differentiate the total variance of the outcomes measures into within-patient variance and between-patient variance. Within-patient variance includes random error as it varies across the three time points. Between-patient variance indicates the variation in baseline (intercept) and the variation in rate of change (slope) between patients. In addition, the covariance between intercept and the rate of change is estimated and may, for example, indicate higher rate of change in patients with low baseline scores [160].

The growth curve modeling for each of the outcome measures, stress, general self-efficacy and HRQoL in Paper III consisted of two steps. In the first step, between-patient differences in baseline (T1) scores were modeled, i.e. the random intercepts, estimating the average within-patient change as well as the difference in rate of change across patients (random slope) (Paper III, Table 3). In the second step, the extent to which the specified explanatory variables; age, gender, co-morbidity and symptoms, accounted for any differences in rate of change in each of the three outcome variables were assessed. For each of the explanatory variables effects of interaction with time was evaluated. Gender, as well as baseline age and co-morbidity, was held constant across time and was considered fixed predictors in our models. The presence of one or more symptoms was considered as a time varying explanatory variable. Average change in stress deviated from linearity, thus, we ran the model using time as a categorical variable, which led to the same conclusion.

The level of statistical significance was set at 0.05 for all analyses. Cronbach's coefficient was

assessed to confirm internal consistency reliability for all measurements. Acceptable levels were considered to be  $> 0.70$  [159]. Effect size (ES) of differences between the sample of patients with NET and the general norm population and the changes in stress, general self-efficacy and HRQoL were calculated in order to estimate and interpret clinical meaningful changes. Effect size was computed as differences in mean scores divided by the pooled standard deviation [159]. SPSS version 15 was used for the statistical analysis.

## 6.5 Power analysis

A RTC design was planned for Phase II of this study. Power analyses were conducted in order to determine sample size. Power to detect a difference between the intervention and control groups was calculated to be 3 points for SF-36 mental component scores, mental health (MH) and social functioning (SF) based on results from Dysvik et al [161]. The analyses in the study were repeated t-tests. Although we may suggest that the eight SF-36 subscores will change differently following the intervention, researchers indicate that changes of 5 points may be considered clinically important [71;161]. Seventy-three patients are needed in the present study given a standard deviation (SD) of 15, a power of 80 % and a significance level of 0.05 %. The estimation of the power matches an effect size of 0.33, which matches the changes of MH and SF in Dysvig's study. However, identification of patients was not possible due to the lack of a consistent national identification code for the diagnosis of NET. Although codes for identification of diagnosis related group (DRG) are used for billing in most all regional hospitals, the DRGs' for Norwegian patients with NET are not consistent. In addition, due to the lack of concentration of patients in the country and the limited number of patients with NET meeting eligibility criteria, a randomized controlled design was not feasible. Thus a single group, exploratory design was employed to evaluate the changes in stress, general self-efficacy and HRQoL (Paper III). A convenient sample was chosen for the study. We identified 137 patients through a period of two years and 41 patients were enrolled in the study. For the cross sectional survey (Paper I, II), we decided to include all the identifiable patients from the NET centers nationwide. As the inclusion criteria in the cross sectional surveys had no limitation for the disease duration, we ended up with 236 eligible patients and 196 patients responded.

## 6.6 Ethical considerations

Research involving humans requires a careful consideration of the procedures to be used in protecting the rights of the participants. Ethical principles in research include the principles of respect for human dignity, justice and beneficence. Exposure to emotional questions may be a distressing experience. An adverse effect of the study could be that the patients were asked emotional questions, in particular questions in the stress and general self-efficacy instrument. The participants in this study may be considered a particularly vulnerable population as they often suffer, experience adverse symptoms as well as stress. In order to avoid asking vulnerable patients to participate in the study, the patients' conditions were discussed with the physician specialist to ensure that the patients were not too critically ill. We followed the Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects [12], that requires that the well-being of human subjects must outweigh scientific interests. In addition, the nurse had the possibility of contacting the physician or the researcher responsible if they detected symptoms of stress related to the burden of attending the study.

The Regional Ethics Committee in Health Region II (South) of Norway (S-05156) and the Norwegian Social Science Data Services approved the study (1823) and (2005/AS/PVO-FO-001). Consent from the patients was assumed with the return of the survey in the cross sectional study, and patients were informed that they could contact the project investigator or more information. Patients who met the inclusion criteria in the exploratory study returned a signed informed consent.

The patients received information about the study and they were invited to question the project investigator and the nurses at enrollment. To enhance informed consent the project investigator took extra time to explain the project, clarify the patients' understanding of the booklet and emphasize the voluntary nature of the research. The project investigator also gave repeated reminders of the right to withdraw or to stop answering the questionnaires throughout the study. Two patients withdrew after enrollment.

Response burden may be of particular relevance to patients with NET in that they experience fatigue and/or weakness. Thus, we considered the amount of instruments as well as the importance of brief questionnaires in selecting instruments. In addition, the questionnaires may cause psychological distress by reminding patients of their health problems. The participants in

the study were instructed to contact health care personal if they needed support during the study. We provided contact through a particular telephone number answered by a nurse from the intervention team. No participants reported fatigue or distress from participating in the study.

## **7. Results**

### **7.1 The characteristics of the study sample**

Characteristics of socio demographic and disease specific variables used in the cross sectional survey (Paper I, II) and exploratory study (Paper III) are presented in Table 1. Description of the average Mental (MCS), Physical (PCS) Component scores and subscores of SF-36, Stress (IES), Social support (SS), General Self-efficacy (GSE) and standard deviation (SD) of the participants in Paper I, II (n = 196) and the baseline data of the subjects in Paper III (n = 41) appear in Table 2. Description and reliability scales and subscales used when evaluating cross sectional data (Paper I, II) and longitudinal explorative data (Paper III) are presented in Table 3.

**Table 1. Characteristics of sociodemographic and disease specific data used in the cross sectional survey (n = 196) (Paper I,II) and the longitudinal survey (n = 37) (Paper III)**

Demographic and disease specific variables	Paper I,II	Paper I,II	Paper III	Paper III
	N (%)		N (%)	
Disease duration				
Years mean (range)		4.8 ( 0-23)		
Months mean (range)				13 (1-24)
Gender				
Male	97 (49.5)		17 (46)	
Female	99 (50.5)		20 (54)	
Age mean	65 (33-85)		60 (61, 36-80)	
Marital status				
Single, divorced, widowed	49 (25)		9 (24)	
Married, cohabitation	147 (75)		28 (76)	
Employed				
Working <sup>a</sup>	54 (28)		13 (38)	
Retired, pension <sup>b</sup>	97 (50)		21 (62)	
Education years				
< 10 years	72 (41)		10 (27)	
10-13 years	47 (27)		11 (30)	
>13 years	57 (32)		16 (43)	
Income NOK	246 000 (229 000, 0-780 000)		542 000 (303 000, 100 000 – 4 500 000)	
Treatment				
Interferon	32 (16)			
Somatostatin analogue n (%)	102 (52)			
Combination of different somatostatin analogues	17 (11)			
Chemotherapeutics n (%)	10 (5)			
No treatment	37 (19)			
Symptoms frequently <sup>c</sup>				
Diarrhea	98 (50)		13 (36)	
Fatigue	97 (49)		13 (36)	
Nutrition intolerance	9 (5)		33 (91)	
Flushing	23 (12)		7 (19)	
Restlessness	38 (19)		7 (19)	
Fluctating mood	41 (21)		11 (30)	
Others	24 (12)		3 (8)	
Co-morbidity (numbers)	179 (91)		11 (31)	
Mean (SD/range)		3.4 (2, 0 – 11)		0.5 (0.5, 0 – 5)

**Table 2. Mental (MCS), Physical (PCS) Component scores and subscores of SF-36, Stress (IES), Social support (SS), General Self-efficacy (GSE) and standard deviation (SD) for Paper I, II, III.**

Paper	I, II	III, Baseline Mean (SD)	III, T2 Mean (SD)	III, T3 Mean (SD)
<b>SF-36</b>				
MCS	39.6 (11)	43.3 (9.3)	43.9 (10.7)	43.7 (12.1)
PCS	45.9 (11.4)	42.1 (10.1)	44.8 (8.5)	45.7 (9.1)
<b>SF-36</b>				
PF	87.3 (19)			
RP	77.7 (37)			
BP	74.2 (26)			
GH	78.8 (20)			
VT	60.9 (20)			
SF	86.8 (21)			
RE	84.9 (32)			
MH	80.3 (15)			
<b>IES</b>				
IES	24.3 (16)	26.5 (13.6)	23.3 (14.3)	24.1 (14.8)
<b>SS</b>				
SS	3.1 (0.5)	3.3 (0.5)	3.3 (0.6)	3.3 (0.5)
<b>GSE</b>				
GSE	29.9 (5.5)	31.2 (3.2)	32 (3.8)	32.3 (3.7)

Mental and physical Components score: Standardized Mean50, SD = 10

Abbreviations: SF-36 Subscale scores PF: physical functioning; RP: role physical ; BP; bodily pain; GH; general health; VT: vitality; SF: social function; RE: role emotional; MH: mental health.

SF-36 subscale score = 0 -100,

IES: Score 0-75

SS: Score: 0-4

GSE: Score: 10-40

Higher scores indicate better PCS, MCS, GSE and SS and SF-36 health related quality of life

Lower score indicate less stress (IES).

**Table 3. Description and reliability of scales and subscales used in the cross sectional study (N=196) and the exploratory study (N=39)**

Instrument	Scales	Items	Total range (mean)	Chronbach's alpha		
				Paper I	Paper II	Paper III
Health Related Quality of Life (SF-36, 8 subscales)	Physical Function	10	0-100	0.93	0.93	
	Role Physical	4	0-100	0.90	0.90	
	Bodily Pain	2	0-100	0.92	0.92	
	General Health	5	0-100	0.78	0.78	
	Vitality	4	0-100	0.83	0.83	
	Social Functioning	2	0-100	0.82	0.82	
	Role Emotional	3	0-100	0.86	0.86	
	Mental Health	5	0-100	0.88	0.88	
Physical Health Summary Score (SF-36)		21	(50)		0.93	0.93
	Physical Function	10	0-100			
	Role Physical	4	0-100			
	Bodily Pain	2	0-100			
Mental Health Summary Score (SF-36)	General Health	5	0-100			
	Vitality	4	0-100			
	Social Functioning	2	0-100		0.89	0.87
	Role-Emotional	3	0-100			
	Mental Health	5	0-100			
General Self Efficacy (GSE)	Total summary	10	10-40		0.87	0.84
	Appraisal Support	6	1-4		0.76	
Perceived Social support (ISEL)	Self-esteem Support	6	1-4		0.63	
	Group belonging	6	1-4		0.69	
	Emotional	6	1-4		0.67	
	closeness	6	1-4		0.91	
	Tangible Aid					
Stress (IES)	Intrusion	7	0-35		0.86	0.83
	Avoidance	8	0-40		0.83	0.79

## 7.2 Sample characteristics for the cross sectional studies (Paper I, II)

The main age of the responders were 65 years (range 33 – 85), and the percentage of men was 49.5. The median duration since diagnosis of NET was 4 years (range = 0 to 23), 68 % of the patients had a high school education, 75 % were married or living with partner and 50 % were retired or were receiving a disability pension (Table 1). The mean scores for stress was 24.3

(SD = 16), for social support 3.1 (SD = 0.5) and for general self-efficacy was 29.9 (SD = 5.5) (Table 2).

### 7.2.1 Health related quality of life among patients with neuroendocrine tumor compared with the general Norwegian population (Paper I).

The aim of the paper was to describe the HRQoL among a nationwide sample of patients with NET compared to the general Norwegian population. Of the 196 patients with NET, better physical functioning was associated with lower age, educational levels above 16 years and working part time or more. Also, patients younger than 60 years of age and those working part-time or more demonstrated statistically significant fewer role limitations physical compared with those above 60 years of age and those who were retired or pensioned (Paper I, table 1).

Results showed that patients with NET scored significantly lower on all SF-36 subscales ( $P < 0.001$ ) except for bodily pain ( $p = 0.017$ ) than the general Norwegian population. The largest difference were in general health ( $d = 0.84$ ), role limitations physical ( $d = 0.57$ ) and vitality ( $d = 0.51$ ) (Paper I, Table 3).

### 7.2.2 Associations between stress, social support, general self-efficacy and HRQoL in patients with NET (Paper II).

This paper aimed to explore the association between stress, general self-efficacy, social support and HRQoL. We also evaluated if general self-efficacy and social support mediated the association between stress and HRQoL.

The main effect model that evaluated the association between general self-efficacy, social support, stress and HRQoL showed that higher stress was associated with poorer mental HRQoL (Beta = -0.54,  $p < 0.001$ ). Higher social support (Beta = 0.41,  $p < 0.001$ ) and higher general self-efficacy (Beta = 0.49,  $p < 0.001$ ) were related to better mental HRQoL (Paper II, Table 3).

Additionally, in a similar model for physical HRQoL, stress was negatively related (Beta = -0.20,  $p = 0.01$ ) (Paper II, Table 3) whereas general self-efficacy was significantly associated with better physical HRQoL (Beta = 0.37,  $p = 0.03$ ).

Evaluation of the mediating effect of social support on the relationship between stress and mental HRQoL is shown in Paper II, Table 3, Model 1. Separately, general self-efficacy and



social support partly mediated the relationship between stress and mental HRQoL. In the combined model, stress and general self-efficacy explained a higher variance than the stress-social support model, indicating that social support does not contribute to greater variance in combination with general self-efficacy (Paper II, Table 3). Results demonstrated that general self-efficacy mediates the influence of stress on mental HRQoL. However, an independent association between stress and mental HRQoL remained.

A similar model for physical component score is shown in Paper II, Table 4. Stress was slightly reduced compared with the main effect model. The association between stress and physical component scores remained statistically significant. Hence, there was no evidence for a modifying role of social support or general self-efficacy on the stress-physical component score relationship.

Table 4 is included in this thesis to demonstrate the bivariate correlations between the background, the independent variables and the outcome variables.

**Table 4. Bivariate Pearson's correlations of gender, age, living with partner or not, education, disease duration, PCS and MCS, IES, ISEL and GSE. (n = 165).**

	1	2	3	4	5	6	7	8	9	10
1 Gender	1									
2 Age	-.11	1								
3 Living with partner or not	-.18 <sup>†</sup>	-.16 <sup>*</sup>	1							
4 Education	-.25**	-.21**	.06	1						
5 Disease duration	.11	.06	-.03	-.16	1					
6 PCS	-.10	-.31**	.08	.26**	-.18 <sup>†</sup>	1				
7 MCS	-.04	-.00	-.04	.01	-.12	.10	1			
8 CRS	.02	.09	.02	-.13	.04	-.24**	-.53**	1		
9 SS	.08	-.26**	.11	-.18*	-.15	.24**	.35**	-.31**	1	
10 GSE	-.02	-.23**	.04	.11	-.12	.24**	.47**	-.18 <sup>†</sup>	.38**	1

\*\* Correlation is significant at the 0.01 level

\* Correlation is significant at the 0.05 level

**Abbreviations:**

PCS: Physical component scores

MCS: Mental component scores

CRS: Impact of event scores

SS: Interpersonal social evaluation list

GSE: General self-efficacy

### 7.3 Sample characteristics for the exploratory study

Those who completed the intervention (N = 37) (Flow diagram) ranged in age from 36 to 80 years and women and men were nearly equally represented (46% and 54% respectively). The majority were currently married or cohabitants (76 %). The participants were relatively well educated. Seventy-three percent had an education level of high school or more. Thirty-five percent were currently working and 56 % were retired. The average income was high (542 000 NOK). Thirty-six patients (89 %) had a disease duration of more than 6 months. Food intolerance was the most frequent reported symptom (89 %) and flushing and restlessness were the least reported symptoms (19 %). Twenty-two percent had co-morbid conditions such as arthritis, breast cancer and myocardial infarction. Of the 41 patients, only 29 subjects completed all three measurements (T1 – T3). Except for those patients who died, the reasons why individuals did not participate in the intervention were unknown. A comparison of demographic and medical characteristics between those who completed the intervention and those who withdrew showed no significant differences in age ( $p = 0.90$ ) and gender ( $p = 0.51$ ).

#### 7.3.1 Patient Education to Improve Stress, General Self-efficacy and Health Related Quality of Life in Patients with Neuroendocrine Tumors – a Pilot Study (Paper III)

The objective of this paper was to explore changes in stress, general self-efficacy and HRQoL in patients with NET following a patient education intervention. Data collected from 37 patients at T1, T2, and T3 were used to evaluate changes in stress, general self-efficacy and HRQoL at baseline (T1), two weeks post-baseline (T2) six months following the intervention (T3).

Description of changes in stress, general self-efficacy and mental and physical HRQoL at T1, T2 and T3 are shown in Paper III, Table 3.

Baseline scores on the SF-36 mental component were 43.3 (SD = 9.3), on SF-36 physical component were 42.1 (SD = 10.1), on stress (IES) were 26 (SD = 13.6) and for general self-efficacy 31.2 (SD = 3.2) (Paper III, Table 3). We estimated the overall change in outcome

measures from T1 to T3. The patients reported significantly improved mean scores over time for stress (-2.10,  $p < 0.01$ ), general self-efficacy (+0.71,  $p < 0.05$ ) and for the physical component score (+3.09,  $p < 0.01$ ) (Paper III, Table 4). The results suggest a significant improvement in stress, general self-efficacy as well as physical status following a patient educational intervention. There was no linear effect of time for the mental component scores (0.36;  $p > 0.05$ ) (Paper III, Table 4). The change in general self-efficacy differed significantly between patients (random slope = 2.5;  $p < 0.01$ ), but the changes in physical component score did not vary between patients (random slope = 4.11;  $p < 0.05$ ). There were significant differences in stress between patients (random slope = 9.5,  $p < 0.05$ ) but the changes did not vary within patients (random slope 36.9,  $p < 0.05$ ). Women had significantly better physical health ( $B = 1.65$ ,  $p = 0.05$ ) at baseline than men (Paper III, Table 4). In addition, the presence of co-morbid conditions and one or more symptoms at baseline were negatively associated with physical component scores ( $B = -8.75$  and  $SE = 2.5$ ;  $B = -4.86$  and  $SE = 1.6$ ) following a patient education intervention.

#### 7.4 Summary of results

In summary, our results support previous research on evidence for associations between demographic and background variables and subscores of HRQoL. The results of Paper I showed that those with lower age had better physical functioning and less role limitations than those who were older. In addition, physical functioning was higher in patients with more than 16 years of education than those with less education than 16 years. Moreover, full time and part time workers had significantly better HRQoL than those who did not work. Disease duration was not associated with with HRQoL. Finally, results provide new knowledge in that patients with NET have poorer HRQoL than the general population.

Overall results included in Paper II, showed that age and gender had little influence on mental and physical HRQoL. Patients with co-morbidity and symptoms had poorer physical component scores than those no co-morbidity and symptoms. Stress had a major negatively influence on mental HRQoL, whereas social support and general self-efficacy influenced mental component score positively. Results support the importance of social support and general self-efficacy as a mediator between stress and mental HRQoL.

Results from the exploratory study reported in Paper III suggest that an educational program might be helpful for patients suffering from NET. The results indicate that patients experienced less stress, improved levels of general self-efficacy, and improved their physical status six months following a patient education program. In addition, those without present comorbidities and those with no symptoms reported better physical functioning compared to those with more than one comorbid conditions and those with more than one disease related symptom.

## **8. Discussion**

### **8.1 Methodological considerations**

#### **8.1.1 Design**

Random assignment to experimental or control groups was planned for this study. However, it became clear that this would not be possible due to the lack of a consistent national identification code for the diagnosis of NET. In addition, the scattered geographic distribution of the limited number of patients who agreed to participate in the study made it impossible to deliver the intervention to a larger sample. Therefore, we combined a cross sectional design (Paper I, II) with a prospective, longitudinal, exploratory design (Paper III).

The main aim of the cross sectional survey was to describe HRQoL among a nationwide sample of patients with NET compared with a general Norwegian population (Paper 1) and to evaluate associations between stress, general self-efficacy, social support and HRQoL (Paper 2). Cross sectional studies are appropriate in describing the status of a phenomenon or describing relationships among phenomena at a fixed point of time [80] such as HRQoL in patients with NET compared with the general norm population and psychosocial factors related to HRQoL. The correspondence in background variables between this study and previous published studies in patients with NET [47;56;121] as well as our large sample size in the cross sectional study are important. Also, 196 of 256 eligible patients consented to participate (paper I and II) representing 83 % of the national population of patients diagnosed with GI-NET at that time. This indicates that our findings have strong external validity. However, the sample was not large enough to determine causal relationships through path analysis.

The main aim of the exploratory study was to evaluate changes in stress, general self-efficacy

and HRQoL among patients with NET following a patient education intervention (Paper III). However, a single group design and small sample size were weaknesses of the study and may cause threats to the study validity because the lack of control group and representativeness. Nevertheless, the exploratory design allowed us to study the dynamics of phenomenon over time [80]. Attrition was another limitation in the study and is especially great when the length of time between points of data collection is long [80]. The present study lasted for 6 months and 26 of 39 patients responded at T3 (attrition 33 %). Although there is no absolute standard for acceptable attrition rates, biases are usually of concern if the rate exceeds 20 % [80]. The small sample in this study resulted in low power, thus increasing the risk of type II errors, i.e. failing to demonstrate statistically significant results even though there is an association between the variables in the population from which the sample is drawn. The characteristics of the patients who dropped is important to know [162] (p. 302), and the enrollment flow diagram shows an overview of participants and the number of dropouts at each point in time. We do not know why patients dropped out of the study except for those two who died. Three men and four women dropped out and the characteristics of the dropouts suggest that they were younger than of the sample. Such high withdrawal rate may be a limitation and may decrease the internal and external validity of our findings [80].

Living with a chronic disease may be experienced as a process (illness trajectory) consisting of regressive steps, with acute, stable and downward phases [54]. Patients with NET may report different HRQoL because they are at different points in their illness trajectory at the time when measurements take place. A longitudinal, RTC would strengthen internal validity by controlling for the possible confounders of individual characteristics, disease progression, treatments, and settings [80].

### 8.1.2 Sample size and representativeness

The sample of the cross sectional, descriptive survey (Paper I, II) consisted of patients with NET from a nationwide population. Cross sectional surveys are appropriate for describing the status of a phenomena or for describing the relationship among phenomena at a fixed point of time [80]. However, a methodological challenge of our survey was to collect data from a representative sample. Because of the lack of codes for identification of the diagnosis related

group, we were dependent on the physicians in the NET centers and their willingness to identify patients in databases based on different search terms. However, the different NET centers had their own identification codes for patients with NET and the patients were identified on that basis. Given the small sample and low power, we were unable to detect small effects which are common in interventional research [71]. Thus, we are cautious in interpreting changes in stress, general self-efficacy and HRQoL in patients with NET. A convenience sampling may have biased our sample in the exploratory study (Paper III) towards subject with less stress, higher general self-efficacy and HRQoL. As the mean values of stress were of a level of a small to medium degree we may indicate that the levels of stress was not so high that it activated the avoidance behavior which would make them less likely to approach the patient education intervention, but still enough to stimulate the initiative to participate the intervention. In addition, the necessitation of a single group design we could not explain the causation of the changes because we had no control group.

### 8.1.3 The Patient Education Intervention

The key goal for the patient education intervention was to help NET-patients strengthen their own competence/capacity and self-efficacy and to be able to take part in their self-development, adaptation and self-renewal over time. There were several strengths of the patient educational program in this study. First, the intervention was designed in accordance with approved guidelines by Lorig [61] based on Bandura's social cognitive agent theory and the construct of self-efficacy [90]. Social cognitive theory is well established and has been used as a basis in interventions in patients with chronic diseases for decades, particularly by Lorig and her colleagues. Results from intervention studies carried out based on the principles of self-efficacy in patients with chronic conditions have shown significantly increased levels of self-efficacy[61]. In addition, interventions based on the theory of social cognitive theory and the construct of self-efficacy have shown improved quality of life in the general population [163]as well as in chronic ill populations [106;123]. Second, researchers claim that individuals patients were motivated by their own goal setting that may lead to healthier behaviors [32;33;61;90;164]. Third, eight nurses organized and carried out the patient educational program at the hospital units where the patients with NET were referred (paper III). One possible advantage of carrying

out a patient educational program by different nurses and not by the project investigator might be that the nurses may not bias the results such as the project investigator may do [165]. Furthermore, the nurses could counsel each other during the implementation. Finally, the nurses were writing logs after every group session and individual telephone call to ensure fidelity to the model of the principles of self-efficacy. The idea of this log was to help the nurses to reflect on the use of the four principles of self-efficacy.

One follow-up per week for 26 weeks was chosen as a reasonable dose and 26 weeks was chosen for the length of time for the intervention [68]. Changes in knowledge and self-development may occur within weeks, but behavioral and lifestyle changes require longer period of time [68]. Longer programs generally achieve more favorable outcomes [32;33].

The intervention groups started either in the spring or in the fall from 2005-2007. The first phase of the intervention took place at a residential rehabilitation facility for patients with cancer. Patients stayed for four days. Partners were welcome to take part in the lectures and separate group talks. The decision to utilize a cancer center which the patients had to travel and stay for four days, may have been a limitation. Some patients reported that the location of the first phase made it impossible for them to participate in the intervention. A strength of the intervention schedule was that patients could chose to participate either in the spring or the fall. In addition, the first phase of the intervention might have been burdensome because of the time commitment required and thus may have excluded eligible patients. For all the groups, the same person gave the lectures every time. The topics of the lectures were chosen in collaboration with the patients, physicians, nutritionist, social worker and nurses. In addition, content was based on evidenced-based knowledge of the disease, symptoms and knowledge of how a chronic disease may affect one's daily life.

#### 8.1.4 Instruments and research data

The measurements used in this study are well established, have shown acceptable psychometric properties, and have been used in studies with cancer patients internationally. Although there may be concerns as to whether the questionnaires may potentially harm participants, some of the patients told the special nurses after finishing the intervention and questionnaires, that their self-understanding had increased as a result of the intervention and that the intervention had been of

help in formulation their own thoughts and feelings throughout the intervention.

#### 8.1.4.1 Health Related Quality of Life

There are several advantages in using a well-established generic questionnaire to measure HRQoL. The SF-36 is widely used which made it possible to compare our results with previous research. It is also possible to determine the burden of disease in different groups of patients when comparing our research with previous research. We wanted to evaluate the health related quality of life as whole and not only factors related to the disease, thus, we chose to use the generic SF-36.

Norm based comparison was performed with an age and gender matched Norwegian sample that had used the same measurement for assessing HRQoL (Paper I)[153]. Norm based comparison may contribute to a better understanding of the research and clinical significance of our results.

#### 8.1.4.2 Impact of Event Scale

We used Impact of Event Scale (IES) to measure stress (Paper II, III). Marit Gilje Jaatun translated the questionnaire (personal email contact with Anniken Hamang Carlsson, 2009). This version was used in earlier Norwegian studies on psychosocial aspects of medical genetics [8] and operable breast cancer [166]. Thus, we considered it an advantage to use this version for comparisons. When comparing results with other studies, it is important to keep in mind that there exist another version of IES with different responses [88].

#### 8.1.4.3 Interpersonal Evaluation List

The Interpersonal Evaluation List (ISEL) was chosen to measure social support. Although the version has five subscales; appraisal support, self-esteem support, group belonging, emotional closeness, tangible aid, we decided to use ISEL as a single variable because we were limited in how many predictor variables we could enter into a regression model. Appraisal support, group belonging and tangible aid demonstrated satisfactory reliability whereas self-esteem support and emotional closeness scale showed lower satisfactory reliability in this sample.

#### 8.1.4.4 General Self-efficacy

The General self-efficacy questionnaire is constructed based on Bandura's theory. However, the



general version reflects various domains of functioning in which people judge how efficacious they are. The total summary of the general self-efficacy scale demonstrated satisfactory reliability in Paper II and III.

## 8.2 General discussion of the findings

The aim of this thesis is to expand the basis of knowledge on HRQoL with regard to patients with NET. In the first paper we described HRQoL in a nationwide sample of patients with NET compared with a general Norwegian population (Paper I). In the second paper, we evaluated how stress, general self-efficacy and social support were related to HRQoL and whether or not general self-efficacy and social support mediate the association between stress and HRQoL (Paper II). In the third paper, we evaluated the changes in stress, general self-efficacy and HRQoL following a patient education intervention based on the principles of self-efficacy (Paper III). The results demonstrated that patients with NET had poorer HRQoL than the general Norwegian population (Paper I), that being diagnosed with NET had a negative influence on HRQoL, and that social support and general self-efficacy played a mediation role in the relationship between stress and HRQoL (Paper II). Finally, we found that general self-efficacy, stress and physical HRQoL improved significantly following an intervention based on the principles of self-efficacy (Paper III).

### 8.2.1 Health related quality of life in patients with NET compared with the general Norwegian population

Findings shown in Paper I demonstrated different patterns with regard to the relationship between background and disease related characteristics and HRQoL in patients with NET (Paper I, Table 3), and they reported worse HRQoL outcomes compared to the general Norwegian population on all subscales of the SF-36 (Paper I, Table 4). Contrary to findings in Larsson's study [167], we found that the background characteristics associating with HRQoL were primarily due to age, gender, education and employment working situation. Variations in the influence of age across studies may be explained by differences in categorizing age [108]. Similar to our findings, Larsson et al [167] found no relationship between length of time since diagnosis and HRQoL measured by EORTC QLQ-C30. However, in another study, HRQoL was

shown to be better 5 years after diagnosis than it was closer to the time of diagnosis [168]. However, no conclusions can be drawn about the degree to which these categories are problematic or important.

After adjusting for background characteristics, our results are consistent with those found in Swedish [48] and two samples compared with American general populations [13;169]. In addition, patients with pancreatic neuroendocrine tumor (n = 44) demonstrated significantly lower MCS than the Italian general population, similar to our results. However, our results were inconsistent with findings of patients with multiple endocrine neoplasia1 (MEN1) relative to the Swedish population, except from the levels of general health and social functioning [47]. Results indicate that patients with NET represent a group with advanced cancer and that the majority of the patients with NET have metastatic disease (70 %) [53;170;171]. The largest differences in HRQoL between patients with NET responding in this study, and the general Norwegian population were general health perceptions, role physical limitation and vitality. Finally, the patients' ability to participate in activities in daily life was limited.

The present study has expanded our knowledge about the relationship between background characteristics and the SF-36 subscales in patients with NET. In addition, this study has confirmed the impact of quality of life when diagnosed with NET compared to the Norwegian general population.

### 8.2.2 Associations between stress, general self-efficacy and social support related to HRQoL

Findings reported in Paper II are consistent with findings of patients treated for breast cancer [11] and long-term survivors of testicular cancer [10], and demonstrated that patients with NET reported higher levels of stress and decreased physical and mental HRQoL. Reduced mean levels of mental HRQoL indicate important signs of stress.

Our results demonstrated that more social support was associated with better mental health (Paper 2, Table III). This has been demonstrated in earlier research [8]. More information, advice and feed-back as well as self-confidence and tangible aid are important factors resulting in better mental HRQoL in patients with NET. Developing a serious disease such as NET may imply difficulties in continuing activities of daily living, thus the need for social support seems

logical. Concerns about receiving adequate information, advice and tangible aid might add to stress in patients with NET. Thus, information and practical support might increase the level of mental health.

Our findings demonstrated that general self-efficacy was positively related to mental and physical HRQoL (Paper II, Table 3). This is congruent with previous results demonstrating a positive relationship between general self-efficacy and physical HRQoL in patients with HIV [172] and mental HRQoL in individuals at risk for hereditary cancer [8]. However, the results contrast with a study of individuals at risk for hereditary cancer for physical HRQoL [8]. One explanation for the findings may be that those who experience more confidence in managing disease may have better capability to handle complex tasks [33;173]. Another explanation may be that those with higher level of general self-efficacy experience are more capable and more confidence to perform physical activities. A third explanation may be that we used a generic questionnaire measuring the patients' self-efficacy. A generic measurement is likely to capture more characteristics of self-efficacy. A disease specific measure may be superior to a generic instruments by tapping aspects of self-efficacy that are of particular relevance to people with the condition of interest [71] (p 5). Thus, including a disease specific self-efficacy questionnaire could be a supplement to a generic questionnaire in order to be more sensitive to symptoms that might cause the stress response related to the disease. Nevertheless, results from this study indicate that positive feelings, thoughts, and expectations are important components for both mental and physical HRQoL in patients with NET.

Finally, social support and general self-efficacy partially mediated the relationship between stress and mental HRQoL (Paper II, Table 3, Model 3). However, general self-efficacy accounted for the largest amount of variance in the combined model of stress and mental HRQoL. Although general self-efficacy played a main role in the mediator model, more research is needed to explore the importance of disease related self-efficacy and the stress-HRQoL relationship. It might be that a combination of social support and disease related self-efficacy play a more important role in the stress-HRQoL relationship. Nevertheless, general self-efficacy decreases the influence of stress on mental HRQoL in patients with NET. No prior studies have reported this relationship, indicating that the present study has expanded the knowledge of social support, self-efficacy, stress, and HRQoL. However, further research is needed to confirm our

findings.

### 8.2.3 Patient education to improve stress, general self-efficacy and HRQoL in patients with neuroendocrine tumors – a pilot study

Results reported in Paper III demonstrated that stress was reduced and general self-efficacy and physical functioning were improved following the patient education intervention. This is consistent with social cognitive theory and the understanding of how self-efficacy may influence how people think, feel and act [90]. Consequently, the findings suggest that the patients' gained knowledge and problem-solving abilities on which skills are grounded, and thus can make appropriate choices for how to overcome barriers associated with NET. Looking at cancer as a reasonable comparison group for our results systematic reviews report on several intervention studies in which new skills were acquired and patients gained confidence to manage their disease [34-36;127]. However, the effects of these interventions show various effects with regard to outcomes such as stress, self-efficacy, and HRQoL. Although the interventions in the studies seem to be of substantial similarities, the concepts of the outcomes being measured are different.

A literature review of RTC by McGregor & Antony show reduced levels of stress following cognitive behavioral interventions in women treated for breast cancer [174]. In a RTC using cognitive-behavioral therapy in the intervention for women with breast cancer (n = 425) stress (measured by the intrusion subscale of The Impact of Event scale) was reduced following the intervention [143]. Chan et al. conducted a RTC including a psycho-educational intervention in women with gynecologic malignancy. The intervention aimed to help patients see the integral link between thoughts, emotions and physical well being. The findings revealed no improvements in stress by The Impact of Event Scale [175].

In our pilot study fifty-seven percent of the patients had moderate levels of stress, and 2.7 % of the sample reported severe stress. Changes in stress following the intervention may reflect that patients did not have stress so high that they activated avoidance behavior and were able to participate in the intervention. Consequently, the significant changes in the levels of stress may be of limited relevance.

Statistically significant changes tell us about effect sizes but do not necessarily reflect clinical

importance. A standardized estimation of effect size could be applied in the interpretation of the results [159]. The effect size for the changes in stress from T1 to T3 was 0.16 and may be considered as small. Thus, though the sample was small we were able to detect change. The clinical relevance of the improvements in stress is probably significant but would require long term follow-up to determine.

General self-efficacy was evaluated adjusting for age, gender, symptoms, and co-morbidity and demonstrated significant improvements. The results indicated that the patients have had the capacity to improve their confidence in managing their general, everyday challenges (Paper III, Table 4). Tamagawa et al summarized benefits from psychosocial interventions in oncology and indicated that those with low levels of self-efficacy initially benefitted from psychosocial interventions however, those with higher levels of self-efficacy at baseline did not. [127]. Similar to our findings in self-efficacy improved following a nurse led RTC for patients with congestive heart failure following a self-management program [176]. Our findings were also similar to patients with long-term conditions improving disease specific self-efficacy following peer led education program based on the principles of self-efficacy [41;105;107]. However, Ritter, Lee and Lorig [177] emphasize that those with lower initial self-efficacy benefit more from a patient education intervention than those with higher levels. In addition, Tamagawa et al [127] claim that benefits of psychosocial interventions are more salient for patients who reported lower psychological and physical HRQoL and fewer social resources at baseline. We did not adjust for baseline levels of general self-efficacy, physical HRQoL, and social support in this study.

The estimated effect size for change in general self-efficacy was 0.32, which may be interpreted as a small to moderate change. This may indicate clinical significance but would require follow-up measures of patient characteristics and outcomes.

Similar to our findings, HRQoL has also been improved through educational interventions in other cancer populations [38;150] showing significantly improvements in physical HRQoL following patient education. Testing of RTC's in two interventions, one based on education-only and education-plus-group discussion, men (n = 279) with prostate cancer demonstrated significant improvements in PCS in the education-plus discussion group [178]. Doorenbos et al. showed that physical function measured by the SF-36 improves significantly in individuals with

solid tumor cancer (n = 237) following an intervention based on cognitive behavioral theory [179]. However, findings from a study in women with gynecologic malignancy aiming to evaluate the effectiveness of psycho-educative and cognitive intervention showed no improvements in cancer specific HRQoL following the intervention [175].

Men had a significantly larger change in PCS compared to women in this study. The lower baseline scores of PCS among men may explain the differences in change, as men had a greater potential for improving their PCS than women. Consistent with earlier research [179] co-morbid conditions were related to reduced physical function. Research has shown that interventions based on principles of self-efficacy have positive effects on those with greater risk of lower physical functioning [179].

The effect size for total change of physical components scores from T1 to T3 was 0.37. This moderate effect may indicate that the change may be meaningful [159]. The patient education intervention was mainly designed to help patients to believe in their own competence by changing thinking patterns. Moreover, the intervention is complex in that, the intervention consists of a number of components such as those who receiving and delivering the intervention, different groups targeted by the intervention and the setting of the intervention. These components may interact and influence the study outcomes [180]. Consequently, which component that is most potent may be uncertain.

Moreover, functional status and symptoms not measured in this study such as fatigue, disturbed sleeping pattern may influence physical HRQoL in patients with NET'. In addition, as aggressiveness of the disease and side effects of NET medication could influence the patients' physical activity. Measuring aggressiveness and side effects would increase the significance of changes in physical HRQoL following an intervention based on the principles of self-efficacy. Hence, future longitudinal RTCs should include biological function and functional status and, side effect of NET medication and treatment in HRQoL studies.

## **9. Conclusion**

The aims of this thesis were to describe HRQoL in a nationwide sample of patients with NET compared with a general Norwegian population (Paper I), evaluate associations between stress, general self-efficacy, social support and HRQoL (Paper II) and, to test the mediation role of

social support and general self-efficacy on the stress – HRQoL association (Paper II) and, to explore changes in stress, general self-efficacy and HRQoL among patients with NET following a patient education intervention (Paper III). The present study provides novel knowledge of these variables that can be used by clinicians for treatment and care of patients with NET. Main findings include:

- Patients with NET had poorer HRQoL than the general Norwegian population on all subscales of the SF-36.
- Lower age, part-time or full-time employment, higher education and higher income levels were associated better HRQoL. Having symptoms and co-morbid conditions predicted poorer HRQoL
- Higher stress was associated with poorer mental and physical HRQoL
- Higher levels of social support and general self-efficacy were associated with better mental HRQoL
- Higher levels of general self-efficacy were associated with better physical HRQoL.
- Social support and general self-efficacy mediated the relationship between stress-and mental HRQoL.
- Stress, general self-efficacy and physical HRQoL changed significantly following a 6-month patient educational intervention.
- Symptoms and co-morbidity were inversely associated with physical HRQoL.

## 9.1 Implications

### 9.1.1 Implications for clinical practice

Poorer HRQoL among patients with NET compared with the general Norwegian population indicate that health care personnel who have frequent contact with patients should intervene as specific mental and physical issues arise. Talking with the patients about their challenges and assisting with goal setting could accomplish this. According to Norwegian legislation requires that [60] patients receive routine information and education that improves their coping, maintains health, independence, and functional ability. Health care personnel should refer patients to other social service agencies or clinicians who can provide social and psychological

support when needed. One major challenge in clinical practice is to identify individual needs. Screening the patients with NET for stress during follow up may give useful information augment care. In the present study, 12 % of the patients reported a severe stress response to cancer indicating a need for assistance with coping. Results also confirm the importance of screening all patients with NET for stress levels since stress was negatively associated with mental and physical HRQoL. IES (Impact of Event Scale, see p 41) might work as a screening tool as it is brief and could be incorporated into nursing assessments.

Encouraging patients with NET to engage in social activities would aid in their coping and increase self-efficacy. Supporting the patients competence in performing specific behaviors and may help them manage symptoms and improve their HRQoL. Because NET is incurable, facilitating and concentrating on increasing general self-efficacy and motivating the individuals' self-care might be useful. Screening for stress, social support, and general self-efficacy at diagnosis should be considered. Information from the screening could be used in discharge planning and in rehabilitation programs.

### 9.1.2 Implication for future research

Because patients with NET report decreased HRQoL compared with a gender and age matched Norwegians, further research on other clinical variables that are predictive of favorable outcomes is warranted.

We found no association between length of time since diagnosis and HRQoL (Paper I) however, cancer specific HRQoL has shown to improve five years after diagnosis in another study [168]. Conflicting results indicate more research on the impact of disease duration on HRQoL would be beneficial. Future research might examine the influence of symptoms such as pain, fatigue and diarrhea. These symptoms may result in decreased physical activity and thus, reduced HRQoL.

Stress was associated with poorer mental HRQoL in NET patients and general self-efficacy seems to be an important predictor of favorable mental HRQoL outcome among patients with NET. Thus, a RTC adjusted for the possible confounders of individual characteristics as well as disease progression, medical treatments, settings, co-morbid conditions and symptoms would be sufficient. Tailored interventions based on age and gender are warranted and more research is



needed to evaluate this. Path analyses would be helpful to determine moderator and mediator variables and facilitate refinement of interventions. In addition, disease specific self-efficacy questionnaire could be a supplement to a generic questionnaire in order to be more sensitive to symptoms that might cause the stress response. In addition, stress specifically related to NET and NET-related HRQoL may add knowledge about specific problems in order to achieve reduced levels of stress related to NET. Finally, the role of social support, which is claimed to be an resource for self-efficacy in the social cognitive theory [90], could be a means to address in a RTC.

Optimal outcomes require supporting principles of patient centered- care and promotion of the principles of self-efficacy. Qualitative methods such as in-depth interviews, focus groups and participant observation may aid in the development of tailored interventions.

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