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HEALTH RELATED QUALITY OF LIFE AMONG WOMEN WITH ADVANCED BREAST CANCER

Issues of measurement, clinical significance and personal meaning

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LEVINNYTTÄ RINTASYÖPÄÄ SAIRASTAVIEN POTILAIDEN TERVEYTEEN LIITTYVÄ ELÄMÄNLAATU

TIIVISTELMÄ

Terveyteen liittyvä elämänlaatu on subjektiivinen, yksilön kokemusmaailmaa kuvaava moniulotteinen käsite, jolla tarkoitetaan ihmisen kokemusta terveydentilastaan sekä siihen liittyvästä fyysisistä, psyykkisistä ja sosiaalisista tekijöistä. Levinnyt rintasyöpä on parantumaton sairaus ja näin ollen sen hoidon ensisijaisena tavoitteena on oireiden lievittäminen ja elämänlaadun kohottaminen.

Tässä tutkimuksessa tarkasteltiin levinnyttä rintasyöpää sairastavien potilaiden elämänlaatua psykologisessa ja lääketieteellisessä viitekehyksessä. Tutkimuksessa verrattiin kahden eri solusalpaajahoidon (doketakseli vs. Methotreksaatti-Fluorourasiili) elämänlaatuvaikutuksia. Tutkittiin, kuinka elämänlaatu muuttuu hoitojen edetessä sekä mikä on lääkäreiden arvioimien sivuvaikutusten ja fyysisen kunnon yhteys potilaiden kokemaan elämänlaatuun. Selvitettiin myös, voiko elämänlaatumittauksilla ennustaa kliinisiä vastemuuttujia: hoitovasteen ja elämän pituutta, sekä osoitettiin elämänlaatumittausten ajoituksen kontrolloinnin merkitys. Näiden lisäksi laadullista haastatteluaineistoa hyödyntäen selvitettiin potilaiden elämänlaadun yksilöllisiä merkityssisältöjä.

Tutkimustulokset osoittivat, että hoitoryhmien välillä ei ole merkittäviä elämänlaatueroja. Fyysinen kunto ja hoidon sivuvaikutukset selittivät vain pienen osan elämänlaadun vaihtelusta. Lähtötason elämänlaatumuuttujista ainoastaan kivut ennustivat elämänpituutta. Muut elämänlaatumuuttujat eivät ennustaneet hoitovastetta, elämän pituutta eikä myöskään muutos lähtötason elämänlaadussa ennustanut em. asioita. Virheellisesti ja oikein ajoitettujen elämänlaatumittausten välillä havaittiin tilastollisesti ja kliinisesti merkitseviä eroja. Näin ollen tutkimus osoitti empiirisesti elämänlaatumittausten ajoituksen kontrolloinnin tärkeyden. Laadullisen aineiston analyysistä nousi kolme keskeistä metateemaa, jotka määrittivät potilaiden kokemusta elämänlaadusta: 1) autonomian tunne (ts. tunne siitä, että mielihyvän tuottaminen on omassa hallussa) 2) sairauden myötä tullut kokemus omasta henkisestä kasvusta sekä 3) toivon merkitys potilaan elämänlaadulle.

Yhteenvetona voidaan todeta, että elämänlaadun mittaamisesta kliinisten lääkeainetutkimusten yhteydessä voitaisiin saada jatkossa yhä suurempi hyöty mikäli tutkimukset toteutetaan menetelmällisesti perustellusti sekä yhä enenevässä määrin hyödyntäen sekä laadullista että määrällistä tutkimusotetta.

Avainsanat: terveyteen liittyvä elämänlaatu, rintasyöpä, laadullinen, EORTC, merkitys

ABSTRACT

Health Related Quality of Life (HRQoL) is understood in this study as a subjective and multidimensional concept, the main dimensions being physical state, psychological well-being, social relations and functional capacity. In the absence of curative therapies, the therapy goals for patients with advanced breast cancer include the prolongation of survival, the alleviation of symptoms, and HRQoL. Therefore, the efficacy of therapeutic interventions should be evaluated in terms of their effect on both the quantity and quality of life. The purpose of the present study was to investigate HRQoL among patients with advanced breast cancer. The QoL effects of two different treatments were compared. Specific emphasis was placed on comparing the patients' HRQoL over time, on the relationship between toxicity variables, physical performance and HRQoL, on assessing the prognostic value of HRQoL in terms of overall survival and time to disease progression, and on the importance of the exact timing of the HRQoL assessments. Furthermore, qualitative methods were used to gain a deeper understanding of personal meanings related to the experience and treatment of cancer.

The participants of the study were, 283 patients with metastatic breast cancer, who were randomly assigned either docetaxel (T) or sequential methotrexate and 5-fluorouracil (M-F) treatment. EORTC QLQ-C30 was used to measure HRQoL. The HRQoL data and the clinical data were merged.

The results of the study showed no major advantage of either treatment over the other. In addition, most of the variance in HRQoL could not be explained by treatment toxicity and physical performance as assessed by the physician. There was only mild to moderate correlation between the physician-assessed toxicity and the patient-assessed toxicity variables. Pain did have a prognostic value for the patients' overall survival. However, no other HRQoL variables were shown to be significant prognostic factors for treatment response or for overall survival. Furthermore, the patients' change scores from the baseline did not predict either survival or time to disease progression. Erroneous timing affected the HRQoL findings in both treatment groups. There were statistically and clinically significant differences between the responses to the ill-timed and the correctly timed questionnaires at baseline and over time. Thus, the study demonstrated the importance of correct timing in QoL assessment.

From the results of the qualitative study, three dominant themes of personal experience emerged over the normative psychometric dimensions of HRQoL: ensuring feelings of autonomy by controlling the illness experience, experienced personal growth, and hope. In summary, in future assessments of and research in HRQoL, it would be useful to complement traditional psychometric methods with more individualised qualitative methods.

keywords: Health Related Quality of Life, advanced breast cancer, qualitative, EORTC, prognostic, meaning, timing, toxicity

LIST OF ORIGINAL PUBLICATIONS (I-V)

The thesis is based on the following publications, which are referred to in the text with Roman numerals I-V

I L. Hakamies-Blomqvist , M-L. Luoma , J. Sjöström , A. Pluzanska , M. Sjödin , H. Mouridsen , B. Østenstad, I. Mjaaland , S. Ottosson-Lönn , J. Bergh, P-O. Malmström, C. Blomqvist (2000) *Quality Of Life in Patients with Metastatic Breast Cancer Receiving either Docetaxel or Sequential Methotrexate and 5-Fluorouracil. A Multicentre Randomised Phase III Trial by the Scandinavian Breast Group.* European Journal of Cancer, (36), 1411-1417

II L. Hakamies-Blomqvist, M-L. Luoma, J. Sjöström, A. Pluzanska, M. Sjödin , H. Mouridsen , B. Østenstad, I. Mjaaland, S. Ottosson, J. Bergh, P-O. Malmström, C. Blomqvist (2001) *Timing of Quality of life (QoL) assessments as a source of error in oncological trials.* Journal of Advanced Nursing, 35, 709-716

III M-L. Luoma, L. Hakamies-Blomqvist J. Sjöström, H. Mouridsen, A. Pluzanska, P. Malmström, N.O Bengtsson, R. Hultborn, B. Ostenstaad, I. Mjaaland, V. Valvere, E Wist, G. Baldursson, J.Ahlgren & C.Blomqvist (2002) *Physical performance, toxicity, and quality of life as assessed by the physician and the patient.* Acta Oncologica, 41(1), 44-49.

IV M-L Luoma, Hakamies-Blomqvist L. , Sjöström J , Pluzanska A., Hultborn R., Mouridsen H., Bengtsson N- O. Bergh J. , Malmström P-O. Palm-Sjövall M, Valvere V. , Tennvall L., Blomqvist C (2003) *Prognostic value of quality of life scores for time to progression (TTP) and overall survival time (OS) in advanced breast cancer*. Eur J Cancer, 39 (10), 1370-6.

V Minna-Liisa Luoma & Liisa Hakamies-Blomqvist. The meaning of quality of life in patients being treated for advanced breast cancer: A qualitative study. In press Psycho-Oncology

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ABBREVIATIONS

AT	doxorubicin and paclitaxel
CR	complete response
CRF	clinical research form
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire-C30
FAC	5-fluorouracil, doxorubicin, and cyclophosphamide
FACT-G	Functional Assessment Cancer Therapy
FDA	U.S. Food and Drug Administration
HRQoL	Health Related Quality of Life
KPS	the Karnofsky Performance Status
LASA	linear analog self-assessment technique
M-F	methotrexate and 5-fluorouracil
OS	overall survival
PR	partial response
QLI	quality of life index
QoL	Quality of Life
SBG	Scandinavian Breast Cancer Group
T	docetaxel
TTP	time to disease progression
WHOQOL	World Health Organisation Quality of Life Assesment

Abbreviations within EORTC QLQ-C30

PF	physical functioning
RF	role functioning
CF	cognitive functioning
EF	emotional functioning
SF	social functioning
GQoL	global quality of life
PA	pain
FA	fatigue
NV	nausea/vomiting
DY	dysopnea
SL	insomnia
AP	appetite loss
CO	constipation
DI	diarrhoea
FI	financial difficulties

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1 INTRODUCTION

1.1 Quality of life

The search term “Quality of Life” in PsycINFO retrieves in 13 578 citations; by adding cancer, 1018 citations are listed and, by adding breast cancer only 244 are found citations. The corresponding figures in Medline are 58 186 citations for Quality of life; with cancer, 14 610 citations are given, while breast cancer only retrieves 2 091 citations. The Quality of life is in vogue; however, there is no consensus on what it really is. Quality of life has been especially widely studied among patients with chronic illnesses in which the condition of the patient can be improved by medical treatment but cannot be restored to normal functionality. The incorporation of this concept means that not only are the cure and survival of the patients important, but also that their well-being must be considered. This is of particular interest in cancer care in which the treatments are often uncomfortable, debilitating and not curative.

1.2 Health Related Quality of Life (HRQoL)

The growing use of HRQoL for appraisal in medical interventions has created a need for the clarification of this concept. The World Health Organisation has defined health “as not merely the absence of disease or infirmity, but a state of complete physical, mental and social well-being (WHO, 1958). The WHO’s definition is widely used and strongly supports the multidimensional aspects of health. This definition has influenced the notion of HRQoL as a multidimensional concept.

In the literature it is widely accepted that there is no generally agreed upon definition of HRQoL. However, there is there is wide agreement that HRQoL is subjective in the sense that it should be assessed by individuals themselves and that (2) it has a multidimensional structure.

There are several suggestions about how this multidimensionality of HRQoL could be incorporated into its definition. One of the most recent definitions of HRQoL is the WHOQOL (World Health Organisation Quality of Life Assesment) group’s definition of QoL as an “individual’s 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 wide-ranging concept affected in

a complex way by the person's physical health, psychological state, level of independence, social relationships and their relationship to the salient features of their environment" ("The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties," 1998).

Cella and colleagues (1990) have proposed a definition of HRQoL, which incorporates individual preferences into the level of impairment. According to them " QoL refers to patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal". This definition stresses the individual appraisal of the advantages and disadvantages of treatments and therefore provides information on whether or not the disability is tolerable (Cella & Tulsky, 1990). According to Pandey (2002) " HRQoL refers to the psychosocial, emotional and physical outcome of healthcare treatments as perceived by the patient. Patients interpret their feelings of well-being using expectations, experience and religious or community beliefs. Each of these may vary and depends on patients' attitude and specific therapeutic intervention" (Pandey et al., 2002). This is a typical example of a psychometric-driven definition of HRQoL in which unobservable constructs (physical, psychosocial and emotional) are measured by a collection of representative questions, as Pandley also has done.

The quality of life, in a general sense, reflects the ways in which a person's mental, social and physical well-being are evidenced in his or her everyday life. In primary HRQoL dimensions, *physical functioning* refers to one's ability to perform various activities at the most basic level of daily living, such as walking and dressing oneself, self-care activities or household tasks. *Social functioning* typically refers to a person's ability to interact with family and friends and to maintain social roles. *Emotional functioning* is commonly assessed as the negative effects of illness such as depression, anxiety or worry. *Cognitive functioning* refers to memory or the ability to concentrate. *Overall life satisfaction* or QoL represents a person's overall sense of well-being.

The majority of HRQoL research has been conducted by interdisciplinary teams that follow the empiricist tradition of medicine. In this tradition, it is assumed that relevant psychological variables, which are pre-existent and distanced from the researcher, can be measured. This tradition leads to the theoretical framework of HRQoL's multidimensional perspective that has formed the basis for development of the psychometric tools for measuring the HRQoL of individuals. Following this tradition the assumptions of the contents of good HRQoL are made a priori. The

constructs or domains of HRQoL are considered latent variables, which are elicited with separate items or questions. In multidimensional questionnaires these domains are not directly measurable. If the questionnaire is well designed, each question should ideally be associated with one latent variable (Fayers & Hand, 2002). These questions typically ask for the frequency or intensity of different symptoms or feelings.

Traditionally, most HRQoL research has been targeted toward solving practical problems, with investigators responding to specific research needs, such as providing tools for investigators to assess care outcomes beyond traditional morbidity and mortality (Wood-Dauphinee, 1999). In light of all this, it is not surprising that a multidimensional evaluation of HRQoL is thought to be appropriate. In addition, it seems unnecessary to attribute a specific meaning to HRQoL outside the psychometric setting.

It has been argued that there are several valid, reliable questionnaires available to measure a person's health related QoL. There are two basic approaches to measurement of QoL; generic instruments that provide a summary health profile and disease specific instruments which focus on specific problems associated with a disease or area of functioning. The multidimensional construct of the definition helps to pinpoint the problem area.

The issues which are measured in HRQoL research are psychological and complex in nature; therefore, an empiricist approach and a naturalistic frame of reference may not fully capture the phenomenon. HRQoL is a highly individual concept and it has also been argued that research-defined psychometric translations of HRQoL may not capture the subjective nature of an individual's experience (Cox, 2004). Furthermore, these measures do not say anything about how these judgements of HRQoL are arrived at and how they are determined by expectations or experience (Carr, Gibson, & Robinson, 2001). Nor do they indicate the person's ability to adjust to the illness experience which could involve constantly changing expectations and insensitivity to changes during the course of the illness (Rosenberg, 1995).

It has been argued that HRQoL concepts are not a part of comprehensive theories of human actions (Rosenberg, 1995). In a recent review article on theory-driven HRQoL models the, authors pointed out that only 15% of those QoL models were categorised as theoretical models (defined as a model that includes the structure of

elements and their relationship within a theory that explains these relationships) (Taillefer, Depuis, Roberg, & Le May, 2003)

Some theorists have attempted to capture and describe HRQoL systematically. To give some examples, Sprangers, who introduced her model of response shift (Schwartz & Sprangers, 1999; Sprangers & Schwartz, 1999), and Leventhal's self-regulation model of illness behaviour (Leventhal & Colman, 1997) have contributed to the field of HRQoL. According to Sparangers, the response shift refers to the changes in internal standards, in values, or in the conceptualisation of QoL, which are catalysed by health state changes (Schwartz et al., 1999).This model is an attempt to capture the adaptation process in which patients change their internal standards. There are several implications of defining the response shift (Schwartz et al., 1999). However, it is nearly impossible to quantify it, i.e., to decide which part of any observable change in HRQoL is due to a response shift.

Leventhal and Colman (1997) suggest a process model, which asserts that judgments of quality of life reflect an individual's evaluation of the level of his or her functioning within a number of life domains, and the value or importance assigned to these domains. The authors propose that the judgment process involves a variety of heuristics or procedures that are affected by contextual factors. The framework suggests that an individual's common sense representations, affective reactions, procedures and actions designed to control the disease as well as contextual factors influence the patient's judgements and behaviour. These factors affect salience, meaning and the importance of domains involved in HRQoL judgements (Leventhal et al., 1997).

Sprangers et al (2002) have explained HRQoL with a crisis theory; i.e., a crisis occurs when the difficulty and importance of a problem are larger than the resources available to deal with it. They found that the patients in crisis reported a poorer HRQoL and the patients post crisis reported a similar overall QoL and psychological distress as healthy individuals (Sprangers, Tempelaar, van den Heuvel, & de Haes, 2002). However, patients post crisis experienced more physical distress and role activity impairment than healthy individuals. There were no significant or systematic differences between the mean levels of coping resources and strategies in the patients post crisis and healthy individuals. The patients in crisis were not able to make their coping resources and strategies more effective, whereas the patients post crisis seemed to have enhanced the effectiveness of self-esteem in restoring their QoL compared to healthy people (Sprangers et al., 2002).

The notion of self-efficacy has been used as a theoretical framework for understanding the results of HRQoL studies. (Self-efficacy refers to the belief that one is capable of performing the behaviour required to produce a desired outcome (Bandura, 1997)). The concept of self-efficacy has been introduced in the self-management of chronic illness and the discrepancy in chronically ill patients' perceptions of the importance and attainability of illness-related goals and their quality of life (Kuijer, 2003). Kuijer (2003) found that more discrepancy in goal importance and attainability was associated with lower levels of HRQoL. However, the association with physical well-being was only marginally significant. They suggest that the discrepancy measure reflects a psychological weighting of what is personally important and of what one is capable of doing, which is more strongly related to psychological well-being than to physical well-being (Kuijer, 2003).

Thus none of the theories related to HRQoL are psychological theories in the sense that they encompass the mechanisms of the human mind that specify all or the key issues studied under the umbrella of HRQoL. One psychological theory which could be adapted to HRQoL research is a principle of psychic self-regulation according to which the individual attempts to function in ways that produce maximally/optimally articulated consequences for self-experience (Vuorinen, 1986a, 1986b, 1986c). Self-regulation covers all functions that exist to control actions and to modify mental processes to maintain psychic equilibrium. The goal of self-regulation is to keep the level of psychic tension low or constant, because an increase in the level of tension is experienced as distress and a decrease or stable level of tension is experienced as pleasure or as having control over a situation (Vuorinen, 1986a).
This theory defines three types of levels of self-regulation: the most fundamental level is psychic work, which refers to the totality of those mental processes which an individual uses for achieving and maintaining his psychic equilibrium. Psychic work consists of various mental operations: intentions, thoughts, affects, and motives. Another level of self-regulation is the psychosocial level, which refers to the need for other people. According to this theory, social relations are shaped to fit both internal goals and situational preconditions, therefore social interaction cannot be explained only by correlating personal and situational variables. The psychophysical level, in turn, involves the use of the body with all its somatic processes for psychological purposes. This also applies when the environment or bodily functions limit a person's external goals. In these situations as well actions are reformed by how mental functions adjust to external constraints, i.e, how these constraints are related to self-experience. People are forced to maintain psychic

equilibrium through psychic work. Moreover, the meanings of other levels are conveyed through psychic work. The importance of psychic work means that external goals are secondary to internal goals, i.e., maintaining psychic equilibrium (Vuorinen, 1986a). This framework offers the systemic psychological explanation of how physical and social factors are formed through psychic work, i.e., according to individuals' own mental processes.

HRQoL research is dominated by an empiricist psychometric tradition and the theoretical status of the HRQoL concept remains ambiguous (Rosenberg, 1995). Consequently, it has been argued that even though empirical research has provided valid and reliable data on the patients' subjective perceptions of their HRQoL, it may preclude the need for especially qualitative approaches. The need has been shown for the added and independent value of an in depth analysis of experience and meaning of the disease and its treatment. Qualitative approaches in HRQoL research have potential for the introduction of new hypotheses, for providing powerful and detailed information about the personal experience, and for the validation of quantitative results (Strang, 2000).

1.3 Breast cancer

1.3.1 Epidemiology and risk factors

Breast cancer is the most common cancer in women, and 210 631 cases were diagnosed in the EU in 1998 (http://www-dep.iarc.fr/eucan/eucan.htm, Last updated on 17/3/2003.). In Finland, 3 644 new breast cancer cases were diagnosed in the year 2001 (FinnishCancerRegistry, 2004). Breast cancer has many risk factors. The risk of developing breast cancer increases with age (Annual, Databank, & Geneva, Last updated: November 2001). Early menarche, late menopause, nullipatrity or late age at first birth, obesity, alcohol use, family history of breast cancer and use of oestrogen and progestin postmenopausal hormone therapy for five years or more are known risk factors for breast cancer (Brekelmans, 2003; Kerlikowske et al., 2003; McTiernan, 2003). Population-based studies of the genetic epidemiology of female breast cancer have shown that only a small proportion of familial aspects of the disease can be explained by what is currently known about its causes. These include mutations in the genes BRCA1 and BRCA2, associated with a 10- to 20-fold increased risk of developing breast cancer (Hopper, 2001). The prognosis of breast cancer has greatly improved during recent decades and the five-year relative survival rate, based on Finnish cancer registry data, is nowadays 85%. However, the prognosis varies widely between different

stages of breast cancer. Despite the improved prognosis, breast cancer is the leading cause of cancer death in women (17%) (Bray, Sankila, Ferlay, & Parkin, 2002). Five-year relative survival rates vary from 93% for patients with localized disease to 69% with localised metastasis and 22% for distant metastasis (Teppo et al., 1999). The most common sites for metastasis are the skeleton, the lungs, the liver, the subcutaneous tissue of the skin and the lymphatic structures. Advanced breast cancer is generally considered an incurable disease and therefore the benefits of therapy (survival and freedom from tumour-related symptoms) must be counterbalanced with treatment toxicity and the patients' quality of life.

1.3.2 Treatment of advanced breast cancer

The first treatment of patients with advanced breast cancer, with no symptoms, who have hormone receptor positive tumours is usually hormonal therapy. When hormonal therapies are effective they are preferred, because they are less toxic than most chemotherapy regimens and have long-standing responses. However, most patients with advanced breast cancer receive chemotherapy at some point during the illness. Chemotherapy is indicated when the cancer is unresponsive to hormonal therapy or is rapidly progressive and life threatening. Chemotherapy provides significant palliation and prolongation of survival in advanced breast cancer patients. The median survival time for metastatic breast cancer with conventional chemotherapy is 12-24 months (Bergh, Jonsson, Glimelius, & Nygren, 2001). As a first line chemotherapy for metastatic breast cancer, polychemotherapy results in a statistically significant survival gain compared with single agent therapy. Antracycline- containing combinations improve survival compared to non-antracycline combined chemotherapy, and higher doses are superior to lower doses (Bergh et al., 2001; Fossati et al., 1998). On the basis of these findings, the antracyclines (doxorubicin and epirubicin) are widely used as first line chemotherapy (Crown et al., 2002).

Second line therapy for metastatic breast cancer refers to the treatment given to patients who had failed to respond to primary chemotherapy for advanced breast cancer. In the treatment of advanced breast cancer there are quite a few treatment opportunities available; however, the choice of second line treatment is determined by the first line regimen used (Crown et al., 2002). Response rates and survival gain for the second line of chemotherapy are lower compared to the first line therapy. The most active second line chemotherapy regimens are the taxanes (docetaxel and paclitaxel). The taxanes are relatively new treatments in breast cancer; in fact, the first study was reported in 1991 (Holmes et al., 1991). The

clinical use of taxanes has now been widely evaluated, and taxanes are commonly considered to be the most effective second line therapy (Crown et al., 2002) with survival gain of up to 15 months (Nabholtz et al., 1999; Sjöström et al., 1999). The taxanes (docetaxel, paclitaxel) have also been proven to be of great therapeutic value in advanced breast cancer, yielding not only high response rates (Nabholtz et al., 1999) but also prolongation of survival (Jassem et al., 2001; Nabholtz et al., 1999). However, taxanes are considered to be relatively toxic treatments causing alopecia, asthenia, haematological and neurological side-effects (Lister-Sharp, McDonagh, Khan, & Kleijnen, 2000). Other treatments, including cyclophasmide, mitomycin c, viblastine, methotrexate, fluorouracil, and platinum compounds are considered to be alternatives to taxanes with antracycline resistant disease (Crown et al., 2002).

1.4 Health related QoL in advanced breast cancer clinical trials

The science of medical decision making has assumed that good choices are made on a rational basis, and in modern medicine the traditional endpoints of cancer treatment have been tumour response, disease free survival or survival. Until the mid 1980s, the length of survival time was the main measure for determining the value of chemotherapy for cancer (Gunnars, Nygren, & Glimelius, 2001). Increasingly, researchers have been faced with situations in which patients may not gain benefits from these traditional endpoints. Treatment should not exceed the positive effects, and small gains in terms of response and survival should be weighed against QoL. In palliative settings, chemotherapy has very limited efficacy in terms of traditional endpoints and therefore HRQoL should be an endpoint. Nowadays, there is greater understanding among researchers that the efficacy of therapeutic interventions should be evaluated by their impact on both the quantity and quality of life.

The assessment of HRQoL is an important endpoint in clinical trials with the aim of complementing the traditional endpoints, i.e., tumour response, response time and survival time. Typically, there are three reasons why investigators are interested in HRQoL in cancer clinical trials: (1) as a means of assessing rehabilitation needs, (2) as an endpoint in evaluating treatment outcomes e.g., when comparing HRQoL against competing treatments and (3) as a predictor of the response to future treatment (Cella & Tulsky, 1993). HRQoL measurements are especially recommended: (1) in a trial in which no significant differences are expected in terms of cure, disease free survival or overall survival but one treatment is expected to be associated with more morbidity; (2) in a trial in which survival

and disease free survival or cure are expected to differ between treatment groups, but advantageous primary outcome is only achieved at the expense of major toxicity (Young et al., 1999).

HRQoL should be the endpoint in advanced breast cancer clinical trials, because treatment is considered to be palliative, as the aim is not to cure and no significant differences are expected in somatic clinical endpoints. Even though it has been recognised that HRQoL is an important endpoint in advanced breast cancer, there have been only a few trials where HRQoL has been studied by using the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life core Questionnaire C30).

Nabholtz and colleagues (2003) compared HRQoL in patients receiving docetaxel and doxorubicin or doxorubicin and cyclophosphamide as first line chemotherapy for metastatic breast cancer. They found no significant differences in global QoL between the treatment groups (Nabholtz et al., 2003). Kramer's et al. (2000) study was to compare the quality of life of patients treated with single-agent paclitaxel versus doxorubicin as first line chemotherapy for advanced breast cancer (Kramer, Curran, Piccart, de Haes, Bruning, Klijn, Bontenbal et al., 2000). They found that doxorubicin was associated with significantly more nausea/vomiting (P=0.001), loss of appetite (P=0.010) and both treatments were associated with improved emotional function and reduction in psychological distress at cycle 3. Norris and colleagues (2002) conducted a comparative study of vinorelbine combined with doxorubicin versus doxorubicin alone in disseminated metastatic or recurrent breast cancer. There were no significant differences in any HRQoL domains between the treatment groups of means scores over the first 6 cycles (Norris et al., 2000). However, QoL scores showed improvement over time in the global, emotional, social, pain and nausea/vomiting domains for patients receiving six cycles. The authors suggest that this might be the result of selection bias because only patients who were stable or responding to chemotherapy received six cycles (Norris et al., 2000).

Jassem et al. (2001) compared the EORTC QLQ-C30 scores for patients receiving doxorubicin and paclitaxel (AT) to 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) as first line therapy for women with metastatic breast cancer. Significant differences were found in that physical functioning and pain, fatigue, insomnia and diarrhea favoured with FAC, whereas nausea/ vomiting favoured AT arm (Jassem et al., 2001). Even third line chemotherapy may improve patients' HRQoL. In a study by Mc Lachlan et al. (1999), 34% of the patients in

third line theraphy achieved a clinically important change (i.e., more than 10 points) in global QoL and 43% achieved a similar change in emotional functioning and 31 % in social functioning (McLachlan, Pintilie, & Tannock, 1999). However, the level of compliance of this study was 94% at the start of chemotherapy and declined to 60%.

Because the taxanes are relatively new treatments for advanced breast cancer and which are demonstrated to be effective, their impact on QoL has been only recently studied. There are only two HRQoL studies in which docetaxel has been compared to another treatment (Chan et al., 1999; Nabholtz et al., 1999). Furthermore, one study compared the capecitabine plus docetaxel combination with docetaxel alone (O'Shaughnessy et al., 2002). In all of these studies HRQoL has been a secondary endpoint, while response rates and survival were the primary endpoints. Chan's (1999) phase III study compared docetaxel and doxorubicin in patients with metastatic breast cancer who had received previous alkylating agent-containing chemotherapy. HRQoL was measured by using the EORTC QLQ-C30. There were no differences in HRQoL scores between the treatment groups. Docetaxel produced a significantly higher rate of objective response than did doxorubicin (47.8% v 33.3%; P =0.008 (Chan et al., 1999). The median time to disease progression was longer in the docetaxel group (26 weeks v 21 weeks; however, the difference was not significant). The median overall survival was similar for the two groups (docetaxel, 15 months; doxorubicin, 14 months). In Nabholtz's (1999) study, docetaxel was compared with mitomycin plus vinblastine in patients with metastatic breast cancer that was progressing despite previous anthracycline-containing chemotherapy. The quality of life was measured by using the EORTC QLQ-C30; however, the analysis was limited to two key variables (global QoL and physical functioning). The results were again similar for both groups: there were no significant decreases in either group in physical functioning or global QoL from the baseline scores (Nabholtz et al., 1999). The compliance of the study was similar for both treatment groups, but the attrition rate was higher in the mitomycin plus vinblastine group. This limits the interpretation of the results, and any conclusions should therefore be drawn with caution. Docetaxel was significantly superior to mitomycin plus vinblastine in terms of response (30.0% v 11.6%; P < .0001), time to disease progression (19 v 1 weeks, P=.001, and survival (1.4 v 8.7 months, P=.0097).

A third clinical study by Sjöström et al. (1999) comparared docetaxel to methotrexate and 5-fluorouracil in advanced breast cancer after anthracycline failure. The clinical findings of the study were the following: there was a

significantly higher overall response rate for docetaxel, 42% (CR 8% + PR 34%), than for the methotrexate and 5-fluorouracil group, 21% (CR 3% + PR 18%) ($P < 0.001$). The median time to disease progression was 6.3 months for the docetaxel arm and 3.0 months for the methotrexate and 5-fluorouracil M-F arm ($P < 0.001$). Docetaxel also had a significantly higher response rate of 27% following the cross-over compared to methotrexate and 5-fluorouracil (12%). The median overall survival, including the cross-over phase, was 10.4 months for the docetaxel and 11.1 months for the methotrexate and 5-fluorouracil arm ($P = 0.79$). Significantly more side-effects (leucopenia, infections, neuropathy, oedema, asthenia, nail changes, alopecia) were seen in the docetaxel than in the methotrexate and 5-fluorouracil group. However, grade 3 and 4 side effects were infrequent with both drugs, with the exception of fatigue, alopecia and infections (Sjöström et al, 1999). In the context of this study, the HRQoL analysis was considered to be of such importance that it was published separately. The results of this study will be examined more closely in the results section (STUDY I in this thesis).

O'Shaughnessy et al. (2002) compared capecitabine and docetaxel with single-agent docetaxel in anthracycline-pretreated patients with advanced breast cancer. The EORTC QLQ-C30 global QoL scale was selected as a primary variable in assessing HRQoL. No significant differences were found over time. However, docetaxel and capecitabine resulted in significantly superior efficacy in time to disease progression (TTP) (median, 6.1 v 4.2 months ;P =.0001;), overall survival (median, 14.5 v 11.5 months; P =.0126), and objective tumour response rate (42% v 30%, P =.006) compared with docetaxel (O'Shaughnessy et al., 2002). Gastrointestinal side effects and hand-foot syndrome were more common with the combination therapy, whereas myalgia, arthralgia, and neutropenic fever or sepsis were more common with docetaxel and capecitabine. More grade 3 adverse events occurred with the combination therapy, whereas grade 4 events were slightly more common in docetaxel with combination (O'Shaughnessy et al., 2002). It is, however, very difficult to conclude the impact of treatments on the patient's global QoL, since the study population in the docetaxel group was only half the size of the study population in the capecitabine and docetaxel group at week 30.

Generally speaking, relatively few studies of HRQoL in advanced breast cancer have reported major differences between the treatment groups (Bottomley & Therasse, 2002). Furthermore, HRQoL outcomes provided little information beyond those obtained from traditional medical outcomes, including toxicity or influenced clinical decision making (Goodwin, Black, Bordeleau, & Ganz, 2003). There might be several reasons: one reason for that might be that, for ethical

reasons, treatments compared in cancer clinical trials must be similar and there are no placebo controlled trials. Another reason is poor compliance or small sample sizes (Bottomley et al., 2002). In the studies where in which nonrandom missing data or selective attrition is evident, it is difficult to interpret the results. This means that patients who respond to the treatment response continue in the study, whereas the patients with disease progression drop out of the study. Therefore, any conclusions from longitudinal HRQoL data can be made from only a very short period of time after the baseline. This is the problem on two occasions in particular: (1) when the compliance is low, because as a result of serious treatment toxicity, progressive disease or death, data are more likely to be missing (Fairclough, Peterson, & Chang, 1998) and (2) when the treatment's efficacy clearly differs, because it is impossible to make any estimations of a patient's HRQoL in whom the disease has progressed. These difficulties make the interpretation of the results difficult as well as decrease the significance of the power of HRQoL results as a basis of clinical decision making.

1.5 The art of measuring HRQoL in cancer clinical trials

The widest application of HRQoL measurements is their use in clinical randomised and descriptive trials. In these trials, the methodology for HRQoL should be as robust as the methodology for clinical outcomes. This requires a clear understanding of the reasons for the measurements, with a priori stated hypothesis and a study protocol in which the practical procedure of data collection and management are explained in detail in order to reduce error variance. In HRQoL methodology, it is essential to understand the possible sources of errors that are typical in measuring psychological aspects of human life. In this research field, however, the use of QoL measurements have been used to solve problems in the tradition of medicine. Many of the difficulties in using HRQoL questionnaires in the past have arisen from the poor design of the studies (Cull, 1997) and from poor compliance (Hurny et al., 1992). Recently, some systematic reviews on methodological issues in HRQoL in randomised trials have been published. The main limitations of the studies have been the following: very few, only about 6%, gave any definition of HRQoL, and only 13-40% of the studies stated a specific pre-trial HRQoL hypothesis (Bottomley, Vanvoorden, Flechtner, & Therasse, 2003). Furthermore, quite common limitations were poor or not reported compliance, the lack of a clear approach to missing data and data analysis, the limited presentation of results and the lack of the use of clinical significance

(Bottomley, Efficace et al., 2003; Bottomley et al., 2002; Efficace et al., 2003; Lee & Chi, 2000).

Despite the recognised weaknesses in HRQoL research, the U.S. Food and Drug Administration (FDA) recognises the benefits of HRQoL as a basis for the approval of new anticancer drugs. Therefore, many international research groups include HRQoL measurements in their studies. However, only about 10% of all randomised controlled cancer trials reported on quality of life (Sanders et al., 1998) and no FDA approvals of oncology drugs between 1990-2002 were based on instruments measuring HRQoL (Johnson, Williams, & Pazdur, 2003). There are several possible reasons why introducing HRQoL into oncology has been difficult. Johnson et al. indicated that the main reasons the HRQoL assessments have not been well-conducted were unblinded assessments, large amounts of missing data, and poorly defined prospective analytic plans (Johnson et al., 2003).

Not only has the field suffered from the methodological problems, but there are also barriers for physicians' use of HRQoL information. Of physicians 84%, felt that their knowledge of HRQoL literature is limited and relied primarily on clinical experience to assess HRQoL. In addition, they felt that QoL information was difficult to understand (Bezjak et al., 2001). It is also difficult to compare results across different studies especially as the studies use different, albeit well-known questionnaires such as the FACT-G (Functional Assessment Cancer Therapy) and the EORTC QLQ-C30. When the pairs of corresponding subscales of the EORTC QLQ- C30 and the FACT-G were compared, only low to moderate correlations were found and discrepancies between the instruments resulted in contradictory conclusions (Holzner et al., 2001).

With the increasing number of studies on HRQoL issues, researchers in the field have faced various challenges associated with methods, concepts, practical applications, and clinicians' attitudes towards HRQoL. However, there has been progress and some methodological problems are slowly being overcome. One reason might be that an increasing amount of literature is devoted to providing guidelines for how to design, organise, analyse and interpret HRQoL in clinical trials. In these guidelines, the following aspects are covered: the rationale of HRQoL measurements as a primary or secondary endpoint and the selection of the appropriate instrument (usually validated instruments the European Organization for Research and Treatment of Cancer (EORTC) and Functional Assessment of Cancer Therapy-General (FACT-G) instruments are recommended). There are instructions on the number of measurement points (at least three points of

measurement before, during and after treatment), on practical procedures for data collection and on how to inform patients and the staff; advice for monitoring compliance; recommendations for enhancing compliance and instructions for data management. There are recommendations for sample sizes, handling and reporting missing data, data analysis, the interpretation of data and clinical significance,and reporting results (Brandberg, 2000; Fayers & Bottomley, 2002; Fayers et al., 1997; Osoba, 1998; Staquet, Hays, & Fayers, 1998; Velikova, Stark, & Selby, 1999; Young et al., 1999).

Even though guidelines are available, there have been problems in reporting the results of those studies. The standards that are lacking on how to report HRQoL studies has made it difficult to interpret individual studies and to conduct systematic reviews (Lee et al., 2000). Only recently have suggestions been made for a minimum set of criteria for assessing reported outcomes in cancer clinical trials (Efficace et al., 2003). Since 1998 there have been guidelines on interpreting clinical significance and reference values for diverse cancer populations available for the EORTC QLQ-C30 (Fayers, Weeden, & Curran, 1998; Osoba et al., 1998) but only few researchers have used them. These aid in the meaningful interpretation of results and are useful for comparison with a group of patients with similar characteristics. .

The present study protocol was written in 1994. At that time, despite the growing interest in measuring HRQoL, only broad instructions on how to measure and the reasons for measuring HRQoL were available (Aaronson, 1992; Cella et al., 1990; Donovan, Sanson-Fisher, & Redman, 1989; Kaasa, 1992; Maguire & Selby, 1989). In the literature, critical reflection on practical and methodological issues was lacking.

In the guidelines for how to design and report HRQoL within EORTC trials, it is stated that in many centres there are no data managers or study nurses helping the clinicians to collect the HRQoL data (Kiebert, Curran, & Aaronson, 1998). In another set of guidelines it is noted that clinicians may or may not collect the HRQoL data. Although, in general, it is recommended that a person other than the physician in charge, administers the questionnaire, because it has been suggested that patients try to please their doctor and thus the responses may be distorted if the person responsible for managing the treatment is present while the patients complete the forms (Fayers et al., 1997). These are implicit statements of optional confidentiality in HRQoL measurements. In the guidelines this source of error can

be due to the vagueness of the data collection procedure and lack of confidentiality is not recognized.

The issue of confidentiality should be especially stressed in randomised clinical trials, in which a new treatment regimen is compared with the usual treatment. After randomisation, patients usually know which treatment is the new one and therefore that kind of research frame is evocative of expectations of treatment efficacy. This is especially important in palliative settings where hope for better HRQoL rather than for excessive survival gain should be given. There is some evidence of how small a chance of gain from a treatment the patients are willing to accept. According to a classic study by Slevin (1990), most patients were willing to accept intensive chemotherapy for a very small chance of benefit; i.e., for a 1% chance of a cure, and when asked about the relief of symptoms, 43% of patients accepted intensive treatment when the chance of relief was very small (Slevin et al., 1990). Even in a palliative setting, 78% of patients favoured chemotherapy to the best supportive care, and patients who were striving more for the length of life than HRQoL had strong preferences for palliative chemotherapy (Koedoot et al., 2003). Jansen et al. (2001) found that 40 % of breast cancer patients receiving adjuvant chemotherapy were willing to accept therapy even if it had no clinical benefit at all, with zero gain in survival (Jansen et al., 2001). This study may not be applicable as such in palliative settings, however, as it seems that treatment has a dual function for patients: to gain a chance for survival and to allay anxiety. This is because as long as thetreatment lasts and new treatments can be proposed, even though there my be only very little or not efficacious at all in terms of survival, fears may be controlled when a treatment offers some possible benefit and hope (de Haes & Koedoot, 2003; Slevin et al., 1990).

These results lend weight to our argument that it is essential that HRQoL measurements are strictly confidential in regard to those in charge of treatment, in order to avoid the bias that might occur if patients try to please the physician in order to continue the treatment. Even in the most recent EORTC guidelines there is only a recommendation that the questionnaires completed by the patients are not to be shown to their physician or other personnel responsible for their treatment (Young et al., 1999). In the light of all this, it seems that is not fully recognised how the lack of the confidentiality of the answers can jeopardise the validity of the results.

The *exactness of the timing* of HRQoL administration has not been focussed on earlier literature. However, due to the cyclic nature of the treatments, this should be

an important issue to control in order to enhance the reliability of the study. In the EORTC guidelines the instructions for the timing of measurements are to be time-based or event-based (Young et al., 1999). Time-based measurements give a set number of days or weeks after randomisation independent of the treatment schedule. In an event-based approach, the measurements are to be given to coincide with specific treatment cycles. It is recommended that assessments are usually scheduled to take place immediately before treatment and the acceptable time windows should be specified beforehand – during the treatment the windows should be narrow (e.g +/- week) (Young et al., 1999). Hence, the recommendations for the exactness of timing are vague.

Thus, although some studies indirectly or directly have touched upon the issue of the timing of HRQoL questionnaires, little attention has been paid to how exact the timing of the HRQoL assessments should be. A classic validation study of the LASA (linear analog self-assessment technique) was the first study to raise the issue of timing. The authors suggested that there were substantial differences in patients' HRQoL if the measurements were done on the day that the treatment was given or 3 days later (Priestman & Baum, 1976). In a study designed to test the responsiveness of the EORTC QLQ-C30, Osoba and colleagues (1994) showed that decreases were seen in physical, role and social functioning and in the global quality of life eight days after chemotherapy compared to the baseline scores. In addition, there was greater fatigue, nausea and vomiting compared to before the chemotherapy (Osoba et al., 1994). Hurny and colleagues (1994) studied the timing of baseline assessment in an adjuvant trial and noted that the timing of assessment in relation to chemotherapy especially affects measures sensitive to toxicity. According to him, the effect of timing was on the same order of magnitude as the effect of treatment (Hurny et al., 1994). Pater et al. (1998) conducted a study altering the time of administration and the time frame of quality of life assessments in clinical trials. Patients who completed questionnaires on day 8 were more likely to report deterioration in the quality of life if their questionnaire had a 7-day time frame rather than a 3-day time frame (Pater J et al., 1998). A clinical model of HRQoL assessments for cancer patients suggested by Klee et al. showed that results from patients who did not complete the questionnaire within the specified time windows tended to dilute the findings from the group who did (Klee, King, Machin, & Hansen, 2000). In conclusion, there are some studies that directly or indirectly show the effect of the timing of HRQoL questionnaires.

1.6 Physical functioning, toxicity and HRQoL

It is widely agreed that HRQoL cannot be reduced to physical functioning or treatment toxicity, even though these are assumed to be important determinants. In cancer clinical trials, physical performance is commonly assessed using the Karnofsky Performance Status (KPS) or WHO performance status scales. The KPS scale ranks performance status ordinally from 100 (asymptomatic, normal function) to 0 (death). The WHO performance status ranks performance from 4 (normal functioning) to 0 (death). When using these scales the patient's physical functioning is assessed by the physician, usually by asking the patient. These measures are widely used and commonly accepted both in clinical practice and in research settings.

If physical functioning is, however, one of the most important determinants of HRQoL, then the two should be highly interconnected. Therefore, in processes of validating HRQoL instruments, in the scoring of physical functioning either the WHO performance or the Karnofsky performance score has traditionally been used as an anchor variable. In research, the validity of the EORTC QLQ-C30, in terms of the ability of the scales to distinguish between subgroups of patients on the basis of clinical status (i.e., known group comparisons) has been proved by using patients with different performance statuses. There is a strong linkage between WHO or Karnofsky performance status scores and several domains of the EORTC QLQ-C30; these are all in the expected direction (Aaronson et al., 1993; Kobayashi et al., 1998; Kyriaki et al., 2001; McLachlan, Devins, & Goodwin, 1998; Osoba et al., 1994; Schaafsma & Osoba, 1994). The strongest correlations were found between the WHO performance score and role and social functioning as well as global QoL (Schaafsma et al., 1994). Significant differences between the groups with different KPS statuses or different performance scores have been documented (Bjordal et al., 2000; Kyriaki et al., 2001). Patients with poorer performance scores reported significantly poorer QoL in all subscales measured with the EORTC QLQ-C30 (Aaronson et al., 1993; Bjordal et al., 2000; Kobayashi et al., 1998) with the exception of emotional and social functioning in Aaronson's (1993) study.

In cancer clinical trials the physician assesses the treatment toxicity most often by using the standardised WHO criteria (Miller, Hoogstraten, Staquet, & Winklaer, 1981). In connection with clinical trials, the HRQoL results and the clinical results are often reported and analysed separately, and therefore the relationship between the treatment toxicity and HRQoL often remains unclear. However, a study by Macquart-Moulin (2000) found that the EORTC QLQ-C30 global score was significantly correlated with the total number of the chemotherapy treatment's side-

effects (correlation coefficient $r = 0.41$; $p < 0.001$) (Macquart-Moulin et al., 2000).Pain, fatigue and sleep disturbance has also been found to correlate significantly to the global QoL scale (McLachlan et al., 1998).

Physicians make their clinical decisions by assessing the treatment efficacy, physical functioning and bearable side-effects. These assessments naturally depend on various uncontrollable variables, such as the nature of the communication between the patient and the physician, the personality of the physician and the patient, etc. However, there has been some evidence that there is a discrepancy between the physician- assessed toxicity and the patient-assessed toxicity. A study by Sigurdardottir (1996) compared the physician-rated clinical outcome and patient reports, and found no correlation between them, with the exception of neurotoxicity (Sigurdardottir, Bolund, & Sullivan, 1996). A study by Stromgren and colleagues (2001) investigated the extent to which the symptoms experienced by advanced cancer patients were covered by the medical records. The analysis revealed good concordance for pain, but most other symptoms or problems (i.e. nausea / vomiting, reduced appetite, dyspnoea and fatigue) were reported much more often by patients than by their doctors (Stromgren et al., 2001). The data collection in cancer clinical trials using clinical research forms (CRF) is a more structured system of collecting information than medical records. Clinical research forms are planned to cover predetermined variables, using a well-known rating system (such as one according to WHO). In a study by Geels et al. (2000) comparing the amount of symptoms recorded in clinical research forms and patient-assessed HRQoL questionnaires, they found that the most commonly reported baseline symptoms were cancer pain in 38% (CRF data) and 81% of patients (QoL data) and tiredness in 26% (CRF data) and 89% (QoL data) of patients (Geels et al., 2000). Hence, of any given symptom, the QoL questionnaires identified a much higher number of patients with that symptom. In a recent study by Brandberg and colleagues, correlations between toxicity registration and the HRQoL questionnaire collected data showed only weak correlations (Brandberg et al., 2003). However, the ratings of any single toxicity assessed by the patient and the doctor were not reported in any of these studies.

When using the same assessment method i.e., the EORTC QLQ-30, there was reasonable agreement in the mean scores between patients, and physicians, for many domains of HRQoL (Wilson, Dowling, Abdolell, & Tannock, 2000) . However, there was substantial discordance between scores when considering individual patients. For patients with metastatic breast cancer, physicians

systematically underestimated overall QoL, social functioning, role functioning and diarrhoea (Wilson et al., 2000).
It is therefore theoretically and practically important to understand the relationship between the structured physician-assessed toxicity and physical functioning parameters and the structured reports by patients of their HRQoL.

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1.7 The prognostic value of HRQoL scores for cancer

According to Cella (1993), one of the main reasons to conduct HRQoL research alongside a clinical trial is to provide a predictor of response to future treatment. It is a popular belief that psychosocial factors, including HRQoL, can influence survival from cancer. However, there is little consistent evidence of important psychosocial factors on survival (Petticrew, Bell, & Hunter, 2002). Several studies have shown that HRQoL data may predict cancer patients' survival. The most convincing evidence for a cause-and-effect relationship between HRQoL parameters and the outcome of a malignant disease comes from randomised controlled clinical trials for which other related factors relevant to outcome, such as treatment and the characteristics of the tumour are controlled. The purpose of studying prognostic factors is to assist clinicians in decision making concerning treatment choices and rehabilitation. The majority of studies examining the association between survival and HRQoL data show a relationship between the HRQoL scores and survival (Blazeby, Brookes, & Alderson, 2001; Coates et al., 2000; Coates, Porzsolt, & Osoba, 1997; Dancey et al., 1997; Jerkeman et al., 2001; Maisey et al., 2002; Montazeri et al., 2001; Seidman et al., 1995; Tamburini, Brunelli, Rosso, & Ventafridda, 1996; Wisloff & Hjorth, 1997).

Only a handful of studies with a sufficient study population examine the prognostic value of the HRQoL score measured using the EORTC QLQ-C30. There are two large studies with heterogenic cancer populations (including breast cancer patients) receiving different types of chemotherapy. In Coates' and colleagues (1997) study, the global scale and the scales of physical, role, emotional, cognitive and social function were each significantly predictive of subsequent survival duration in the univariate analysis. In the multivariate analysis, physical, social and global scales provided independent prognostic data (Coates et al., 1997). In Dancey's study, the univariate analysis showed that physical, role , social functioning, global QoL and symptoms of fatigue, pain, dyspnoea, appetite loss and constipation were predictive of survival. Surprisingly, according to the multivariate analysis, the HRQoL variables associated with prolonged survival were the absence of dyspnoea, a high

global QoL and low emotional functioning (Dancey et al., 1997). In addition, they found that the emotional functioning score was not associated with survival with those patients who had high global QoL scores. These somewhat ambiguous results may have raised the question of the prognostic value of HRQoL data in controlled cancer clinical trials with a very specific study population.

There are two studies by Coates and colleagues exploring the prognostic value of HRQoL scores in breast cancer patients using LASA (linear analog self-assessment) and the QLI (quality of life index) (Coates et al., 1992; Coates et al., 2000). In a classic study by Coates, the patient LASA scores for physical well-being, mood, nausea and vomiting, appetite, and overall QoL (but not pain) at the commencement of treatment were significant predictors of subsequent survival. In addition, they found that both the QLI and physical well-being were prognostically independent of tumour response (Coates et al., 1992) Another interesting and large study by Coates et al. (2000), in which they compared the prognostic value of HRQoL scores in the adjuvant setting and after relapse in two randomised trials in more than 2000 breast cancer patients. Their results showed that any prognostic significance of HRQoL scores in the adjuvant setting is minimal or obscured by chemotherapy effects, but there is a strong prognostic significance of HRQoL scores after disease relapse (Coates et al., 2000). This result increases the ambivalence towards the prognostic value of HRQoL data.

There has been some evidence that change scores from baseline HRQoL can predict overall survival. In Blazeby's study, improvements in emotional functioning were significantly associated with longer survival in 38 patients (Blazeby et al., 2001). In another study with 64 advanced breast cancer patients, change scores in physical well-being, mood, pain, and overall QoL were predictive for longer overall survival (Coates et al., 1992).

When compared to the extent of use EORTC QLQ-C30 in cancer clinical trials (over 3000 studies worldwide), surprisingly few reports have focussed on the HRQoL score's value for prognostic survival or treatment response (Coates et al., 2000; Jerkeman et al., 2001; Kramer, Curran, Piccart, de Haes, Bruning, Klijn, Van Hoorebeeck et al., 2000; Maisey et al., 2002; Norris et al., 2000; Roychowdhury, Hayden, & Liepa, 2003; Wisloff et al., 1997). The results of even those few studies show somewhat confusing results. In the studies using a univariate analysis, all other domains than the financial domain EORTC QLQ-C30 scales have been identified as significant independent predictors of survival. However, which combinations of the EORTC QLQ-C30 domains have had predictive value varies

from study to study. According to the results based on multivariate analysis, only physical functioning (Wisloff et al., 1997) global QoL (Jerkeman et al., 2001; Maisey et al., 2002; Montazeri et al., 2001; Norris et al., 2000), dyspnoea, fatigue and emotional functioning have been identified to be prognostic for survival (Kramer, Curran, Piccart, de Haes, Bruning, Klijn, Van Hoorebeeck et al., 2000). In Roychowdhury et. al's (2003) study high physical functioning and low role functioning and the absence of appetite loss were predictive for longer survival.

Most studies have reported that HRQoL is only significant for overall survival, although two studies have included the response to treatment as an outcome (Kramer, Curran, Piccart, de Haes, Bruning, Klijn, Van Hoorebeeck et al., 2000; Roychowdhury et al., 2003). In the univariate analysis, global QoL, physical, social, emotional functioning, pain, fatigue and anorexia were significant predictors for time to progression of the disease and time to treatment failure; in addition, role functioning and insomnia were predictors for progression of the disease, and dyspnoea for time to treatment failure (Roychowdhury et al., 2003). In the multivariate model, positive prognostic factors for time to the progression of the disease were good performance status and minimal fatigue; for time to treatment failure, they were minimal fatigue and no anorexia. Global QoL was a significant predictor of outcome in the univariate analysis but was not retained in the multivariate model (Roychowdhury et al., 2003). In Kramer's (2000) study for treatment response, dyspnoea, fatigue and global QoL were significant predictive factors in the univariate analysis. The final multivariate model for response to treatment selected dyspnoea (P=<0.001) using forward selection, but model instability was indicated by the inclusion of fatigue and emotional function in the final model when backward selection was used (Kramer, Curran, Piccart, de Haes, Bruning, Klijn, Van Hoorebeeck et al., 2000).

Thus, it can be argued that some HRQoL parameters seem to have independent prognostic value for treatment response; their prognostic importance needs further evaluation. The evidence linking HRQoL and survival is somewhat incoherent and some of these studies suffer from methodological problems. There are limitations in the study population (heterogeneity connected with cancer types and stages, the size of the study population), the various differing questionnaires used and problems of compliance. The very limited number of studies and inconstant results raise the question of publishing bias towards negative results. In the light of all this, it is very difficult to make conclusions about the prognostic value of HRQoL. Therefore, further work is required to confirm the prognostic value of HRQoL. To our knowledge, there were no earlier studies of the prognostic value of EORTC

QLQ- C30 scores for both survival and the time to disease progression in patients receiving second line chemotherapy for advanced cancer.

1.8 Qualitative approaches assessing cancer patients HRQoL

Using questionnaires as research methods for HRQoL issues represents a compromise between the desire for quick, practical, easily understood simple questions and, on the other hand, our recognition that such a simple method never gives us in depth understanding of the unique situation of individual. In the field of HRQoL research, there is a polarisation of qualitative versus quantitative approaches, as well as a mutual misunderstanding of the complementary potential of such different approaches. There is an epistemological difference between the qualitative and quantitative approaches to the study of HRQoL. Qualitative approaches such as phenomenology focus entirely on subjective meanings of health-related experiences, and the analyses of these are not primarily for the sake of comparison.

When using quality of life instruments, one presumes that the point of reference does not move, i.e. that individual attitudes towards a particular construct remain stable (Breetvelt & Van Dam, 1991). Thus, it has been argued that cognitive states are important for Quality of Life, because the intensity with which the patient suffers from her physical state often depends on the way these are cognitively or emotionally interpreted, e.g., as indicators of remission or progression or as side-effects of a successful or of an unsuccessful treatment (Birnbacher, 1999). This kind of personal meaning is always underlying the experience of QoL. According to the theory of the principle of psychic self-regulation, a person uses psychic work i.e. mental processes (intentions, thoughts, affects, motives) for achieving and for maintaining her psychic equilibrium (Vuorinen, 1986a, 1986b, 1986c). In the light of this systemic approach, it is no wonder that correlative theories of QoL cannot capture the phenomenon called HRQoL, and therefore qualitative approaches are needed to complement the HRQoL research. It is encouraging that there is so much knowledge about the basic patterns of patients' HRQoL, and to some extent, even knowledge of more subjective views of cancer patients' experiences. One of the greatest challenges of future research is how to integrate both kinds of information in a meaningful way.

So far there have been only a handful of researchers, most typically in the field of nursing science, who have adopted a qualitative approach in assessing the HRQoL

of patients with cancer. Because there are only few qualitative studies exploring the subjective meanings for breast cancer patients and the nature of the findings is descriptive, other studies than those on breast cancer will also be discussed in this section.

A classic interview study of breast cancer patients' adjustment to threatening events is not precisely a study of HRQoL as such; however, it cannot be ignored, because it has systematically documented the means of adjustment to breast cancer. Taylor's (1983) theory of cognitive adaptation to illness suggests that coping with breast cancer consists of three processes: (1) a search for meaning (e.g., patients' attempts to understand why they developed cancer, (2) a search for mastery (the belief that they can control the course of illness, and (3) self-enhancement (social comparison, whereby women analyse their condition in terms of others they know). These cognitive restructurings are in large part based on illusion (defined as a perception that represents what is perceived in a different way than it is in reality), i.e., unrealistically positive self-evaluation, exaggerated perceptions of control or unrealistic optimism (Taylor, 1983; Taylor & Brown, 1999). These illusions appear to foster traditional criteria of mental health, including the ability to be happy, and to help people to profit from negative life events that are unavoidable by enabling them to put those events in the best light (Taylor, 1983; Taylor et al., 1999).

Lam & Fielding (2003) conducted a phenomenological study of 17 Chinese women with breast cancer. Patients were interviewed on the completion of their initial treatment. In this study the treatments and stages of the disease varied widely (tumour stage from III to I, the treatments were chemotherapy, radiation or hormonal therapy or a combination). Thematic analysis suggested that the identification and treatment of the disease included the difficulty of living in uncertainty and of maintaining and regaining normalcy in a superstitious society. The initial uncertainty of disease detection and the diagnostic process were characterised by shock and disbelief mingled with a fear of death. The thematic analysis of that study suggested that breast cancer not only disrupts the fabric of daily life but changes in appearance proved to be problematic for those women who tried to hide their disease to protect themselves against stigmatisation and social exclusion. (Lam & Fielding, 2003).

Another qualitative study of breast cancer patients focussed on the existential issues of 10 newly diagnosed breast cancer patients. Again there were broad variations in the sense of disease development and the type of cancer treatment (Landmark, Strandmark, & Wahl, 2001). They found that the existential aspects connected with

the core category, the will to live, were a central issue in recovery and survival. The patients' energy was all channelled into the fight for life. This included different levels of life expectations, the fight against death, life related to the future, religious beliefs and doubts and increased awareness of the values of life. However, these meanings may not be adapted as such to patients with advanced breast cancer, even though adherence to treatment can be seen as a manifest of the will to live.

Nelson (1996) explored the experiences of uncertainty of 9 women with breast cancer. Living with the vicissitude or irregularity of emotions was found to be a powerful aspect of uncertainty. The presence of support during uncertainty influenced the patients' perceptions and interpretations. Relying on support through relationships included a sense of optimism and hope from others. Uncertainty challenged the patients to learn new ways of being in the world and although breast cancer was a negative life experience, the women began to focus on the positive aspects of life, which made them more aware of what was important in their lives. Moreover, the reflection of self in the world had a powerful effect on the patients' uncertainty experiences. To deal with uncertainty, the patients had to understand their disease and put it into a broader and meaningful life perspective (Nelson, 1996).

A consecutive series of qualitative research on breast cancer patients at different stages of the disease and receiving different treatments was performed by Arman (Arman & Rehnsfeldt, 2002; Arman, Rehnsfeldt, Carlsson, & Hamrin, 2001; Arman, Rehnsfeldt, Lindholm, & Hamrin, 2002). The studies focussed on experiences of life changes, the search for meaning , and suffering. In her first study, she used qualitative content analysis in order to understand the reported changes of life perspective in interviews with 59 women (Arman et al., 2001). The women experienced both beneficial and harmful changes in life perspective. The findings of that study indicated that these women's views of their relationships with others grew more valuable, and their relationships with husbands were described as improved. Their self-confidence and experience of strength improved, and they regarded life as being more enriched. The disease made them look more positively at life and gave life a deeper value. The women experienced a change in their disposition towards becoming more fragile and low-spirited as a hardship. They described the aetiology of the disease from several interacting perspectives that also affected their ideas of how to achieve well-being and health. Often mentioned were the emotional conditions (grief or stress) they had experienced during their life. Arman's second study was a qualitative case study (four women were interviewed four times) focussing particularly on changes in life perspective and on obtaining a

deeper and more profound understanding of the lives of women living with breast cancer (Arman & Rehnsfeldt, 2002). The women experienced an increased awareness of the relationship between life and death, which constituted a disclosure rather than an actual change in life perspective, and often underwent an increase in the desire to live their lives in accordance with their own values. This revitalised view of life increased the desire for taking control of one's life and daring to be oneself. However, when it proved impossible to live in accordance with their new insights, the women were particularly frustrated (Arman & Rehnsfeldt, 2002).

The challenges for women with ovarian and for advanced breast cancer are similar both physically and psychologically because of the advanced nature of the disease, the side effects of the chemotherapy treatments, the repetitive cycles of aggressive therapy, and the perceived loss of femininity. Therefore, results of the qualitative studies of one cancer might be applicable to the other. Howell and colleagues have conducted qualitative studies of 18 patients with ovarian cancer (Howell, Fitch, & Deane, 2003a, 2003b). The women reported the myriad day-to-day changes in their lives including the inability to continue employment, feeling different about themselves, altered relationships with friends, the impact on the family, changing roles and fears for husbands, altered sexuality and worries about children (Howell et al., 2003a). The major challenges they had to face were living with uncertainty, lack of control, the fear of the unknown and the stigma of cancer and facing death. The women described many sources of support (including family members, friends, andchurch community) that helped them to get through the experience of living with ovarian cancer. (Howell et al., 2003a). Howell conducted another study to describe ovarian cancer patients' experiences confronting disease recurrence (Howell et al., 2003b). Treatment for recurrent ovarian cancer is always palliative. Four primary themes emerged from the analysis of the interview transcripts: (1) waiting for recurrence was described as frightening, (2) facing the diagnosis of recurrence, (3) managing treatment-related concerns in that patients felt that there were few treatment options available, and for patients who had had difficult complications with the earlier treatment, facing the treatment again was described as particularly challenging, and (4) attempting to regain control by engaging in unproven alternative therapies. Those women (12 of 18) who used alternative therapies felt that alternative therapies helped them feel that they had a sense of control over their disease.

There are three qualitative studies exploring the meanings of suffering in persons living with cancer (Arman & Rehnsfeldt, 2003; Kuuppelomäki, 1998; Ohlen, Bengtsson, Skott, & Segesten, 2002). Kuuppelomäki (1998) identified three

different dimensions in patients' experiences of suffering, i.e. the physical, psychological and social, in a study of 32 patients with incurable cancer. Physical suffering was divided into two categories: caused by illness itself such as fatigue and pain or treatment- related suffering i.e. the side- effects of chemotherapy. Psychological suffering was most typically manifested in depression. Social suffering was expressed when the general deterioration and the fear of infection caused them to withdraw into their home or hospital. Ohlen and colleagues (2002) explored the meanings of alleviated suffering in persons living with life-threatening cancer. In that phenomenological study, 16 patients with cancer who were receiving palliative treatment were interviewed. The meanings that were related to the alleviation of suffering were (1) having endurable bodily experiences; (2) being independent and feeling at home; (3) having feelings of connectedness with other people; (3) taking a long term view of the suffering as pleasure and joy give the strength and courage to face the suffering again; (4) being lifted out of the suffering, meaning that joy and pleasure arise from the bottom of the soul and make the person less vulnerable to suffering , and (5) having an inner peace. As an interpreted whole, the alleviation of suffering was found to be an embodied experience of "being in a lived retreat." This means that a person with life-threatening cancer experiences time and space as being herself, on her own conditions and in ways that alleviate suffering (Ohlen et al., 2002). This lived retreat can provide a feeling of being at home in an existential sense, creating peace, rest, confidence, and breathing space in the person's suffering. It means coping with an altered body and feeling dignified (Ohlen et al., 2002).

In Arman's third study, she focussed on the suffering experiences of a sample of 17 women (Arman, Rehnsfeldt et al., 2002). The findings elucidate how the suffering experience touched the women's inner existence and values. According to Arman, suffering can metaphorically be described as a "field of forces", which contains the movement of changes, adjustment, emptiness but also growth, insight and power, that affected everything in the women's lives, including their views of themselves and their relationships. Existential questions were raised about life, death, and the meaning of life. The suffering was encompassed by questions of why, causal explanations and the search for meaning. In their suffering, the women's dependency upon significant others, as well as healthcare personnel, was prominent. Suffering seemed to be expressed, increased, created, and alleviated in the relationship to the other person, and increased when the person was denied the possibility to be authentic in his or her relationships (Arman, Rehnsfeldt et al., 2002).

Very few qualitative studies focus on the meaning of chemotherapy. In a classic study by Nerenz et al. (1982) based on a structured interview of 61 patients receiving chemotherapy, it was found that vague, diffuse side effects such as tiredness and pain were more likely to be associated with distress than were acute, specific side effects such as nausea and vomiting (Nerenz, Leventhal, & Love, 1982). Another study focussed on the meanings assigned to the experience of receiving chemotherapy among women recently diagnosed with breast cancer (Richer & Ezer, 2002). The findings were based on 56 interviews of ten women, with different kinds of chemotherapy treatments for different stages of breast cancer. Women described three dimensions of their experience with breast cancer and chemotherapy: 1) "living in it" represents an interpersonal dimension that includes cognitive and emotional processing of the experience of having cancer and receiving chemotherapy, 2) "living with it" represents an interpersonal dimension which included sparing the family, unwanted sympathies and life around the clinic, and 3) "moving on" represents the phase when women started to face their future, by seeking a new balance and making plans for the future. All these experiences occurred with both existential and situational meanings. The existential meaning seemed to be present in varying degrees of intensity throughout the treatment, whereas the situational meanings were predominant at the beginning of the treatment phase and became less important as the treatment progressed (Richer et al., 2002).

Common themes, which emerge from qualitative studies of cancer patients' experiences: namely the uncertainty, changed attitudes, the life search for meaning, attempts to regain control, the importance of relationships and altered lifestyles. Although most of the qualitative studies of breast and advanced cancer patients have explored important areas of personal experience and the meaning of cancer, none of those qualitative studies of breast cancer patients has focussed primarily on HRQoL as a multidimensional construct and has explored the meaning of HRQoL as a research question. None of these studies has been conducted in the context of clinical trials and therefore used very diverse samples of patients. In addition, in most of the studies the primary purpose has been the possible implications for nursing theory and practice. Therefore, a qualitative study of advanced breast cancer patients' subjective meanings of HRQoL, conducted by a psychologist and in the context of a clinical trial, is important and useful.

2 AIMS

The general aim of this thesis was to investigate the feasibility of extracting valid information on patients' HRQoL by using various types and sources of data, and to find out how these different data sets contribute to the knowledge of breast cancer patients' HRQoL.

The specific aims were:
To describe and compare the HRQoL findings of a phase III multicentre trial comparing docetaxel (T) to sequential methotrexate and 5-fluorouracil (M-F) in order to find out whether either treatment has a superior benefit in terms of HRQoL and to explore HRQoL changes over time.

To demonstrate empirically the importance of the exact timing of HRQoL assessments.

To estimate the contribution of physical performance and different toxicity variables in explaining the patients global QoL. To evaluate the agreement between the information on side-effects scored by the physician and the patient.

To study whether baseline HRQoL or changes in HRQoL scores from the baseline or both together are prognostic for the time to disease progression or overall survival.

To gain a deeper qualitative understanding of the personal meanings that are related to patients' HRQoL. To identify possible important dimensions of HRQoL not captured by traditional psychometric methods.

3 METHODS

3.1 Patients in studies I-IV

The patients in this study were required to have histologically proven breast cancer that had progressed during or after first line anthracycline treatment for advanced disease or that had relapsed within 12 months after discontinuation of adjuvant anthracycline therapy. The ages of the patients were required to be $\geq$ 18 and $\leq$ 70 years with a performance score of $\leq$ 2 and with normal values of white blood cells ($\geq 3 \times 10^9$/L), platelets ($\geq 100 \times 10^9$/L), serum bilirubin, and serum creatinine.

Patients were ineligible if they had more than one previous chemotherapy regimen for advanced disease (with the exception that multiple endocrine treatments and radiotherapy were allowed), prior treatment with taxanes, any concurrent serious medical illness, cerebral or leptomeningeal metastases or a history of other malignancy except contra lateral breast cancer, basal carcinoma of the skin or in situ cervical cancer.

The study was an open randomised phase III study comparing docetaxel to methotrexate-5- fluorouracil after anthracycline failure. Cross-over to the alternative treatment after relapse was recommended. In all, 283 patients with metastatic breast cancer were randomised into this study between December 1994 and October 1997 from 22 centres in Scandinavia, Estonia and Poland. From the 283 patients, one patient in the M-F group was later found to have no recurrence and was excluded from all the analyses. Oral and written consent by the patient was mandatory for both the trial and the HRQoL measurement. The clinical study and the HRQoL studies were approved by the ethical committees with jurisdiction for the participating centres.

3.2 Patients in study V

In Finland, 32 consecutive breast cancer patients were asked to participate in this qualitative study from the study population participating in randomised phase III study comparing docetaxel to methotrexate-5- fluorouracil. Two agreed to participate, but died after the first course of treatment. One patient was Swedish speaking and therefore could not participate in the study. Three patients refused to participate and 2 patients agreed to participate, but constantly cancelled the appointment for the interview, and therefore the researcher got the impression that they were nevertheless not willing to participate. Altogether, 25 patients participated in the study.

3.3 Procedures

3.3.1 Studies I, II,III and IV

In order to maximise compliance and minimise error variance due to uncontrollable differences in the timing or in the external conditions of the assessments, QoL data acquisition was integrated into the clinical routine of the patients. The questionnaire was administered at the hospital, whenever possible in a room where the patient was not disturbed. The responsible study nurse, or failing that, another member of

the staff, gave the patient the questionnaire and demonstrated for her the two different answering modes (yes-no, and the scales) in order to make sure that the patient understood the task correctly. The patient was asked to answer all the questions by choosing the best alternative available even if no alternative offered an exact match. Before answering, the patient was informed about the confidentiality of the answers; it was explicitly stated that they would not be shown to the physician in charge of the treatment. When all questions had been answered, the questionnaire was put in a sealed envelope that had been placed in front of the patient. The envelope was then mailed to the centre responsible for the SBG9404 (Scandinavian Breast Cancer Group) data entry (Helsinki). The responsible study nurses had participated in a one-day training session during which they were given a checklist of how to organise and monitor the HRQoL measurements.

The first, i.e., the baseline measurement, was made immediately preceding the administration of the first treatment; hence, when filling in the form, the patients were aware of which treatment they would recieve. During treatment, HRQoL assessments were to be completed on day one of every treatment cycle, before the administration of the treatment. A time window of –4 to +0 days (anchored to the administration of the treatment) was determined for an acceptable assessment. This window was accepted on pragmatic grounds: many patients visited the clinic a few days before they received the treatment and completed the questionnaires during that visit. Allowing for –4 days made it possible to include those patients whose visits were interrupted by a weekend; in contrast, delaying the assessment until after the treatment was not acceptable, since receiving treatment was expected to produce effects that would have an immediate impact on HRQoL. HRQoL data collection was continued as long as the randomised treatments continued i.e., until the cross-over.

3.3.2 Study V

Participating in the study was voluntary. It was especially emphasised that participating is optional and does not influence treatment decisions or clinical trial participation. It was also stressed that the research is conducted on behalf of the University of Helsinki, Department of Psychology, not on behalf of the Department of Oncology. Confidentiality was stressed in the written patient information form and always discussed before the interview. It was stressed that the interview was conducted for research purposes and was strictly confidential (including physicians and nurses in the clinic). The only person who will ever see the content of the interviews as such is my supervisor in the department of

psychology and, even so, the patients' personal particulars will remain confidential. Permission for tape-recording was asked before starting the interview. Oral and written consent was mandatory for the interview. The study was approved by the ethical committee of the Helsinki University Hospital.

One of the criticisms of single interviews is that HRQoL issues may cause distress to patients and cannot be followed up. For this reason, the patients were given the opportunity to contact the researcher at any time if desired or needed; none of the patients got in touch with the researcher outside the interview. The interviews took place in a quiet hospital room that was not the physicians' office. The timing of the interviews was after the second or third treatment course, by which time the patients had had personal experience of the randomised treatment.

For the opening question, patients were asked to tell about themselves, their family, their current situation in life and to describe their course of illness. A semi-structured interview format was used. After the opening question, the structure of the interviews broadly followed the structure of the HRQoL questionnaires encompassing global ratings of HRQoL , physical, emotional, social, cognitive and role functioning. However, the interviews were conducted in an open manner, giving the patients the freedom to discuss important issues in their own way.

The original material consisted of 25 audiotaped interviews, with a mean the duration of about 60 minutes. The researcher who transcribed them verbatim for analysis, also conducted the interviews. The AtlasTi 4.1 for Windows software package was used for analysis (www.atlasti.de, 2003).

3.4 Instruments

3.4.1 EORTC QLQ-C30

To assess HRQoL, we used the EORTC QLQ-C30 (The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30) (Aaronson et al., 1993). This questionnaire has been developed to cover aspects of life particularly relevant to cancer patients. It has been translated and validated into 49 languages and has been used in more than 3,000 studies worldwide. The questionnaire is designed to assess the patients' physical functioning (PF), role functioning (RF), cognitive functioning (CF), emotional functioning (EF), social functioning (SF), global quality of life (GQL), pain (PA), fatigue (FA), nausea/vomiting (NV) and, means of multi-item scales, and disease- and treatment-

related symptoms by means of single items: (dysopnea DY, insomnia (SL), appetite loss (AP), constipation (CO), diarrhea (DI) and financial difficulties (FI).

The first generation of the core questionnaire, the EORTC Quality of Life Questionnaire-Core 36 (QLQ-C36) was developed in 1987 (Aaronson et al., 1993). The QLQ-C36 questionnaire was designed to be cancer specific, multidimensional in structure, appropriate for self-administration, and applicable across a range of cultural settings. The subsequent versions of the core questionnaire were the EORTC QLQ-C30 (version 1.0), the EORTC QLQ-C30 (+3), the EORTC QLQ-C30 (version 2.0) and the EORTC QLQ-C30 (version 3.0). The EORTC QLQ-C30 (version 3.0) is the most recent version. We used the validated version 2.0 in Finnish, Swedish, Norwegian, Danish and Polish; the Estonian translation EORTC QLQ-C30 was made ad hoc.

The EORTC QLQ-C30 has been shown to be a reliable and valid instrument (Hjermstad, Fossa, Bjordal, & Kaasa, 1995; McLachlan et al., 1998; Osoba et al., 1994; Sigurdardottir et al., 1996). The usefulness of the instrument in a clinical setting depends on its ability to detect clinically significant differences in terms of sensitivity (the ability to detect differences between groups) and in terms of responsiveness (the ability to detect changes over time within the patient) (Fayers & Hand, 2002). The EORTC QLQ-C30 has been shown to have the ability of detecting changes (Osoba et al., 1994).

There are some suggestions on how to interpret the clinical significance of the results of the EORTC QLQ-C30. Various investigators using a variety of HRQoL instruments have found that an absolute change of 10% or more on HRQoL scores corresponds to a moderate change in the average patient's condition (Fayers, 2001). This seems to be applicable to the EORTC QLQ-C30, as well. According to Osoba, the clinically significant changes on a scale of 0-100 are the following: a difference of 5 to 10 indicates a small change either for the better or the worse; a difference of 10-20 stands for "moderate" change, and a difference greater than 20 for "very much" change (Osoba et al., 1998). The EORTC QLQ-C30 has population-based reference data from the following countries: Denmark, Norway, Sweden and Germany (Hjermstad, Fayers, Bjordal, & Kaasa, 1998; Klee, Groenvold, & Machin, 1997; Michelson, Bolund, Nilsson, & Brandberg, 2000; Schwarz & Hinz, 2001). There are also reference values available by cancer site and stage (Fayers et al., 1998). All these together provide important aid for the interpretation of results from EORTC QLQ-C30 scales.

3.4.2 Medical data

Physicians completed the trial specific case report forms (CRF) before each treatment cycle. Toxicity (i.e., nausea/vomiting, stomatitis, diarrhoea, alopecia, infection, allergy, skin changes and local and other symptoms of toxicity, i.e. nail changes, fatigue dermatitis, neuropatia, oedema) from the previous chemotherapy cycle and the WHO performance status (WHO PS) were assessed before each treatment by physician interviews. Toxicity and response evaluation were evaluated according to WHO criteria (Miller et al., 1981). The toxicity grades ranged from 0 (absent) to 4 (life- threatening). In these data, the WHO performance score ranged from 0 (normal activity), 1 (symptoms but ambulatory), 2 (in bed < 50% of waking time) to 3 (in bed > 50% of waking time). All adverse reactions and reasons for the discontinuation of treatment were collected on the clinical research forms. Overall survival and time to disease progression were calculated from the day of randomisation.

3.5 Statistics

In our study, even in the light of the most recent guidelines in comparison with reports published since 1999, the data meet a high standard of validity and reliability. The compliance (percentage received of expected forms) of the study was 96% and the overall compliance for the first 14 cycles was 89.8%. When forms were completed outside the accepted time window (–4 to +0 days) were excluded, the corrected compliance was 82.4%. The compliance level of our study is one of the highest reported in the field and shows that high compliance, even in patients with advanced cancer, can be achieved. The HRQoL data were available for 245 patients in this analysis: TABLE 1

Table 1 Number of correctly timed EORTC QLQ-C30 questionnaires received by treatment group and treatment cycle with docetaxel (T) methotrexate and 5-fluorouracil (M-F)

Treatment cycle	T	M-F
1 Baseline	129	116
2	106	96
3	104	86
4	86	64
5	80	49
6	66	40
7	58	33
8	37	30
9	39	21
10	17	15
11	11	13
12	9	9
13	7	6
14	6	5
15	7	5
16	4	4
17	3	2
18	1	1
19	1	1
20	1	1

Following the instructions in the EORTC QLQ-C30 scoring manual, a linear transformation to a 0 to 100 scale was carried out (Fayers, Aaronson, Bjordal, & Sullivan, 1995). A higher mean score for functional scales (physical functioning (PF), role functioning (RF), cognitive functioning (CF), emotional functioning (EF), social functioning (SF) and global quality of life (GQoL)), reflects a higher level of functioning, but a higher mean score for symptom scales, (pain (PA), fatigue (FA), nausea/vomiting (NV)), and for disease- and treatment-related symptoms i.e. the single items: (dyspnoea DY, insomnia (SL), appetite loss (AP), constipation (CO), diarrhoea (DI) and financial difficulties (FI)) reflects more symptoms or problems.

The percentages of missing values for single items were the following: 0.8% of all items, ranging between 0.3% to 1.4% across the items. They were replaced by values calculated as suggested in the QLQ-30 manual (Fayers et al., 1995).

3. 5. 1 STUDY I

The means and standard deviations were calculated for each domain of EORTC QLQ-C30. The means of the two treatment groups on all scales were compared at each point of assessment i.e. at the baseline (i.e. 1st cycle), 2nd, 3rd , 4th, 5th, and 6th treatment cycles.

Mean change scores were selected as an additional outcome measure. The calculation of change scores was made by subtracting the mean scores from the cycles 2 to 6 from the patients' corresponding baseline scores.

The Mann-Whitney U test was used to investigate the statistical significance of the differences between the two treatment arms at each point of assessment.

3. 5. 2 STUDY II

In the clinical database, separate variables were used to indicate day 1, i.e., the starting date of every treatment cycle and, in the QoL database, a separate variable was used to indicate the actual date of every QoL assessment. By comparing these dates in these two datasets, it was possible to identify measurements performed at dates different from the prescribed ones.

table 2 The number of correct and incorrect timings by treatment group and cycle

	M-F		**T**	
	incorrect	correct	incorrect	correct
	n	*n*	*n*	*n*
Baseline	17	116	8	129
Cycle 2	12	96	9	106
Cycle 3	14	86	6	104
Cycle 4	12	64	6	86
Cycle 5	5	49	1	80
Cycle 6	7	40	6	66
Cycle 7	2	33	2	58
Cycle 8		30	1	37
Cycle 9	1	21		39
Cycle 10	2	15	1	17
Cycle 11		13		11
Cycle 12	2	9		9
Cycle 13	2	6	1	7
Cycle 14	1	5		6
Total	77	583	41	755

In order to evaluate the difference between correctly timed and incorrectly timed HRQoL assessments, the mean scores of EORTC QLQ-C30 scale points were compared. The two treatment groups were analysed separately since it was expected that erroneous timing might affect the patients' responses differently because of the different toxicity profiles of the two treatments. We chose to include in the analysis the first 14 treatment cycles, after which the number of patients became very small.

We compared the ill timed and correctly timed assessments at the baseline, at which point the effects of dropout had not disturbed the similarity between the two groups and average over the cycles, because the number of ill timed assessments per treatment cycle was very small.

T-tests were conducted to investigate statistical differences between incorrectly and correctly timed assessments. A significance level was set at 5%.

3. 5. 3 STUDY III

To study the correlation between the EORTC QLQ -C30 scales and the WHO PS as well as between the EORTC QLQ-C30 scales and the corresponding WHO toxicity scales, Spearman's rank correlation coefficients were used.

Multiple linear regression analysis was conducted to investigate the impact of toxicity variables on the global QoL. In these analyses, the WHO PS and the toxicity variables were defined as independent variables. Multivariate models were created by using general linear modelling with a stepwise procedure. A significance level of P <=.01 was set.

3 .5. 4 STUDY IV

All baseline EORTC QLQ-C30 variables were dichotomised at the median to yield "good" or "poor" scores. Change scores were calculated indicating change in the EORTC QLQ-C30 between the baseline (i.e., the first measurement) and the 3rd treatment course. The 3rd course was selected because patients had had experience of the treatment and attrition from the study was minimal. This procedure ensured the most representative samples in both treatment groups. Extreme baseline scores (i.e., 0 or 100) were omitted from analysis, since in these patients, HRQoL could

change in only one direction. The percentage of cases omitted from the analysis for that reason depended on the scale and varied from 11% for social functioning to 45% for role functioning with a mean of 36%. The change data was available for 173 patients.
Time to disease progression (TTP) and overall survival (OS) were calculated from the day of randomisation.
Differences in TTP and OS were tested with the log-rank test. Survival curves and probabilities were estimated using the Kaplan-Meier technique. Univariate and multivariate analyses were performed with the Cox proportional hazards regression model to explore the relationship between baseline QoL variables and TTP as well as OS. For the multivariate analysis, Cox regression analysis was performed using the stepwise method and both forward and backward procedures were used, yielding the same results. The importance of single prognostic factors was assessed using the p value of the Wald chi-square statistics, the hazard ratio and its 95 % confidence interval for both TTP and OS.

To explore the relationship between the change in HRQoL variables and TTP as well as OS, the Cox proportional hazards regression model was used for univariate analysis.

A significance level of 1% was chosen, because of the multiple testing.

3. 5. 5 STUDY V

A qualitative research paradigm was applied and, more precisely, a phenomenological research method was chosen to explore the experiences of the women (Giorgi & Aanstoos, 1996). The method contains 4 essential steps: (1) The investigator reads the entire description to obtain a general idea of the whole statement. By thoroughly reading and rereading each interview file, the researcher acquires an idea of the women's experiences. To gain a general sense after reading is the basis for the next step. (2) The discrimination of meaningful units from a psychological perspective is done and with a focus on the phenomenon being investigated. In this step, the subjects' language is not changed in any way. Since it is impossible to analyse the entire interview file simultaneously, it must be broken down into manageable units. The meaningful units in this phase of study were at first relatively broad and followed the broad areas of the interview. The researcher repeated this phase many times and as a result, the meaningful units that emerged as a consequence of the analysis sharpened and narrowed. These meaningful units

do not exist in the text as such, rather only in relation to the attitude or viewpoint of the researcher. (3) The subjects' everyday expressions were transformed into psychological language. These transformations were necessary because we wished to elucidate the psychological aspects in depth. This is essential for understanding the phenomena being researched. (4) Transformed meaningful units were synthesised into a consistent statement. The criterion was that all the meanings of the transformed meaningful units at least implicitly contain one consistent statement. This can be referred to as the structure of the experience. In the present study, the structure of the experience broadly followed the architecture of the EORTC QLQ-C30.

4 SUMMARIES OF RESULTS Studies I-V

4.1 STUDY I: Quality of life in patients with metastatic breast cancer receiving either docetaxel or sequential methotrexate and 5-fluorouracil. A multicentre randomised phase III trial by the Scandinavian Breast Group

This study was to compare the effects of two alternative treatments on HRQoL and to evaluate the possible gains offered by the alternative treatments during the six treatment cycles.

Baseline HRQoL data were available for 245 patients: 130 in the docetaxel (T) group and 115 in the methotrexate and 5-fluorouracil (M-F) group. Data were available for both treatment groups for 20 cycles of treatment, however, due to sample attrition, the groups after 6 cycles were no longer comparable.

Table 3. Reasons for sample attrition at cycle 6

	T	**M-F**
QoL questionnaires recieved	66	40
QoL Protocol violation	13	12
Treatment discontinued due to		
Progressive disease	36	74
Death	6	5
Adverse event	8	2
Patient refusal	9	3
Other	3	3
Missing	1	1
Total attrition due to treatment discontinuation	63	88

The mean baseline scores of the study were compared against reference values of breast cancer patients with advanced disease produced by the EORTC QoL study group (Fayers et al., 1998) and against the normative values of the general Swedish population (women aged 50-59) (Michelson et al., 2000). This data was chosen because the median age of the patients of our study population was 51 and the Swedes were the largest sample population in this data (82 of 282 patients were randomised in Sweden.)

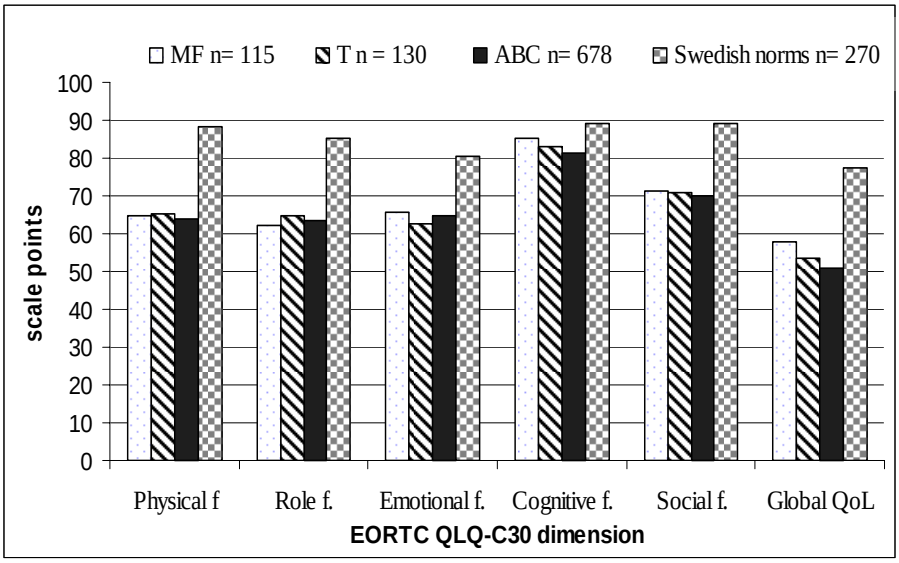
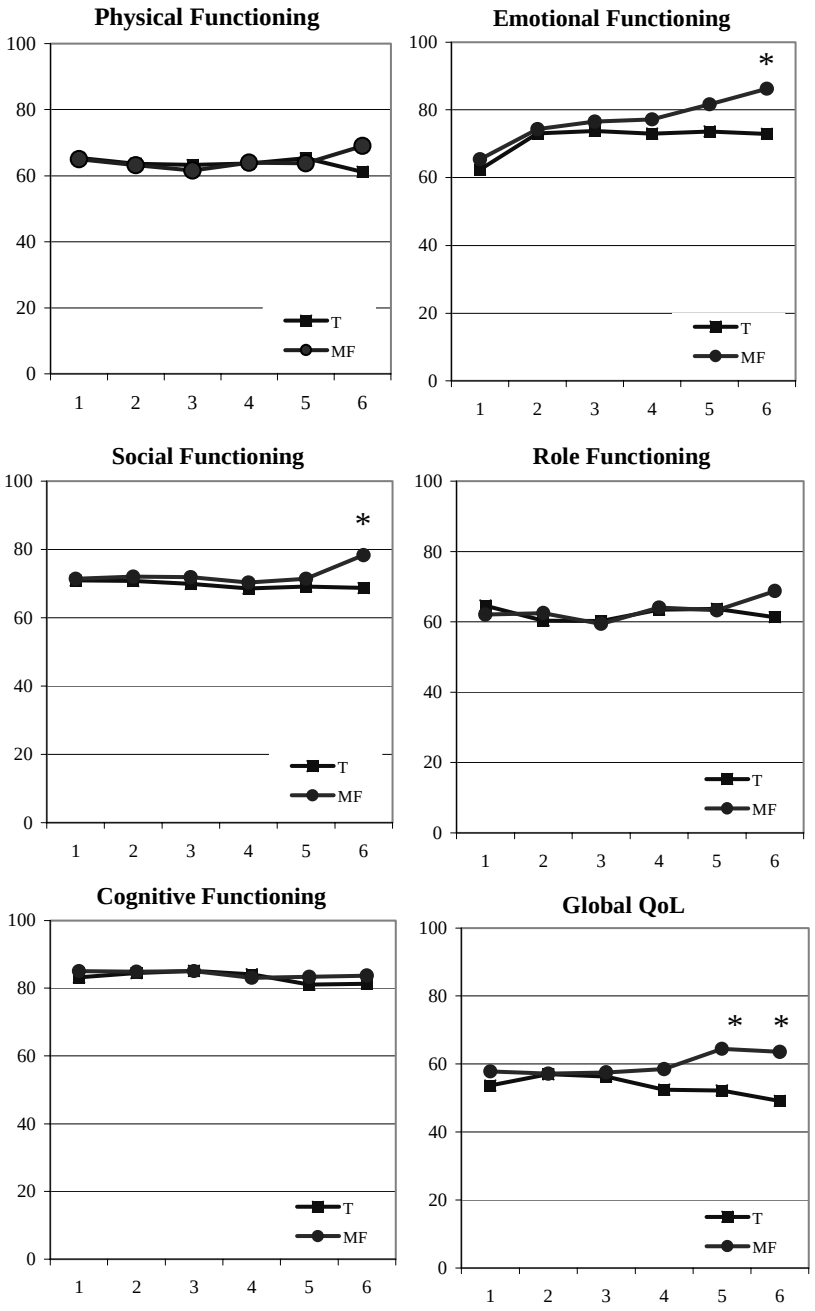


Figure 1. Baseline the mean functional scale scores by treatment group, M-F= methotrexate and 5fluorouracil, T = docetaxel, ABC= reference values for advanced breast cancer patients, Swedish norms = Swedish normative values for women 50-59 years of age. The number of questionnaires is indicated by *n.* Higher scores mean better functioning or better global QoL .

Hence, the data compared against the available reference values seem plausible. The data are coherent with that of advanced breast cancer patients. There are considerable and clinically significant differences in the subscales of physical, role, emotional and social functioning as well as global QoL scales compared against the average scores of 50-59 year old Swedish women.

In the longitudinal analysis of six courses of the treatment, both treatment groups showed clinically significant improvement in emotional functioning from the baseline, with a statistically significant difference favouring the M-F group at treatment cycles 5 (T 73,6 and M-F 81.6 P= 0.028) and 6 (T 72,9 and M-F 86,3 p= 0,002). In the T group, the scores on the other functional scales remained stable throughout the first six cycles. There were significant differences favouring the M-F group on the social functioning scale at treatment cycle 6 and on the Global QoL scale at treatment cycles 5 (T 52. 2 and M-F 64.4; p= 0.004 and 6., (T 49.1 and . M-F 63.5 p= 0.001). (Figure2)



* for statistically significant difference between the two treatment groups (P<0.05)
Higher score indicates higher functioning or better Global QoL (scale 0-100)

Figure 2 Functional scale mean scores by treatment group from baseline to 6th treatment cycle

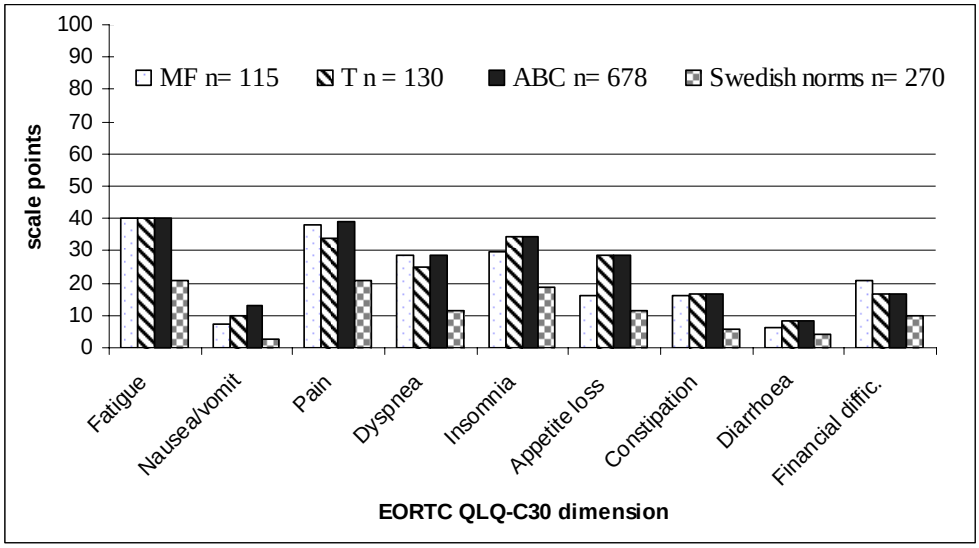


Figure 3 . Baseline the mean symptom scale and single item scores by treatment group (T= docetaxel M- merhotrexate fluorouracil), ABC= reference values for advanced breast cancer patients, Swedish norms = Swedish normative values for women 50-59 years of age. Higher scores mean more problems or symptoms.

Again, when comparing our data against these reference values available, the data seems to be reliable.

There were significant differences in mean scores at the baseline, as the T patients suffered significantly more from appetite loss (T 24.3 versus M-F 15.9 ; p=0.02) and M-F patients reported more nausea/vomiting at treatment cycles 2 (T 8.3 versus M-F 12.8; p= 0.013), 3 (T 6.3 vs. M-F 12.0; p=0.002) and 4 (T 4.3 versus M-F 11.4; p=0.002). At treatment cycle 6, the T group suffered more from the following symptoms: fatigue (T 43.6 versus. M-F 34. 0 ; p=0.04), dyspnoea (T 33.3 versus. M-F 22.5 ; p=0.017) and insomnia (T 25.3 versus M-F 15.8 p=0.04).

The potential HRQoL gains offered by the two treatments were evaluated by choosing the mean change scores as an additional measure of outcome. The calculation was made by subtracting the mean scores from the cycles 2 to 6 from the patients' baseline score. The median values of the change scores remained stable, with the exception of emotional functioning and fatigue; however, the variance was higher in the group. The change scores showed no differences between the treatment groups.

To summarise: Both treatment groups showed improvement in emotional functioning after the baseline. There were some significant differences in HRQoL favouring M-F patients, with the exception of nausea/ vomiting. During the 6 cycles of treatment all functional scale scores remained stable in the T group. In the M-F group there was an increase in the social functioning scores at treatment cycle 6 and also on the Global QoL scale at treatment cycles 5 and 6. There were some significant differences in symptom / single item scales, which corresponded well to the toxicity profiles of the different treatments; however, there were no differences when mean scores were compared.

4.2 STUDY II Timing of quality of life (QoL) assessments as a source of error in oncological trials

This study was to give an empirical demonstration of the importance of the exact timing of HRQoL measurements in connection with clinical trials comparing treatments with cyclic side effects and to estimate of the nature and the magnitude of the error produced by incorrect timing.

At the baseline in the M-F group there was a significant difference between incorrectly and correctly timed assessments on the nausea/vomiting scale with ill timed assessments showing more symptoms, 18 scale points vs. correct 7 scale points for the correctly timed assessments (p= 0.006). In the T group, the statistically significant difference between incorrectly and correctly timed assessments was found in physical functioning (PF), with ill timed assessments showing better physical functioning, 85 vs. 65 for the correctly timed assessments (p= 0.047).

However, in both treatment groups on several other scales there was a clinically significant difference (10 or more points) between correctly and incorrectly timed assessments. In the M-F group on the physical (PF) and the social (SF) functioning scales, the difference between incorrectly and correctly timed assessments was 10 points (PF correct 65, incorrect 55; SF correct 71, incorrect 61, p=ns) and in the T group this was found for emotional functioning (correct 62 vs. incorrect 74; p=ns), social functioning (correct 71 vs. incorrect 83; p=ns), global QoL (correct 53, incorrect 66; p=ns), fatigue (correct 40 vs. incorrect 25; p=ns), and pain (correct 33 vs. incorrect 20; p=ns) scales.

The results over the first 14 cycles showed that in the M-F group there was a significant difference between incorrectly and correctly timed assessments for physical functioning, global QoL , nausea/vomiting, insomnia, appetite loss and constipation scales. These significant differences were very consistent; the scores of ill timed assessments were worse on the functional scales, and on the symptom and single item scales, all significant differences were in the same direction, with ill timed assessments producing more symptoms. In the T group the findings were not consistent. The only significant difference found on the functional scales was found on the physical functioning scale with an incorrect assessment indicating better physical functioning. On the symptom and single item scales, the significant differences went in different directions: for dyspnoea the correctly timed assessment reported more symptoms, whereas on the insomnia scale the patients reported more problems if assessment was made outside the time window.

Table 4 Mean scores and difference in mean scores for correct and incorrect timing by treatment group by trial.

	M-F				T			
Functional scales	Incorrect *(n=77)*	Correct *(n=583)*	difference *Incor-Cor.*	p	Incorrect *(n=41)*	Correct *(n=755)*	difference *Incor-Cor.*	p
Physical	59.9	66.4	-6,4	0.013	73.7	63.4	10.3	0.006
Emotional	75.5	77.2	-1,7	ns.	69.1	71.6	-2.5	ns.
Social	67.8	74.1	-6,3	ns.	77.6	69.2	8.4	ns.
Role	61.0	64.3	-3.3	ns.	63.8	62.5	1.3	ns.
Cognitive	82.2	85.2	-3.0	ns.	79.7	83.8	-4.1	ns.
Global QoL	51.2	61.1	-9.9	0.000	59.6	53.8	5.8	ns.
Symptom/single item scales								
Fatigue	46.3	39.5	6.8	0.022	38.1	40.2	-2.1	ns.
Nausea / vomiting	16.2	9.2	7.0	0.000	4.9	6.9	-2.0	ns.
Pain	23.8	25.6	-1.8	ns.	22.8	24.0	-1.2	ns.
Dyspnoea	25.5	25.6	-0.1	ns.	17.1	28.1	-11	0.011
Insomnia	29.4	22.2	7.2	0.005	33.3	25.8	7.5	0.047
Appetite loss	24.2	17.4	6.8	0.028	15.4	17.2	-1.8	ns.
Constipation	21.6	15.1	6.5	0.011	15.4	11.2	4.2	ns.
Diarrhoea	16.0	15.1	0.9	ns.	17.1	15.3	1.8	ns.
Financial difficulties	16.2	22.1	-5.9	ns.	24.1	29.8	-5.7	ns.

To summarise: Within both treatment groups, the erroneous timing of HRQoL assessments produces significant differences on some HRQoL scales. The results of this study demonstrate that the inaccuracy of the timing of HRQoL measurements

seriously jeopardizes both the reliability and the validity of the findings, and therefore must be carefully controlled and reported.

4.3 STUDY III Physical performance, toxicity, and quality of life as assessed by the physician and the patient

The specific aims of this study were the following : (1) To find out the correlations between the physician-assessed WHO performance status and different domains of patient-assessed HRQoL. The Spearman rank correlations between physician-assessed physical performance and patient- assessed HRQoL in functional scales were the following: physical functioning (varying from the baseline to treatment cycle 6) -0.49; -0.52; -0.56; –0.59; – 0. 38; - 0.59 and -0.49*;* global QoL (from the baseline to the 6th cycle) -0.31; -0.29; -0.35; -0.45; -0.48; -0.41; social functioning -0.30; -0.33; -0.39; -33; -0.42; -0.31; role functioning -0.32; -0.39; -0.37; -0.41; -0.42; -0.22; emotional functioning -0.14; -0.15; -0.14; -0.19; -0.19; -0.30; and cognitive functioning -0.19; -.16; -0.12; -0.15; -0.26; -0.18.

(2) To explore the agreement between nausea/vomiting and diarrhea toxicity assessments made by the physician and the patient. The correlations for both these toxicity scales were moderate varying between 0. 46 and 0.56 for nausea/vomiting, with the exception of nausea/ vomiting at treatment cycle 4 in which the correlation was 0. 36. The diarrhoea toxicity correlation varied from 0.50 to 0.56.

(3) To detect the contribution of physical performance and of different toxicity variables in explaining the patients' global QoL. As a result of a stepwise linear regression analysis, the contribution of treatment toxicity to the global QoL scores was the following: having worse WHO physical performance, severe infection and nausea predicted worse a global QoL. These three variables explained 16 % of the variation in the global QoL (F value =51; p= 0.0001).

To summarise: Variation was found in the correlations between physician assessed PS and the different the EORTC QLQ-C30 scales. The strongest correlations were between the EORTC QLQ-C30 scales and the WHO PS were found in physical functioning and in global QoL with fairly low correlations in emotional functioning and cognitive functioning. The toxicity assessed by the physician and the patient had moderate correlations. When using physical performance and toxicity as independent variables to explain the variation of global QoL, 84% of the variance remains unexplained.

4.4 STUDY IV Prognostic value of quality of life scores for the time to disease progression (TTP) and overall survival time (OS) for advanced breast cancer

This study was to examine whether HRQoL scores have prognostic value, or more precisely
(1) Wether baseline HRQoL or changes in HRQoL scores from the baseline or both were prognostic for TTP.
The results of this study show that baseline HRQoL scores had no prognostic value for the duration of TTP. HRQoL change scores from the baseline did not predict TTP.

This clinical study was a cross-over study and there was no significant difference in overall survival between the two treatment groups. This setting and the results of the study gave us an opportunity also to examine (2) whether baseline HRQoL or changes in HRQoL scores or both had prognostic value for overall survival (OS).

In univariate analysis, more severe pain (8.5 months vs. 12.9 months p=0.0044) and fatigue (8.6 months vs. 14.5 months p=0.0008) at the baseline were predictive for shorter OS. There was borderline significance on the following scales: global QoL (9.6 months vs. 14.8 months p=0.0130), physical functioning (9.9 months vs. 13.3 months p=0.0256), and appetite loss (9.9 months vs. 13.2 months p=0.015) for predicting shorter OS. In multivariate analysis, more severe pain at the baseline (p= 0.0020) was an independent predictor for shorter OS. QoL change scores from the baseline QoL had no predictive value for OS.

Moreover, the aim was to study (3) whether the WHO performance status had independent prognostic value for TTP or OS or both. The WHO performance score was associated with TTP and OS, and a better WHO performance score predicted a longer TTP (WHO 2 vs. WHO O p= 0.0092 and WHO 1 p= 0.029) and longer OS (WHO 2 vs. WHO O p= 0.0044 and WHO 1 p= 0.0073).

Table 5 Median TTP and OS by WHO performance score

Variable	*n*	Median time to progression in months	Median overall survival in months
WHO 0	72	5.0	12.9
WHO 1	140	4.8	11.3
WHO 2	32	3.0	7.1

To summarise: The results suggest that HRQoL scores have no outstanding prognostic value. However, pain and the WHO performance score have a predictive value for OS and the latter for the TTP as well.

4.5 STUDY V The meaning of quality of life in patients being treated for advanced breast cancer: A qualitative study

The aim of the study was to gain a deeper qualitative understanding of the personal meanings that are related to patients' HRQoL and to complement the findings of our earlier studies from a predetermined study setting using the EORTC QLQ-C30.

The present findings show that cancer and its treatment limited the patients' *physical functioning*. impacting on the patients' ability to perform their usual activities of daily living, such as driving, walking, housework, family and leisure activities and self care. These limitations were translated into dependency on others and led to decreased feelings of autonomy (referring to the extent of control over life that the patient subjectively feels). The patients tended to ensure their autonomy by engaging in less strenuous activities or by changing their internal standards. The feeling of being able to do something useful for the family became important. The treatment was perceived as an enemy and many felt that they suffered because of the treatment. At the same time the treatment meant hope, not only for themselves, but also for the family and for future cancer treatments. Treatment adherence meant perseverance and stopping the treatment meant caving in and dying.

The patients' ability to carry out roles and responsibilities became restricted due to changes in appearance and decreased physical condition. The limitations on *role functioning* were difficult to accept and feelings of uselessness became predominant, especially when they had to face the reality of being on sick leave or a disability pension. Most women used to work outside the home, and therefore felt useless in society, when forced to give up their employment.

The patients' social *functioning* was shattered by changes in lifestyle and appearance. Changes in appearance complicated keeping up normal interface, since many patients did not want to reveal their illness. By not telling friends about their cancer, they ensured that they would maintain their relationships as they had always been. Changes in lifestyle and appearance often led to retreating from social

relationships with colleagues, neighbours and distant friends. The patients maintained control of to what extent their illness was recognised in social relationships, which was important to their feelings of autonomy. Even social isolation was used in controlling the illness experience and maintaining autonomy. The importance of being able to sustain reciprocal relationships was often stressed. A close family was the main source of instrumental and emotional social support, but also a major source of concern.

The meaning of *emotional functioning* crystallised around the ability to enjoy life day by day and to persevere through treatment even though most patients reported feeling bad-tempered, feeling down, being epressed and being less tolerant than they had been previously. Patients used denial to sustain emotional functioning and to ensure the capability of feeling joy. As a positive consequence of the illness experience, feelings of personal growth were expressed. The patients often felt that the illness also meant the capability to enjoy things more fully and more sensitively.

The patients' difficulties with *cognitive functioning* were more characteristic of anxiety. Some patients complained of difficulties in concentration, and beginning things was especially difficult. The importance of untouched cognitive functioning was the ability to escape from the illness experience in that patients were able to concentrate on leisure activities, for example, on reading, and for those who worked, on being able to complete their work.

Global QoL was dependent on the patients' ability to live as normally as possible, to maintain reciprocal relationships and to control their illness experience. Normalcy in life was expressed in the terms that the illness would chang their lifestyle as little as possible. However, the patients were aware that they were not able to maintain a normal life and, therefore, being able to participate in the same or similar activities they took part in before the breast cancer diagnosis or current treatment were described as moments of a good life. Normal mutual relationships were seen to be important for maintaining a good QoL while not being able to have them indicated a poor QoL. The patients' ability to control the illness experience was the most striking indicator of maintaining a good QoL. Patients used various ways to control the experience of feeling ill.

The three dominant themes that emerged from the data were clearly linked around the other dimensions of experiences of HRQoL; that is, the patients' ability to control the illness experience, experienced personal growth and hope. The first was

the patients´ ability to control the illness experience, which stood out as the single most important meaning of the patients' physical, social, emotional and role functioning as well as their global QoL. The patients' ability to compensate for decreased physical functioning by engaging in less strenuous activities can be interpreted as an effort to safeguard their feelings of autonomy. The interviews showed that the patients' need to control the illness experience appeared as decreased social functioning, of which the extreme form was social isolation. The change from being needed to needing someone was difficult to accept and led to decreased feelings of autonomy. Emotional reactions towards the illness experience were controlled by using denial. Activities and events during which patients were able to hold on to feelings of autonomy were characteristic in describing a good QoL, because they offered an escape from the reality of being ill. The importance of controlling feelings of autonomy was evident in the patients HRQoL; however, the means of ensuring feelings of autonomy varied from patient to patient.

Another meta theme that emerged from the data was the patients' changes in overall life perspective. Patients restructured their view of themselves. They felt that the illness experience also resulted in positive effects in their lives. They were more able to put the impact of events in a proper perspective and to focus on day to day living instead of the future. The patients attributed these changes to personal growth. Feelings of personal growth were important interpretations of the illness experience, especially in improving self-esteem.

Hope emerged as the third meta theme in the present study. Hope and especially not losing hope were central to the patients' HRQoL. Patients had to hold on to feelings of hope even though they seldom had high hopes for recovery, but rather hope for better physical condition, hope for response to the treatment, hope for dying with dignity, hope for sufficient pain control, hope for being able to share important family occasions. To hold on to these feelings of hope, most patients did not want to know their possible survival time or to know what would happen after the progression of the disease. Treatment was seen as the greatest source of hope while termination of the treatment meant losing hope and giving up. Hope was seen to be important in determining the HRQoL for the patients themselves, but also for close family members. Hope for future cancer treatment was expressed as a motive for participating in the trial.

5 DISCUSSION

5.1 General discussion

The consecutive series of studies in this thesis contributed towards a better understanding of HRQoL among women with advanced breast cancer. We have been able to produce comparisons on HRQoL between the patients receiving two different treatments, to assess the connection between clinical variables and HRQoL, and to evaluate the importance of the prognostic value of HRQoL. We have also focussed attention on one important methodological issue in HRQoL research and provided a deeper understanding of the subjective meanings that the patients have given to HRQoL.
One of the most important contributions of this study is that this thesis has made a serious attempt towards bridging the gap between qualitative and quantitative research in the field of HRQoL, providing information on how and why patients with advanced breast cancer experience HRQoL.

We used the EORTC QLQ-C30 to measure HRQoL. This decision is well-grounded, since the EORTC QLQ-C30 has been developed to assess the relevant aspects of the quality of life of cancer patients, especially in cancer clinical trial settings. In addition, at the time the protocol was written the EORTC QLQ-C30 was the only instrument available with standardised translations for all of the native languages of the patients included in the study, with the exception of the Estonian translation, which was made ad hoc. Clinical research and data collection were performed according to the Declaration of Helsinki. The study protocol was approved in local ethical committees. Data collected by using clinical research forms was monitored against medical records by Aventis Pharma (formerly Rhone Poulenc Rorer).

We have critically compared our study protocol with more recent guidelines and found it to be in harmony. It is worth noting that, in addition to the fact that this study is in harmony with recent guidelines, two additional important issues have been considered us and implemented, firstly, the *confidentiality* of the answers and secondly, the *exactness of the timing* of the HRQoL administration. In this study we wanted to stress the confidentiality of the answers. This was considered to be important in order to make it clear that the HRQoL study is independent from the physician in charge and, therefore, the answers in the HRQoL questionnaires cannot influence decisions on treatment. We did not want to interfere with the patient – physician relationship by evoking expectations that HRQoL issues are discussed in detail in the physician's reception. We found this procedure to be

important for ethical reasons, as participating in the HRQoL study was voluntary and the data were collected for a scientific purpose.

The response rate was 96% at the baseline and the overall compliance was 89%. Even after excluding ill-timed questionnaires, the overall compliance of the entire study was 82%. This compliance is among the highest published. There might be several reasons for this a successful study design, an explicit study protocol, a one day training session for the study nurses, and a highly motivated staff, together with patient information which stressed confidentiality and explained the nature of the QoL study. The use of a standardised questionnaire which has well-documented psychometric properties, the large sample size, the high compliance, and the baseline data being in harmony with the reference data available contribute greatly to the reliability and validity of studies I-IV .

In our first study we found no major advantage for either treatment over the other (STUDY I). The results are in harmony with the earlier results reported from comparable studies concluding that there are no major differences in the HRQoL outcome between docetaxel and alternative regimens (Chan et al., 1999; Nabholtz et al., 1999; Nabholtz et al., 2003; O'Shaughnessy et al., 2002). HRQoL in the docetaxel group remained stable throughout the assessment points and increased in some domains in the M-F group, producing significant differences in some domains. Nevertheless, we might have expected that the toxicity of the docetaxel would have affected the results of HRQoL in a more pronounced way. The findings have relevance, since docetaxel has been shown to be the most effective treatment for advanced breast cancer thus far. It seems that survival gain is not reached at the cost of decreasing HRQoL.

However, all longitudinal studies, particularly in palliative settings in which survival may be relatively short, are subject to difficulties of interpretation because of the selective attrition of the studied patient populations (Aaronson et al., 1993; Bernhard et al., 1998; Fairclough et al., 1998; Giaccone et al., 1998; Norris et al., 2000; O'Shaughnessy et al., 2002; Sigurdardottir et al., 1996). The present findings are affected by an increasing number of non-random dropouts over time, which complicate the analysis and interpretation of longitudinal data. The attrition due to disease progression was larger in the methotrexate and 5-fluorouracil group (M-F). Consequently, the M-F patients remaining in the study through treatment cycle 6 were a more select and less representative subgroup of the baseline study population than the patients remaining in the docetaxel group. Our manner of handling the problem of selective dropout in group comparisons was to use

variables summarised within individuals, i.e. by also exploring the mean change scores. In the present study, all statistically significant differences favouring the M-F group disappeared when comparing change scores over the treatment rather than the group means at specific points in time. We decided to conclude on the basis of the result of this study that the present HRQoL findings show no major advantage for either treatment over the other. Since there was large interindividual variance, especially in the docetaxel group, further studies are needed to better understand how the variation of the quality of life during treatment is related to patient physical functioning and toxicity. The findings of the first study were the prime motivation for our third study, namely exploring *physical performance, toxicity, and quality of life as assessed by the physician and the patient.*

Assessing treatment toxicity and physical performance is important in evaluating the beneficial value or the burden of treatment. Nevertheless, the present findings show that physical performance and toxicity explained only 16 percent of the variance in global QoL (STUDY III). The findings suggest that physician-rated clinical outcome variables do not necessarily measure patient-rated HRQoL . The findings show weak to moderate correlations between the WHO PS and the different EORTC QLQ-C30 scales. Furthermore findings from earlier studies suggest that (Aaronson et al., 1993; McLachlan et al., 1998) the correlations are stronger for those EORTC QLQ-C30 scales that more directly address physical well-being. It may seem surprising that correlations between toxicity assessments made by the patients and the physician were only moderate; however, these findings are consistent with more recent findings studying breast cancer patients receiving extremely toxic treatments (Brandberg et al., 2003). The weak associations between physician-assessed and patient-assessed treatment toxicity suggest that the two different manners of measurement are not assessing the same construct. Indeed, it is questionable whether detailed toxicity assessment is meaningful within HRQoL instruments. The development of new treatments is a continuous process and it may be an impossible task to continuously update, validate and translate the HRQoL instruments to adequately cover all different toxicity profiles of all treatments available. Rather, the development of HRQoL instruments might be steered towards an even better capturing of the psychological, social and cognitive aspects of HRQoL .

The findings of one study (IV) suggest that while HRQoL measurements are important as such; however, they have no great importance in predicting primary clinical endpoints such as overall survival or time to disease progression. Despite the general conclusion made from the present study, the results of this study are in

harmony with the results that indicate that pain has prognostic significance for survival in advanced breast cancer patients (Kramer, Curran, Piccart, de Haes, Bruning, Klijn, Van Hoorebeeck et al., 2000). However, the general conclusion of a number of other studies is opposition to our study (Blazeby et al., 2001; Coates et al., 2000; Coates et al., 1997; Dancey et al., 1997; Jerkeman et al., 2001; Maisey et al., 2002; Montazeri et al., 2001; Seidman et al., 1995; Tamburini et al., 1996; Wisloff et al., 1997).

Before concluding in either direction, it is worth noting that there are also some issues that must be taken into account when comparing our results to others. There are some paradoxical results in other studies e.g. the association between low emotional functioning and prolonged survival, which was practically strong in patients with low global quality of life scores (Dancey et al., 1997). Furthermore, in one study higher role functioning was a positive prognostic factor in the univariate analysis; however, in the multivariate analysis, longer survival was associated with low role functioning (Roychowdhury et al., 2003). In a study by Kramer et.al. (2000), different selection methods for multivariate analysis produced different results for response, with backward elimination including fatigue and good emotional functioning with dyspnoea as predictors of poor response to treatment.

It is also important not to overlook the fact that in some of the studies the study population has been relatively small (Blazeby et al., 2001; Jerkeman et al., 2001). There has been some evidence that change scores from the baseline HRQoL can predict overall survival. It is questionable whether these results can be generalised because the number of patients alive in those studies was reduced (Blazeby et al., 2001; Coates et al., 1992). In our study, we selected the 3rd treatment course as the change value from the baseline in order to reduce thebias produced by selective dropout. In contrast to earlier studies, the results of our study, based on 173 patients, suggest that the change from the baseline HRQoL does not predict either overall survival or time to disease progression.

Although a large number of studies exists on HRQoL in cancer clinical trials, very few have incorporated information on HRQoL as a prognostic factor. In 2001 there were about 110 studies including HRQoL assessment EORTC cancer clinical trials (Bottomley, Vanvoorden et al., 2003). Compared to the extensive use of HRQoL as a secondary endpoint in cancer clinical trials, there has been only a handful of studies addressing the issue of prognostic value. Furthermore, those studies published have had positive findings. Hence, it can be argued that there may be a

publishing bias towards positive findings (Cleophas & Cleophas, 1999), because of the absence of other published negative findings. Disharmony in the findings and in the methods used, as well as the absence of negative findings, make a robust meta-analysis difficult.

The methodological study of the timing of HRQoL assessment has focused attention on an important issue (STUDY II). The findings suggest that an erroneous timing of HRQoL assessments in oncological trials seriously jeopardises both the reliability and the validity of the findings. In all longitudinal and especially multicentre studies, some missing data due to various reasons are inevitable. However, the present study was carefully planned and monitored to avoid errors in timing, and the number of ill timed HRQoL assessments therefore was relatively low. Nevertheless, within both treatment groups, a comparison between assessments performed within and outside the accepted time window produced statistically significant differences on some scales. The size of the differences observed was in some HRQoL domains 10 pts or more, which is considered clinically significant (Osoba et al., 1998). Hence, within treatments, error variance due to incorrect timing is clearly an important reliability issue. Another impact of this study is that the result of this study raises a question of how one should treat findings from earlier studies that either have specified their accepted time window for HRQoL measurements loosely, or have not specified it at all. On the basis of the present findings, we would be extremely cautious in letting clinical decision making be affected by any HRQoL findings of chemotherapy trials in which the issue of timing has not been treated with sufficient scientific rigor.

We were able to compare patients' HRQoL between the two treatment groups and to provide meaningful information on patients' HRQoL by using the EORTC QLQ-C30. Since the clinical study had cross-over setting, it can be argued that we should have continued the HRQoL data after the cross-over, in order to have even a rough estimation of those patients' HRQoL who dropped out of randomised treatment because of the progression of the disease. This can be considered a limitation of the present study. We, however, decided not to collect the HRQoL data for logistical reasons: the number of the patients who received cross over treatment was limited, and it was expected that while receiving the cross-over treatment many of those patients could not continue as outpatients. Furthermore, the study nurses were no longer responsible for those patients, i.e., the HRQoL data collection procedure was no longer qualified. In light of all this, the data collected after cross-over might not have been reliable.

The ability of a standardised QoL questionnaire to cover all important issues concerning the patients' HRQoL must be considered limited. Correlative explanations of HRQoL are able to generalise the results over groups. However, the interpretation of a HRQoL result is always to some extent qualitative. Clinical significance is subjective and a matter of opinion, depending on values and opinions, which in turn differ among patients, clinicians and societies (Fayers, 2001). Treating the cancer patient is always about treating the individual; furthermore, individual physicians make the decisions to some extent qualitatively. This stresses the importance of assessing HRQoL on a more individual basis and of gaining understanding of the individual meanings encountered by the patient when receiving cancer treatment. Being able to rise to the challenge of more individualised research in cancer clinical trials, HRQoL research has at least complemented the current HRQoL research with more individualised methods. Therefore, adapting phenomenology, qualitative research, and more structural theories of human behaviour are essential. In phenomenological psychology, HRQoL can be studied using descriptive or interpretive techniques, including disciplined reflection. These technigues are used to develop clear, accurate and believable descriptions of HRQoL. Those descriptions reveal the structure of a phenomenon as it is experienced, including its parts or elements (Hein & Austin, 2001). In structural theories, various explanatory structures are postulated. The explanatory structure within an organism is comprised of relatively stable structures with individual, various functional mechanisms embedded in these structures and all relevant processes occurring within them (Vuorinen, 1981). Such internal systems serve to maintain an adaptive interaction between the organism and a continuously changing environment, offering thereby a basis for psychological explanation (Vuorinen, 1981). Structural theories base their explanation on the specifies of the mediating processes which covert the effects of internal and external factors. Adopting such a systemic approach to HRQoL study has the value of offering a theory- based understanding of individual differences. Hence, it provides interpretive and complementary resources for understanding the results gleaned from the quantitative research.

The qualitative (V) study was conducted to increase the understanding of the meaning of advanced breast cancer and its treatment for patients' HRQoL. In this study, the patients' ability to control the illness experience manifested as the single most important structure of HRQoL. This point is particularly relevant in understanding the meanings of physical, social, emotional and role functioning as well as patients' global QoL. It increases the understanding of how these meanings are conveyed through psychic work. These meanings and the means of fulfilling

them are secondary to psychic work. In order to maintain their psychic equilibrium, the patients are forced to change the meanings of ther physical, social, role and global QoL by utilising the psychic work. Consequently, actions or moments when enjoyment is under the person's own control are important. Moments during which they escaped the reality of illness were described as good QoL. The descriptions of how patients utilised feelings of autonomy differed between individuals and the experience being discussed; however, the analysis of several patients' descriptions revealed that the extent of control of life that the patient subjectively feels is an important structure or meaning for patients' HRQoL.

The present study has some points of contact with earlier qualitative studies. In our study, securing the feelings of autonomy, by at least trying to live as normal a life as possible, is consistent with Lam's (2003) earlier findings on patients trying to regain normalcy as an important meaning. The patients in our study who experienced personal growth have some similarities to (Nelson, 1996) results about how uncertainty influences patients to focus on important aspects of life. The meaning of close relationships and family is concurrent with earlier studies (Arman et al., 2001). Patients in our study described the changes they experienced in emotional functioning as being bad-tempered, feeling down, depressed and being less tolerant than they had been previously, and in Arman's study, being more sensible and low-spirited (Arman & Rehnsfeldt, 2002). Patients with ovarian cancer had similar experiences to our patients reporting changes in everyday life such as the inability to continue employment, altered relationships with friends, the impact on the family, and worries about children (Howell et al., 2003a).

This study differs from previous research in a number of respects. In our study, having a sense of control was profound, not in the sense of having control over the course of illness but rather gaining control over the illness experience. This differs from Taylor's (1983) and Howel's (2003b) findings of gaining a sense of control over the disease .The present study explored the important meanings following the widely agreed key HRQoL dimensions in HRQoL research, rather than focusing on one meaning in particular.

The use of empirical phenomenological analysis of data was well-grounded, since the purpose of the study was to focus on the individual personal experiences of the patients and, in doing so, to reveal structures that for participants have in common. One of the characteristics of empirical phenomenological research is that its aim is to produce the description of experience in order to understand its essential structure (Hein et al., 2001). The structure defines commonality that reveals the

many diverse appearances of a phenomenon. Concepts such as reliability, validity and generalisability are irrelevant to the evaluation of qualitative research as they are based on a positivistic perspective. According to Lincoln & Cuba, research should be evaluated on the basis of its trustworthiness, applicability as well as consistency and neutrality (Lincoln & Guba, 1985).The sample size of qualitative studies is determined not by the number of participants but by theoretical saturation, which is evident when no new information is discovered on the study phenomenon. In this study, theoretical saturation was achieved with a sample of 18 women.

5.2 Concluding remarks

One way of interpreting the results of the findings of two of the studies (I & III) is to consider the findings according to Vuorinen's framework for psychic self-regulation. According to this conceptual framework, the analyses of mental activities are separated by defining the three types of levels of self-regulation. This distinction allows one to analyse not only how somatic and social factors impose their influence on mental processes, but how they are utilised on the most fundamental level in psychic work. Our finding, that patients' emotional well-being increases from the baseline, even when the treatment's side- effects, not any potential treatment efficacy are in evidence, can be explained by psychic work that patients are forced to apply to the sense of hope that treatment offers. The finding of our study (II) showing that physical functioning and treatment toxicity can explain only 16% of the variance of global QoL seems plausible according to the view that somatic factors are utilised in psychic work, in order to maintain psychic equilibrium. This framework explains the findings that the majority of studies reported no significant HRQoL differences between treatment groups in advanced breast cancer trials (Bottomley et al., 2002). In terms of QoL research and clinical decision making, zero-difference results between treatments should be treated with caution as they may well be due to the standard instrument's limitations in catching important meanings of HRQoL. Future research in HRQoL should be complemented with more individualised methods, and research questions should be posed more in the direction of why patients experience their HRQoL in the way they do. Hence, qualitative research methods and phenomenological psychology offer real potential for description and explanation of the patients' HRQoL in a more meaningful way.

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