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Are Korsnes Kristensen

Quality of life in patients with advanced non-small-cell lung cancer

Doctoral thesis

NTNU
Norwegian University of Science and Technology
Thesis for the Degree of
Philosophiae Doctor
Faculty of Medicine and Health Sciences
Department of Clinical and Molecular Medicine

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Trondheim, December 2020

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As an oncologist, when I sit with patients to discuss starting a new chemotherapy regimen, their first questions are often:
"How will it make me feel?" and "How did patients like me feel with this treatment?"

Ethan Basch, New England Journal of Medicine, 2013

Livskvalitet hos pasienter med lungekreft

Lungekreft er den kreftformen som tar flest liv. Pasienter med lungekreft har ofte symptomer fra sykdommen, samtidig som de kan oppleve plagsomme bivirkninger fra behandling. Ved spredning er målsetningen ved behandling forlenget overlevelse og bedre livskvalitet.

I denne avhandlingen har vi brukt data fra tre randomiserte kliniske studier for å undersøke hvordan kreftsykdom og cellegiftbehandling påvirker livskvalitet hos pasienter med avansert ikke-småcellet lungekreft.

Vi har vist at det er en betydningsfull variasjon i livskvalitet under cellegiftbehandling, og at denne variasjonen fulgte et gjentakende mønster gjennom behandlingssyklus. Valget av måletidspunkt kan påvirke muligheten til å påvise forskjeller i livskvalitet mellom ulike cellegiftregimer. Vi påviste også at enkelte symptomer, som utmattelse og kvalme, var mer uttalt hos pasienter som hadde lave blodverdier under cellegiftbehandling. Videre har vi undersøkt endringer i livskvalitet gjennom det siste leveår. De vanligste symptomer i hele denne perioden var utmattelse, tungpust og redusert matlyst. Fram til fire måneder før død økte de fleste symptomer kun langsomt, men deretter så man en rask og tiltakende forverring.

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Funding: St Olavs hospital – Trondheim University Hospital

The thesis is found to be worthy of public defence for the degree of Philosophiae Doctor in palliative medicine. The defence takes place on Friday 18. December 2020 at 12.15 pm

Avhandlingen er funnet verdig til å forsvares offentlig for graden ph.d. i palliativ medisin. Disputas finner sted fredag 18. desember kl. 12.15

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First of all, I express my gratitude to the patients who have participated in the clinical studies that this thesis builds upon, and offered time and effort to the benefit of future patients.

I am very thankful to my supervisors for giving me the opportunity to embark on this project, and guiding my work over these years. Thanks to my main supervisor, Tora S. Solheim, for rapid and constructive feedback, and for always being supportive and caring. Bjørn Henning Grønberg`s sharp-mindedness and engagement for clinical research in lung cancer has been essential to the design and writing of the papers. Thanks to Stein Kaasa for introducing me to the research group, and for valuable scientific input along the way.

Thanks to all co-authors, your contributions have improved the manuscripts and has been much appreciated. A special thanks to Bjørn Henning Grønberg and Øystein Fløtten for giving me the opportunity to benefit from previous research.

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Finally, thanks to my family for your support and all the joy you bring. Anette, you are the love of my life and my best friend. Alva, Åste and Olaus; thanks for keeping me busy and adding so much value to my life.

Abbreviations

ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
BSA	Body Surface Area
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
GC	Gemcitabine and carboplatin
HRQOL	Health-related quality of life
HT	Hematologic toxicity
LC13	Quality of Life Questionnaire Lung cancer module
LMM	Linear mixed model for repeated measures
MAR	Missing at random
MCAR	Missing completely at random
MID	Minimally important differences
MNAR	Missing not at random
NLCG	Norwegian Lung Cancer Group
NSCLC	Non-small-cell lung cancer
PC	Pemetrexed and carboplatin

PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
PRO-CTCAE	Patient-reported outcomes version of the Common Terminology Criteria for Adverse Events
QLQ-C30	Quality of Life Core Questionnaire
RCT	Randomized controlled trial
SCLC	Small-cell lung cancer
TKI	Tyrosine kinase inhibitor
TNM	Tumor, Node, Metastasis
VC	Vinorelbine and carboplatin
VG	Vinorelbine and gemcitabine
WHO	World Health Organization

Summary in English

Lung cancer is the leading cause of cancer-related deaths, and many patients experience distressing symptoms. Novel therapies like targeted agents and immunotherapy have represented a paradigm shift in the treatment of advanced non-small-cell lung cancer (NSCLC), but cytotoxic chemotherapy still retains an important role for many patients. The main goals of anticancer treatments are to allow patients to live longer and to live better. Accordingly, evaluations of cancer treatments should focus not only on effects on survival and tumor response, but also on effects on patients` symptoms, functioning and overall well-being. The sometimes delicate balance between symptoms, disease control and treatment side effects makes health-related quality of life (HRQOL) an important outcome for patients with advanced NSCLC, both in clinical trials and in clinical practice.

The overall aim of this thesis is to increase the understanding of how chemotherapy and the cancer disease affects HRQOL in patients with advanced NSCLC. Paper I was the primary publication of a single-center study, aiming to evaluate the variation in HRQOL during chemotherapy cycles and investigate whether the timing of HRQOL assessments influenced the comparison of different treatment regimens. Fifty-two patients were randomly assigned to receive three cycles of carboplatin plus vinorelbine or gemcitabine every three weeks. The variation of mean scores of global health status, nausea/ vomiting and fatigue showed a consistent pattern during chemotherapy cycles. Day 4 appeared to be the timepoint when chemotherapy influenced HRQOL the most. The differences in HRQOL between the chemotherapy regimens varied at different timepoints, especially for nausea/ vomiting.

Paper II and III were secondary analyses of pooled data from two large multicenter RCTs of first-line chemotherapy in patients with advanced NSCLC. The aim of paper II was to examine whether hematologic toxicity (HT) during chemotherapy was associated with HRQOL impairment, and, consequently, if blood counts could be used to predict the need for supportive care. Of the 766 patients included in the study, 177 (23%) developed severe HT during the first chemotherapy cycle. Patients experiencing severe HT had worse changes in fatigue and nausea/vomiting, but similar global quality of life

and dyspnea as patients with no severe HT. Overall, the association between HT and HRQOL impairment was not strong enough to suggest that blood counts can be used to identify patients in need of more clinical attention and supportive care during chemotherapy.

The aim of paper III was to assess the trajectory of HRQOL during the last year of life, and examine when and to what degree deterioration of symptoms and physical functioning accelerate towards the end of life. Fatigue, dyspnea, appetite loss and cough were the most pronounced symptoms in all phases of the disease trajectory, and significantly worse than in the reference population even 9-12 months before death. The deterioration rate of physical function and key symptoms pain, appetite loss, fatigue and dyspnea were relatively slow until four months before death. Then, the decline accelerated and for physical function, fatigue and dyspnea there was a very rapid decline in the last two months of life. The findings suggest that regular symptom monitoring may help identify where patients are in the disease trajectory, serve as a trigger for changes in anticancer and symptomatic treatment and facilitate discussions about end-of-life care.

Norsk sammendrag

Lungekreft er den nest vanligste kreftform blant både menn og kvinner, og den vanligste årsak til kreftrelatert død. De siste årene har nye målrettede medisiner og immunterapi revolusjonert behandling av avansert lungekreft, men for mange pasienter er tradisjonell cellegift fortsatt en viktig del av behandlingen. Målsetningen ved kreftbehandling er at pasientene ikke bare skal leve lengre, men også leve bedre enn hva de ville gjort uten behandling. Evaluering av hvordan en kreftbehandling virker må derfor ikke fokusere bare på overlevelse og skrumping av tumor, men også på endring av symptomer, funksjonsnivå og livskvalitet. Pasienter med avansert ikke-småcellet lungekreft (NSCLC) har ofte symptomer fra kreftsykdommen, samtidig som de kan oppleve plagsomme bivirkninger fra behandling. Systematisk evaluering av livskvalitet er derfor viktig både i kliniske studier og i klinisk praksis.

Målsetning ved denne avhandlingen er å øke kunnskapen om hvordan kreftsykdom og cellegiftbehandling påvirker livskvalitet hos pasienter med avansert NSCLC. I artikkel I undersøkte vi hvordan livskvalitet varierer under cellegiftbehandling, og hvorvidt måletidspunkt har betydning for å påvise forskjeller i livskvalitet ved sammenligning av to ulike cellegiftregimer. I en studie ved St Olavs hospital ble 52 pasienter randomisert til å motta karboplatin kombinert med enten vinorelbine eller gemcitabine, gitt i 3-ukers syklus. Variasjonen i livskvalitet fulgte et repeterende mønster gjennom de tre behandlingssyklusene. Global livskvalitet, fatigue og kvalme/oppkast forverret seg den første uken etter behandling, for så å bli gradvis bedre fram mot tidspunkt for neste kur. Forskjellene mellom cellegift-regimene varierte ved ulike tidspunkt i behandlingssyklus, spesielt for kvalme og oppkast.

Målet med artikkel II var å undersøke hvorvidt hematologisk toksisitet (HT) under cellegiftbehandling er assosiert med forverring av livskvalitet, og således om en blodprøve kan predikere hvilke pasienter som vil ha ekstra behov for støttebehandling. Analysene ble gjort på data fra to nasjonale randomiserte kliniske studier. Blant de 766 pasientene som ble inkludert i analysene, utviklet 177 (23%) alvorlig HT i første behandlingssyklus. Pasientene som utviklet alvorlig HT hadde mer uttalt forverring av fatigue og kvalme/oppkast, men lik global livskvalitet og tungpust som pasienter uten

alvorlig HT. Konklusjonen var at det er en sammenheng mellom alvorlig HT og svekkelse av livskvalitet, men at denne er for liten til å bruke blodprøve som et verktøy for å identifisere pasienter som bør følges ekstra tett under cellegiftbehandling.

Målet med artikkel III var å undersøke hvilke endringer i livskvalitet pasienter opplever i det siste leveår, og når og i hvilken grad forverring av fysisk funksjon og symptomer akselererer mot slutten av livet. Gjennom alle perioder i siste leveår var fatigue, tungpust, redusert matlyst og hoste de mest uttalt symptomer. Også 9-12 måneder før død var disse plagene betydelig verre enn i normal-populasjonen. Fram til fire måneder før død var forverringen av fysisk funksjon og vanlige symptomer nokså langsom. Deretter skjedde endringene raskere, og spesielt fysisk funksjon, fatigue og tungpust ble betydelig verre de siste to månedene. Disse funnene indikerer at regelmessig måling av livskvalitet kan bidra til å identifisere hvor i sykdomsforløpet pasienten befinner seg, og oppdage om det er behov for å endre tumorrettet behandling eller intensivere symptombehandling.

List of papers

Paper I

Measurement of health-related quality of life during chemotherapy - the importance of timing.

Kristensen A, Solheim TS, Amundsen T, Hjelde HH, Kaasa S, Sorhaug S, Gronberg BH.

Acta Oncologica. 2017 May; 56(5):737-45.

Paper II

Associations between hematologic toxicity and health-related quality of life during first-line chemotherapy in advanced non-small-cell lung cancer: a pooled analysis of two randomized trials.

Kristensen A, Solheim TS, Flotten O, Gronberg BH.

Acta Oncologica. 2018 August; 57(11):1574-9.

Paper III

Trajectory of health-related quality of life during the last year of life in patients with advanced non-small-cell lung cancer

Kristensen A, Gronberg BH, Flotten O, Kaasa S, Solheim TS

Submitted

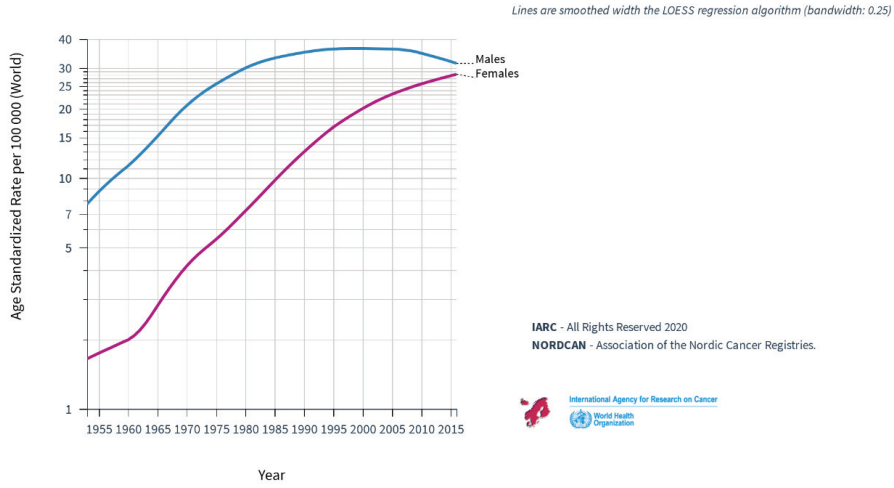
1 Background

1.1 Lung cancer

In the last century, lung cancer has progressed from an uncommon and obscure disease to the most common cause of cancer death in the world. In 1912, Isaac Adler identified only 374 published cases and stated that "primary malignant neoplasms of the lungs are among the rarest forms of disease" (1). In 2018, global statistical analysis estimated 2.1 million new cases and 1.9 million deaths due to lung cancer (2). This represents close to 1 in 5 (18.4%) of all cancer deaths.

In Norway, 1 674 women and 1 677 men were diagnosed with lung cancer in 2018 (3). This makes lung cancer the second most frequent malignancy in both sexes. While the incidence in men has been levelling off over the last two decades, a persistent and almost tenfold increase has been observed in women since the beginning of the 1960s (Figure 1).

Figure 1. Time trends in age-standardized incidence rates in Norway for lung cancer, 1955-2015



The main reason for the lung cancer epidemic is tobacco smoking, accounting for 80-90% of cases (4). Worldwide, there is a 20-fold variation in lung cancer rates by region, largely reflecting the historic patterns of tobacco exposure. Women took up smoking at a later period than men, and in most countries the incidence in females is still rising (5). Risk factors other than tobacco smoking include passive smoke inhalation, residential

radon exposure, air pollution, occupational carcinogens including asbestosis and genetic susceptibility.

In a global perspective there is still an increase in tobacco consumption, especially in developing countries, and this will probably be followed by ascending trends of lung cancer incidence. Due to aging of the population, the absolute number of new cases is expected to rise also in more developed countries.

1.1.1 Pathological classification

The two main types of lung cancer are small-cell lung cancer (SCLC) and non-small-cell-lung cancer (NSCLC), whereas the latter comprises approximately 85% of all cases. The histological subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma and large-cell carcinoma (6). Recent advances in the understanding of the molecular pathogenesis have demonstrated that NSCLC is a heterogeneous group of diseases, and the molecular characterization of tumor tissue increasingly serves as a guide to treatment. Subsets of patients have driver mutations, which are genetic alterations targetable to specific therapy. These include mutations in the genes encoding epidermal growth factor receptor (EGFR) and BRAF, anaplastic lymphoma kinase (ALK) translocations and c-ROS oncogene 1 (ROS1) fusions (7, 8). Following the introduction of immunotherapy, testing for biomarkers for response to immune checkpoint inhibitors has become mandatory. Currently, this is usually evaluated by the level of programmed death-ligand 1 (PD-L1) expression on tumor cells.

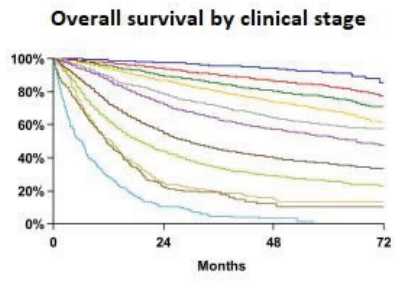
1.1.2 Diagnosis and staging

The clinical manifestations of lung cancer can be caused by local effects of the primary tumor, regional or distant spread, or paraneoplastic phenomena. At presentation, patients may have a wide range of symptoms, the most common being cough, dyspnea, pain and weight loss (9). The evaluation of patients with suspected lung cancer should assess the extent and stage of disease, histological subtype, comorbid conditions and functional status. The initial radiological investigation is usually a contrast-enhanced computed tomography (CT) scan of the chest, upper abdomen and any site of clinical suspected metastasis. PET/CT is more accurate for the detection of mediastinal involvement and distant metastases (10), while Magnetic Resonance Imaging has high sensitivity for e.g. brain, bone and liver metastases (11). The histopathological diagnosis

is usually established with bronchoschopy with endobronchial ultrasound-directed biopsy or a CT- or ultrasound-guided needle biopsy.

The tumor, node, metastasis (TNM) staging system is used to characterize the extent of disease. The TNM classification determines the overall stage grouping, and is linked to treatment recommendations. The eight version of the TNM classification system is the current standard worldwide (Figure 2) (12, 13).

Figure 2. Overall survival by clinical stage according to the eight edition of the TNM classification system.



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

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1.2 Treatment of advanced NSCLC

Patients with stage I or II are treated with curative intent using surgery, sometimes combined with adjuvant chemotherapy (stage II). Stereotactic body radiation therapy is an alternative for medically inoperable patients. Patients with stage III represents a highly heterogeneous group with differences in the extent and localization of disease, and treatment decisions are individualized based on multidisciplinary discussions. Treatment approaches with a curative intent include surgery combined with adjuvant chemotherapy and concurrent chemoradiotherapy.

Patients with stage IV or stage III not eligible for curative treatment are usually referred to as having advanced NSCLC. The aim of treatment for patients with advanced NSCLC is palliation of symptoms and prolongation of survival. Systematic therapy options are cytotoxic chemotherapy, molecularly targeted therapy and immunotherapy.

Selected patients with isolated metastasis (e.g. brain or adrenal) may benefit from resection and/ or radiotherapy of the metastases and the primary tumor (14, 15).

1.2.1 Chemotherapy

The role of chemotherapy in advanced NSCLC remained controversial until the 1990s. In 1995, a meta-analysis using individual patient data from randomized trials found a significant survival benefit for chemotherapy over best supportive care (16). For platinum-based regimens, there was a 27% reduced risk of death, equivalent to an increase in median survival of 1.5 months and 10% improvement in 1-year survival. An updated analysis published in 2008 confirmed these findings (17). Notably, the survival benefit of chemotherapy was independent of histology, age and performance status (0-1 vs. 2).

During the 1990s several new agents such as vinorelbine, gemcitabine, taxanes and irinotecan proved effective in advanced NSCLC (18-21). Two-drug combinations with these so-called third-generation drugs and a platinum compound was superior to single drug therapy, and equally effective and but less toxic than three-drug regimens (22). Meta-analyses suggested that cisplatin-based chemotherapy gave slightly better survival outcomes compared to carboplatin-based combinations (23, 24). However, in clinical practice the easier to administer carboplatin was often preferred (25).

The use of non-platinum regimens was also investigated aiming to improve outcomes by excluding the toxic platinum compound (26, 27). Although the toxicity profiles differed, there were no clear advantages to the non-platinum regimens in survival or quality of life outcomes. The first trial identifying histology as a predictive factor for chemotherapy effect was published in 2008 (28, 29). The results suggested that regimens containing pemetrexed were more effective than combinations without pemetrexed in patients with adenocarcinoma, and less effective in patients in squamous cell carcinoma (29).

1.2.2 Targeted therapy

In contrast to cytotoxic chemotherapy, targeted therapies do not work by damaging the DNA of dividing cells, but by targeting cancer cell signaling. In lung cancer, the first step towards molecular-guided precision therapy was the identification of activating mutations in the EGFR gene as predictor for effect to EGFR tyrosine kinase inhibitors

(TKIs) (30, 31). EGFR mutations are present in only 10 to 20% of white patients with adenocarcinoma, while in Asian populations the incidence is substantially higher (32, 33). Several randomized trials and meta-analyses have consistently demonstrated improved outcomes with EGFR TKIs in patients with activating mutations of the EGFR, compared with chemotherapy (34-36). Despite the efficacy of EGFR TKIs, patients inevitably develop resistance and subsequent treatment usually consists of cytotoxic chemotherapy. Other genetic alterations with a matching targeted drug include rearrangements involving ALK and ROS1.

1.2.3 Immunotherapy

Specific antibodies that target the programmed death 1 pathway, so-called checkpoint inhibitors, have opened new treatment options in advanced NSCLC, especially in patients without targetable mutations. The efficacy of checkpoint inhibitors correlates with the PD-L1 expression on tumor cells and immune cells. In a trial published in 2016, first-line monotherapy with a checkpoint inhibitor in patients with high PD-L1 expression (≥50%) was associated with prolonged survival compared to chemotherapy (37). At the most recent follow up, median overall survival (OS) was 30.0 months with immunotherapy and 14.2 months with chemotherapy (38). Of note, the 5-year OS rate in patients with high PD-L1 expression has exceeded 25% (39). More recently, the combination of immunotherapy and chemotherapy has improved overall and progression-free survival relative to chemotherapy alone, regardless of the level of PD-L1 expression (40-42).

1.2.4 Supportive and palliative care

Although the origin of supportive care and palliative care differ, their similarities and goals far outweigh their distinctions and the terms are often used interchangeably. Both are patient-centered care that aim to optimize quality of life by anticipating, preventing and treating suffering. The World Health Organization (WHO) defines palliative care as follows: “Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual” (43). Important components of palliative care include a team-based approach

to address the needs of patients and their families, clarification of treatments goals and treatment of pain and other distressing symptoms. For the latter, systematic symptom monitoring is key.

In 2010, Temel et al. published a landmark RCT of early integration of palliative care into standard oncology care in patients with newly diagnosed metastatic NSCLC (44). The results of this US single-center study showed that patients assigned to early palliative care had better quality of life, fewer depressive symptoms, received less aggressive end-of-life care and lived longer than patients assigned to standard care. Later, several large clinical trials have concluded that concurrent palliative care improves quality of life, symptoms and patient-clinician communication compared with oncology care alone (45-48). Dedicated attention to the palliative and supportive care needs of patients with advanced lung cancer is now recommended as the standard of care as reflected in international guidelines, including those of the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) (49, 50). The optimal model on how to deliver early palliative care remains to be defined (51).

1.3 Health-related quality of life

Quality of life is a complex concept, meaning different things to different people and taking different meanings according to the area of application. In health services research its meaning is restricted to aspects related to health and healthcare, and the health focus is made explicit in the term *health-related quality of life* (HRQOL). Various definitions of HRQOL have been proposed (52-56), but no universal consensus definition has been established. Generally, there is broad agreement that HRQOL is a multidimensional construct encompassing positive and negative aspects of dimensions, such as physical, emotional and cognitive functions, and disease symptoms and side effects of treatment (57). HRQOL is a subjective phenomenon, and is best evaluated directly by the patient her-/himself.

The term “patient-reported outcome” (PRO) was proposed by the US Food and Drug Administration (FDA) in 2006, and defined as “a measurement of any aspect of a patient`s health status that comes directly from the patient, without interpretation of the patient`s response by a physician or anyone else” (58). The instruments used to measure

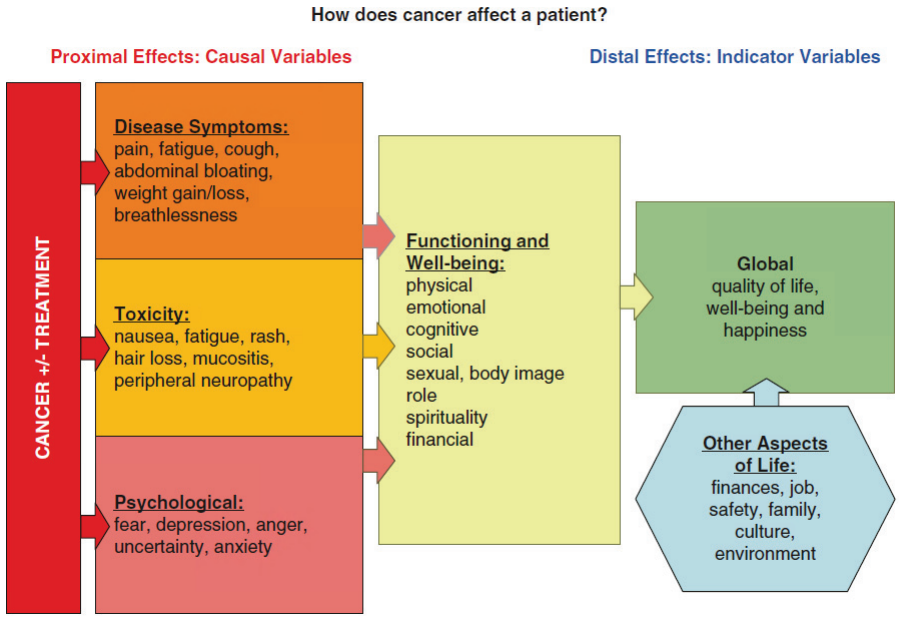
a PRO are often referred to as “patient-reported outcome measures” (PROMs). HRQOL can be considered to represent a specific type of PROs, distinguished by its multidimensionality. PROs can also refer to information not included in the HRQOL concept, like satisfaction with care, treatment adherence or unmet needs for information or support services.

1.3.1 Conceptual models

A conceptual model is a schematic representation of a theory used to provide a better understanding of a phenomenon. A variety of HRQOL models have been proposed, which is not surprising considering its multidimensional aspects and the varied use of the term across diseases (59). The model in Figure 3 illustrates how cancer may affect HRQOL (60). Like the widely cited Wilson and Cleary model (61), this simpler model proposes a linear sequence of causal links between the components. The proximal effects are direct consequences of the cancer and/ or its treatment, such as cancer symptoms and treatment toxicities (60, 62). The proximal effects may again affect patients` functioning and overall sense of well-being, i.e. cause distal effects. In addition, both proximal and distal effects are modified by patient-specific factors, such as personality, motivation and comorbidity, and external factors, as family support and access to health care.

Distinguishing between proximal and distal effects may have practical implications when choosing a HRQOL instrument and defining endpoints in a trial. Since it can be expected that distal outcomes (such as global quality of life) will be more influenced by factors external to healthcare, the effects of treatment will be smaller the more distal the measure becomes (60, 63). Thus, a proximal outcome is more likely to be sensitive to treatment effects than a distal measure.

Figure 3. How cancer affects HRQOL: proximal versus distal effects



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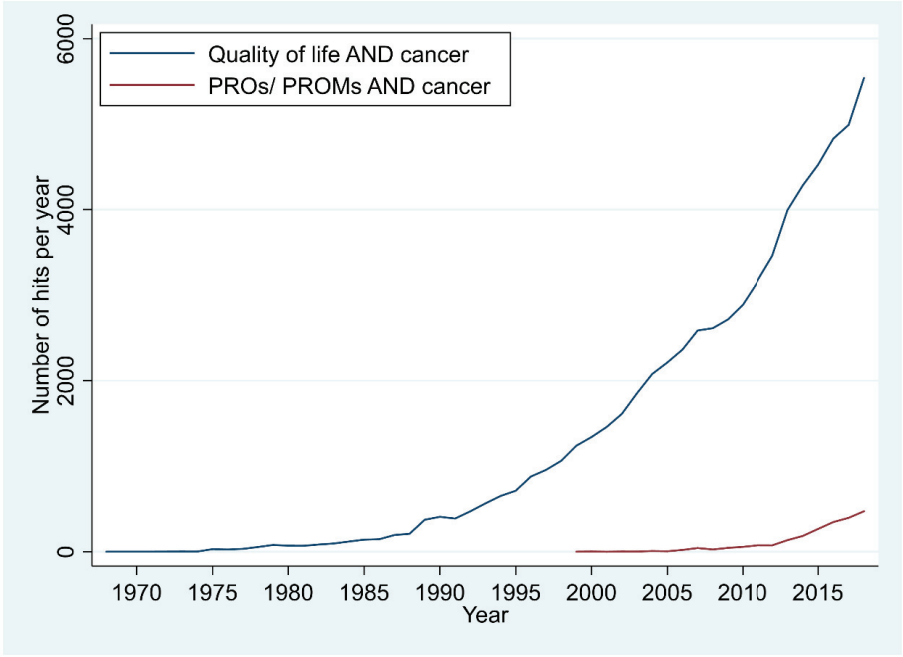
1.3.2 HRQOL research in oncology

Oncology has led advancements in HRQOL assessment and research. One of the first instruments that broadened the assessment of patients was the Karnofsky Performance Scale, introduced in the late 1940s to describe a patient`s functional status (64, 65). This 11-points scale ranged from 0 for "dead" to 100 indicating "no evidence of disease, no symptoms". An even simpler, five-grade performance scale was developed by Zubrod and colleagues from the Eastern Cooperative Oncology Group (ECOG) in the 1950s and endorsed by the WHO in a 1979 handbook (66, 67). Both the Karnofsky and the WHO/ECOG scale were scored by the healthcare personnel.

The observation that cancer patients were often distressed by adverse (but unmeasured) symptoms evoked the need for better methods to measure patients` pain, distress or suffering (68). In 1985, the FDA asserted that quality of life, like survival, was a basis upon which new anticancer drugs could be approved for marketing (69). During the past decades there has been a sharp increase in HRQOL research and cancer trials with

HRQOL as an outcome (Figure 4). The assessment of PROs in the development of new anticancer drugs has been encouraged both by the FDA and the European Medicines Agency (70, 71). Moreover, tools proposed by ASCO and ESMO to evaluate the magnitude of clinical benefit of anticancer drugs include HRQOL as a key component (72-74).

Figure 4. The number of hits retrieved in PubMed using "quality of life AND cancer" and "patient-reported outcomes/ patient-reported outcome measures AND cancer" as search terms.



1.3.3 How to measure HRQOL

A standardized approach is needed to yield reliable measurements of HRQOL. This is done in the form of a questionnaire, asking standard questions about relevant issues with a standard set of response options. The questionnaire and the algorithm used to transform responses into scale scores for analysis and reporting is often referred to as the HRQOL instrument. Development of a HRQOL instrument is a complex and lengthy process. It involves interviews with patients and clinical experts, field studies

testing the questionnaires upon patients, and statistical and psychometric analyses of the collected data (75).

HRQOL instruments should satisfy different properties (56, 60, 76): The *validity* refers to the extent to which the instrument measures what it purports to measure, and covers the range of issues relevant to its use. The *reliability* of a scale is its ability to yield reproducible and consistent results. *Sensitivity* is the ability to discriminate different states of HRQOL, and *responsiveness* the ability to detect changes.

Some HRQOL instruments are intended for general use, irrespective of the illness or condition of the patient and may be applicable also for healthy people. Examples of such generic questionnaires are the Medical Outcomes Study short form (SF-36) health survey and the Euro-Qol (EQ-5D) (77-79). During the 1990s several cancer-specific instruments were developed to assess the impact of cancer on patients` health and functioning. Compared to their generic predecessors these questionnaires had more relevant content, including common cancer symptoms and side effects, and were more responsive to clinically relevant changes (80). Commonly used instruments in lung cancer include the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core (QLQ-C30) and the lung cancer module LC13 (81, 82), the Functional Assessment of Cancer Therapy (FACT)–Lung (83) and the Lung Cancer Symptom Scale (LCSS) (84).

The QLQ-C30 is the core instrument in EORTC`s modular approach to HRQOL assessment. The QLQ-C30, which was released for general use in 1993, contains 30 questions examining global quality of life, functions and symptoms relevant to a broad range of cancer patients irrespective of specific diagnosis (82). The questionnaire has been translated and validated in over 110 languages and used in more than 3 000 studies worldwide (85). Additionally, there are disease-specific and treatment-specific questionnaire modules.

The first disease-specific module to be used in conjunction with the QLQ-C30 was the lung cancer module LC13, which covers 13 typical symptoms in lung cancer (81). Recognizing the major advances in the treatment of lung cancer, the EORTC decided to update the LC13 (86). The revision process followed specific phases, including

generation of relevant HRQOL issues based on review of literature and interviews with patients and experts, transforming issues into questionnaire items and testing of the questionnaire in an international multicenter study (87, 88). Recruitment of patients started in 2011, and included subgroups treated with surgery, radiochemotherapy and targeted therapy. The updated module, now called LC29, was published in 2017 and contains questions related to side-effects of these therapies. Immunotherapy was not established at the time the study started, and thus the questionnaire was not formally validated for this specific treatment.

Including HROQL measures in clinical trials raises issues besides the selection of an appropriate questionnaire. International collaborative efforts have been made to optimize the quality of PRO data, so that they can better inform patient care. Important consensus guidelines include the SPIRIT-PRO for how to include PROs in trial protocols (89), SISAQOL for how to analyze the data (90), and CONSORT-PRO for how to report the data in publications (91).

1.4 Health-related quality of life in patients with advanced NSCLC

In clinical trials, assessment of HRQOL can elucidate the effects of cancer and treatments on patients` lives, and provide information that enhances clinical endpoints used to determine the benefits and toxicities of therapies (92). Given the poor prognosis, high symptom burden and potential toxicity associated with treatments, HRQOL assessment is especially important in diseases like advanced NSCLC.

The first RCTs in lung cancer including HRQOL measurements were conducted already in the 1980s (93, 94). The increase in survival with chemotherapy was modest (16, 17), and many clinicians were reluctant to prescribe chemotherapy due to the risk of unpleasant side effects. Thus, it was an important finding that in trials comparing chemotherapy to best supportive care, HRQOL was either no worse or improved for the patients receiving chemotherapy (95-102).

During the 2000s, platinum-based doublets was standard treatment for advanced NSCLC. Since survival outcomes between different doublets were equivalent, it was investigated whether specific regimens, including non-platinum combinations, were associated with superior HRQOL outcomes (103). In Norway, the Norwegian Lung

Cancer Study Group (NLCG) conducted several RCTs comparing chemotherapy regimens with HRQOL as a secondary and even primary outcome (27, 104, 105). Despite significant differences in objectively measured toxicity and a clinical impression that some doublets were better tolerated than others, the trials failed to show differences in HRQOL. It was speculated whether this could be explained by suboptimal timing of the measurements.

The most common timepoint to measure HRQOL in clinical trials is when the patient attends the clinic for a new cycle of chemotherapy. By this time, however, symptomatic adverse events occurring shortly after administration of the previous cycle may no longer be present. Only few studies had investigated how timing of assessments affects HRQOL results. In the 1980s, the UK Medical Research Council designed a diary card for daily quality of life assessments. In several clinical trials, the eight-item instrument demonstrated transient changes in HRQOL during cancer therapy (106, 107). Often, these changes disappeared by the time of the next clinic attendance and tended not to be recorded by the clinicians. More recent studies, using modern instruments such as the EORTC QLQ-C30, have also found in increased symptom following chemotherapy administration (108, 109). These studies included patients with different cancer types, receiving various chemotherapy regimens.

The variation of HRQOL during chemotherapy has not been evaluated specifically in patients with advanced NSCLC. Neither has it been investigated whether the timing of measurements in clinical trials can influence the comparison of treatment regimens. This issue may have broad implications for the study of quality of life in situations where the negative impacts of therapy are likely to be short-term or periodic.

1.4.1 HRQOL during chemotherapy

Many patients experience side effects during chemotherapy that impact their quality of life negatively (110), but the ability to predict the risk of toxicity remains a challenge. In clinical practice, factors such as performance status, age and comorbidity are often used to assess the risk of treatment toxicity. However, studies have found that performance status measures fail to identify patients at increased risk of chemotherapy toxicity (111, 112). And although older age and comorbidity are risk factors for toxicity, elderly patients and those with comorbidity may derive benefit from chemotherapy similar to

other patients (113-115). Withholding chemotherapy from these patient groups because of concerns regarding the ability to tolerate treatment may thus lead to undertreatment and poorer outcomes.

Given the lack of standardized consensus tools to characterize the risks of toxicity before starting chemotherapy, monitoring of symptoms and side effects during treatment is paramount. However, several studies report that although symptoms among patients receiving anticancer treatment are common, they often go undetected by health care personnel (116-121). Potential consequences of not detecting patients` symptoms include poor symptom control, emergency department visits and missed treatments.

Hematologic toxicity (HT) is the main dose-limiting toxicity of cytotoxic chemotherapy and causes some of the most important complications, such as neutropenic infections and thrombocytopenic bleedings. Several studies have reported that chemotherapy-induced HT is associated with favorable survival outcomes (122-125), and it has also been suggested that the grade of chemotherapy-induced HT could be used to rank patients according to their need of supportive care (126).

It seems reasonable that there might be an association between HT and HRQOL impairment, but only few studies have investigated this and the results are inconsistent (127-131). If there are associations between HT and HRQOL impairment, blood counts could represent a simple and objective method to identify patients who may benefit from close monitoring and intensified supportive care during the treatment period.

1.4.2 HRQOL during the cancer trajectory

In addition to the negative effects of therapies, patients may suffer from cancer-related symptoms. Certain symptoms, including pain, anorexia and fatigue, appear to be common as disease progression occurs (132, 133). The typical cancer illness trajectory has been described as a reasonably predictable decline in physical health over a period of months or years, followed by a short period of evident decline and increased symptoms at the end of life (134).

Knowledge about the typical changes in HRQOL during the disease trajectory may help clinicians assess prognosis, and identify need for changes in anticancer treatment. Moreover, supportive care can also be a form of preventive care, and by anticipating

care needs health care personnel can prevent symptom crises by introducing appropriate interventions in a timely fashion (51). For patients and their next of kin, information about the disease and its consequences is requested in order to deal with their situation (135, 136).

Studies in various cancer types have found that most aspects of HRQOL are considerably impaired during the last year of life (137-142). However, these studies have predominantly focused on the terminal phase (137, 139), included small and/or heterogeneous patient samples (138, 140, 141) or used assessment tools which evaluate symptoms, but not functioning or overall quality of life (141). It was not clear whether symptoms deteriorated steadily towards the end of life or if the decline accelerated at some timepoint, or how these changes were for different aspects of HRQOL.

Patients with lung cancer have more symptoms as compared with other cancer patients (143-145). Consequently, analyses of data derived from this specific patient group is pertinent when trying to understand the pattern and magnitude of changes in symptom burden and functional abilities during the last year of life.

2 Aim of the thesis

The overall aim of this thesis was to increase the understanding of how chemotherapy and the cancer disease affect health-related quality of life in patients with advanced non-small-cell lung cancer.

More specifically, the following research questions were asked:

Paper I:

1. What is the variation of HRQOL scores during chemotherapy cycles?
2. Does timing of HRQOL assessments influence the chances of detecting differences between treatment regimens?

Paper II:

3. Do patients who experience severe hematologic toxicity (HT) in their first cycle of chemotherapy report more negative changes in HRQOL than patients with no severe HT?
4. Is there an association between experiencing severe HT and overall survival?

Paper III:

5. What characterizes the HRQOL trajectory during the last year of life in patients with advanced NSCLC?
6. When and to what degree does deterioration of symptoms and functioning accelerate towards the end of life?

3 Material and methods

3.1 Study design and patient population

The analyses in this thesis were based on data from three randomized clinical trials conducted in patients with advanced NSCLC. Paper I was the primary publication of the HELIK trial. This was a single-center study designed to investigate the variation of HRQOL during chemotherapy. Paper II and III were based on secondary analyses of pooled data from two previously published RCTs, namely the PEG and VG trials. These were both national multicenter studies, comparing the efficacy of different chemotherapy doublets in the first-line setting. Detailed methods and results of the PEG and VG trials have been published previously (27, 104).

The main eligibility criteria were the same for all three RCTs:

- NSCLC stage IV or IIIB not eligible for curative treatment
- WHO performance status (PS) 0-2
- Age > 18 years
- Adequate bone marrow, kidney and liver function
- No previous chemotherapy for NSCLC
- No other active malignancy

Additionally, patients in the VG trial should have no gastrointestinal disease affecting absorption of vinorelbine. Presence of brain metastases was not an exclusion criterion in any trial, and none of the trials had an upper age limit.

HELIK trial, 2009-2012, n=52

The objective of the HELIK trial was to evaluate the variation of HRQOL during chemotherapy, and explore whether the exact timing of measurements could influence the possibility to detect differences between treatment regimens. The trial was initiated as previous trials in patients with advanced NSCLC had failed to show improvements in HRQOL, despite differences in toxicity and a clinical impression that some regimens were better tolerated than other (27, 104, 105). It was hypothesized that the lack of HRQOL differences could be explained by the timing of the assessments. To explore

this hypothesis the HELIK study was designed and conducted at St Olav`s hospital, Trondheim.

PEG trial, 2005-2006, n= 436

The PEG trial was designed to compare a novel pemetrexed/ carboplatin (PC) combination with a standard regimen, gemcitabine/ carboplatin (GC) (104). The primary endpoints were global quality of life, nausea/ vomiting, dyspnea and fatigue during the first 20 weeks. Secondary endpoints were overall survival and toxicity.

There were no clinically relevant differences in mean HRQOL scores between the treatments for either of the primary endpoints. Overall survival was similar (PC, 7.3 months; GC, 7.0 months, p=0.63). Patients who received GC had significantly more grade 3-4 hematologic toxicity, including neutropenia (51% vs. 40%, p=.0024) and thrombocytopenia (56% vs. 24%, p<0.001). The conclusion was that PC provides similar HRQOL and overall survival as GC, with a more favorable toxicity profile.

VG trial, 2007-2009, n= 437

The VG trial compared the non-platinum combination of vinorelbine/ gemcitabine (VG) to vinorelbine/ carboplatin (VC) (27). The primary endpoint was overall survival. Secondary endpoints were toxicity, the use of palliative radiotherapy and HRQOL, prespecified as differences between the treatment arms in global quality of life, pain, nausea/ vomiting, dyspnea and fatigue.

Median survival was 6.3 months in the VG arm and 7.0 months in the VC arm (p=0.8). Patients in the VC arm had a statistically significantly higher mean score for nausea/ vomiting at week 3 and 6 (4 points; p <0.05), but the difference was not considered clinically significant. Fewer patients in the VG arm experienced grade 4 neutropenia (7% vs. 19%; p<0.01), but there was no corresponding difference in febrile neutropenia. The use of palliative radiotherapy did not differ between the treatment arms. The conclusion was that VG provides similar survival as VC, with a slightly better toxicity profile.

Table 1. Overview of RCT and patient characteristics

	HELIK	PEG	VG
Paper	I	II & III	II & III
Enrolment period	September 2009 – May 2012	May 2005 – July 2006	September 2007 – April 2009
Number of centers	1	35	35
Location	Trondheim (N)	Norway	Norway
Number of included patients	52	436	437
Age - years			
Median	64	65	65
Range	50-87	25-90	43-87
Sex			
Male	56%	58%	58%
Female	44%	42%	42%
Performance status			
0-1	92%	78%	75%
2	8%	22%	25%
Stage of disease			
IIIB	15%	28%	15%
IV	85%	72%	85%

3.1.1 Study treatments

In all RCTs, patients were randomly assigned to receive a chemotherapy doublet, given in 3-week cycles (Table 2). The oral dose of vinorelbine 60 mg/m^2 is comparable with the intravenous dose of 25 mg/m^2 (146). Patients who were 75 years or older had a 25% dose reduction from the first cycle. Before the start of each cycle, the absolute neutrophil count (ANC) had to be ≥ 1.0 x10^9/L and platelets ≥ 75 x10^9/L. Doses were reduced by 25% if ANC was 1.0-1.49 x10^9/L, platelets were 75-99 x10^9/L, or preceding nadir ANC was < 0.5 x10^9/L. Doses were reduced by 50% if the nadir platelet count was < 50 x10^9/L. Dose reductions were maintained for subsequent cycles.

Table 2. Overview of chemotherapy regimens in the three RCTs

Regimen	Chemotherapy Day 1	Day 8	No. of cycles
HELIK trial			
VC	Vinorelbine 25 mg/m^2 + carboplatin AUC = 5	Vinorelbine 25 mg/ m^2	3
GC	Gemcitabine 1 000 mg/m^2 + carboplatin AUC = 5	Gemcitabine 1 000 mg/m^2	3
PEG trial			
PC	Pemetrexed 500 mg/m^2 + carboplatin AUC=5		4
GC	Gemcitabine 1 000 mg/m^2 + carboplatin AUC = 5	Gemcitabine 1 000 mg/m^2	4
VG trial			
VG	Vinorelbine capsules 60 mg/m^2 + gemcitabine 1 000 mg/m^2	Vinorelbine capsules 60 mg/m^2	3
VC	Vinorelbine capsules 60 mg/m^2 + carboplatin AUC = 5	Vinorelbine capsules 60 mg/m^2	3

Carboplatin dose calculated according to Calvert`s formula, AUC=5

3.2 Assessments

In all RCTs, patients underwent a chest X-ray and CT scan of thorax and upper abdomen before randomization. At start of each treatment cycle, patients underwent clinical examination, evaluation of performance status and assessment of body weight.

3.2.1 Assessment and grading of hematologic toxicity

Blood counts were performed before the start and on days 8 and 15 of every cycle of chemotherapy. Neutropenia, thrombocytopenia and anemia was graded using the Common Terminology Criteria of Adverse Events (CTCAE) version 3.0.

3.2.2 Assessment of HRQOL

All RCTs assessed HRQOL using paper-and-pencil versions of the EORTC QLQ-C30 and LC13 (81, 82). QLQ-C30 evaluates five functions (physical, role, cognitive, emotional and social), nine symptoms (fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation, diarrhea, and financial difficulties) and global health status. The LC13 questionnaire measures symptoms commonly associated with lung cancer and its treatment (dyspnea, coughing, hemoptysis, sore mouth, dysphagia,

peripheral neuropathy, alopecia, pain in chest, pain in arm or shoulder and pain in other parts). Global health status employs a 7-point response scale, ranging from “very poor” to “excellent”. All other items have four response options reading “not at all”, “a little”, “quite a bit” and “very much”.

In the HELIK trial, patients completed the questionnaires on days 1, 4, 8, 11 and 15 of every 3-week cycle of chemotherapy. Questionnaires on days 1, 8 and 15 were completed at the hospital, and on days 4 and 11 at home. To avoid overlapping assessment intervals, the recall period of the questionnaires was changed from “the past week” to “the last three days”. Since the primary interest in this study was the variation of HRQOL during cycles of chemotherapy, the HRQOL assessments were only performed as long as the patient received chemotherapy.

In the PEG and VG trials, HRQOL was assessed at inclusion, before each treatment cycle, 3 weeks after the last cycle and then every 8 weeks up to week 52 (PEG) or 57 (VG). The baseline questionnaire was completed before random assignment. Remaining questionnaires were mailed to patients` home addresses, and the completed forms were returned to the study office in a pre-stamped envelope. One reminder was sent if a questionnaire was not returned within 14 days.

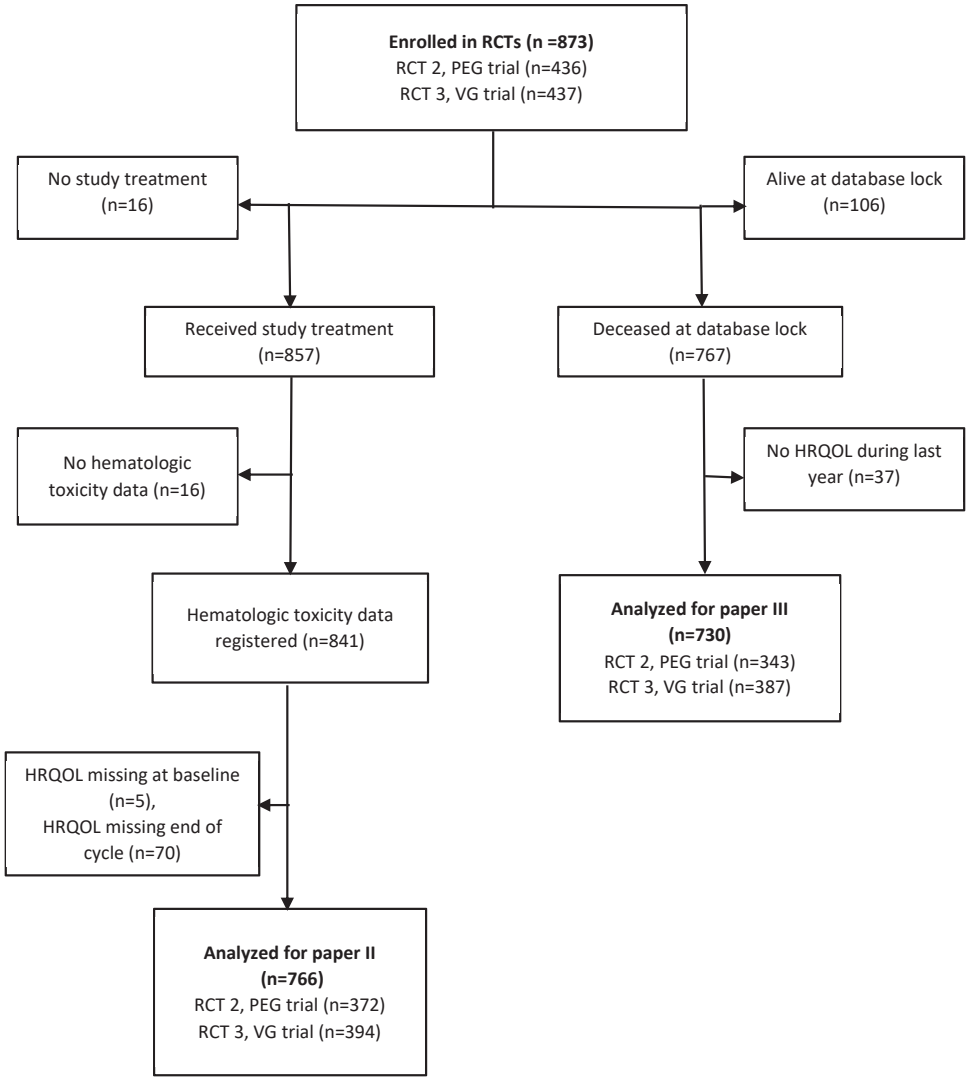
Domain scores of the QLQ-C30 and LC13 were linearly transformed into a scale from 0 to 100 according to the EORTC scoring manual (147). A high score in global quality of life and on the functional scales represents a good health status, while a high symptom scale score represents more symptoms. Previous studies have aimed to determine which changes in HRQOL scores that could be considered as clinically meaningful. In a study based on patients with breast and small-cell lung cancer it was proposed that a mean change of 5-10 points corresponds to “a little difference”, 10-20 points to a “moderate difference” and a change of more than 20 points to “a large difference” (148). Results from studies including patients with NSCLC have been in line with this proposal, but have also suggested that the minimal value that represents a clinically meaningful change vary between different scales and depends on whether patients are improving or deteriorating (149).

3.3 Patient selection

All patients enrolled in the HELIK trial were included in the analyses in paper I. In paper II and III, data from the PEG (n=436) and VG (n=437) trial were analyzed jointly (Figure 5). For the analyses in paper II, patients were eligible if they received study chemotherapy, had at least one blood count registered during the first cycle, and completed the HRQOL assessment at baseline and end of the first cycle (week 3). A total of 873 patients were enrolled in the two RCTs, of whom 766 were eligible for the analyses (Figure 5). Reasons for exclusion were no study treatment received (n=16), no hematologic toxicity data registered (n=16) or missing HRQOL data at baseline (n=5) or at the end of cycle 1 (n=70).

In paper III, eligible patients were those who were registered as deceased in the RCT database and had completed at least one HRQOL assessment within 365 days prior to death. At database lock, 767 patients were deceased of whom 730 had completed a HRQOL assessment during their last year of life.

Figure 5. Patient selection for paper II and paper III



3.4 Statistical analyses

The statistical analyses were done using STATA (College Station, TX, USA) version 13.1 (paper I and II) or version 15.1 (paper III). For all papers, the level of statistical significance was defined as $p < 0.05$.

3.4.1 Paper I

The primary outcome was the variation in HRQOL scores during chemotherapy cycles. Secondary outcome was the differences in HRQOL scores between treatment arms at different timepoints in the chemotherapy cycle. The HRQOL scales of primary interest were defined as global quality of life, nausea/ vomiting, fatigue and dyspnea (LC13).

The variation in HRQOL over time was examined graphically by plotting mean HRQOL scores of reported values at each timepoint. To explore potential differences in HRQOL scores between the two treatment arms, we also applied a linear mixed model for repeated measures (LMM). In these models treatment arm, time (as a categorical variable), treatment-by-time interaction and the baseline score were included as fixed effects. Random intercepts for patients accounted for the dependence of repeated measurements. The clinically relevant minimum difference in mean HRQOL scores was defined as 5 points. The purpose of the analyses was to estimate effect sizes, and p-values or confidence intervals were not reported. Sensitivity analyses were performed including only questionnaires completed on the scheduled date, plus/ minus one day.

3.4.2 Paper II

The primary outcome was changes in global quality of life, fatigue, nausea/ vomiting and dyspnea (LC13) according to grade of hematologic toxicity (HT) during the first treatment cycle. Secondary outcome was overall survival.

Severe HT was defined as grade 3 or 4 neutropenia (absolute neutrophil count $< 1.0 \times 10^9$ cells/L), thrombocytopenia (platelets $< 50 \times 10^9$/L) or anemia (hemoglobin < 8.0 g/dL) occurring on any day during the first cycle.

Patient characteristics according to grade of HT was summarized using proportions, means and standard deviations. Differences between subgroups were investigated by t-test for continuous variables and Pearson`s Chi-square for categorical variables. To analyze the impact of HT on changes in HRQOL, we used LMMs including assessment

time (baseline or end of cycle 1), HT (grade 0-2 or 3-4), the interaction term and the baseline score as fixed effects and a random intercept for patients. The Kaplan-Meier method was used to estimate median overall survival, and the log-rank test to compare subgroups. Median follow-up was estimated using the reverse Kaplan-Meier method.

3.4.3 Paper III

The primary outcome was mean HRQOL scores in 3-month intervals relative to time of death. Secondary outcome was the deterioration rate in months before death in global quality of life, physical function and key symptoms fatigue, pain, appetite loss and dyspnea.

All questionnaires completed during the last year of life were included in the analyses. The HRQOL assessments were aligned relative to the time of death. For example, month 1 included assessments 1-30 days before death. The mean HRQOL scores within four intervals were then calculated: The last three months, the last 3-6 months, the last 6-9 months and the last 9-12 months. If patients had completed multiple questionnaires within an interval, the average score for that patient was used. The difference in mean HRQOL scores between the last 9-12 months and the last three months of life was tested with a LMM with time period as a categorical predictor. The QLQ-C30 scores were compared with age- and gender-adjusted reference values from the general Norwegian population (150, 151).

The change over time in global quality of life, physical function and the key symptoms were investigated using LMMs, with days prior to death as the explanatory variable. To test if we could identify timepoints for accelerated decline we fitted piecewise models, that allowed the change to vary at each month before death. A backward elimination procedure retaining only the significant parameters for the change rate was used to select a more interpretable final model.

3.5 Ethics

The studies in this thesis were approved by the Regional Committees for Medical and Health Research Ethics in Norway. The HELIK study was also approved by NSD – Norwegian Center for Research Data, and the PEG and VG trials by the Norwegian Medicines Agency and the Norwegian Social Science Data Services. All patients gave

written informed consent. The research was conducted according to the Helsinki Declaration and principles of Good Clinical Practice.

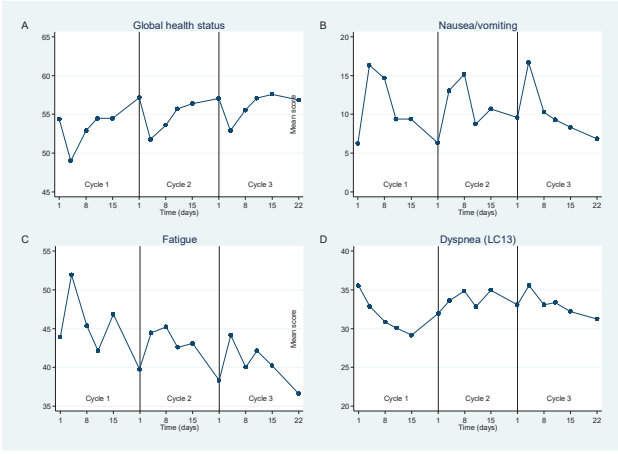
4 Results of papers

4.1 Paper I

"Measurement of health-related quality of life during chemotherapy –the importance of timing"

Fifty-two patients starting chemotherapy were enrolled, of whom 41 completed all three cycles (VC: 68%, GC: 89%). Overall, the patients completed 693 of 756 (92%) HRQOL questionnaires. The variation in mean scores during the chemotherapy cycle for global quality of life, nausea/ vomiting and fatigue reached the threshold for clinical relevance (Figure 6). Day 4 appeared to be the timepoint when chemotherapy influenced HRQOL the most. In contrast, the mean score for dyspnea was not related to timepoint in the chemotherapy cycle. Among the scales not defined as primary endpoints, the following showed a consistent pattern of intra-cycle changes: appetite loss (highest score at day 4 and 8), constipation (highest score days 4-15) and insomnia (lowest score on day 11).

Figure 6. Mean scores of primary HRQOL scales over time (all patients).



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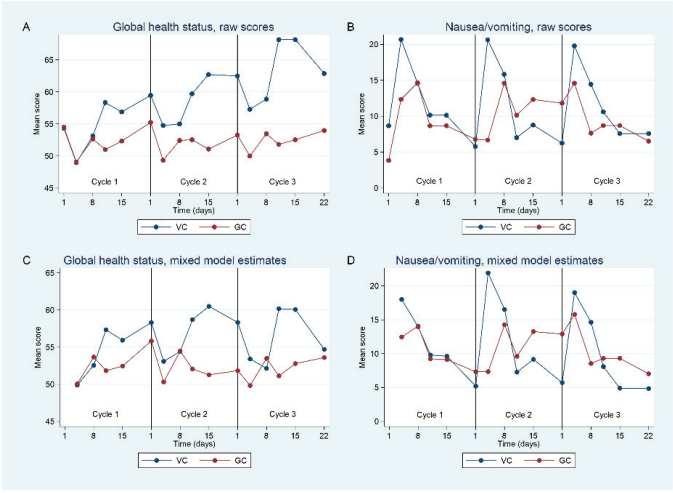
The differences in HRQOL between the two treatment regimens varied at different timepoints, especially for nausea/vomiting (Figure 7). Patients in the VC arm tended to

have worse scores for nausea/ vomiting in the first week following treatment, but better mean scores for global health status during the last part of chemotherapy cycles.

Figure 7. Mean scores and linear mixed model estimates for global health status and nausea/ vomiting over time (by treatment arm). VC: Vinorelbine/carboplatin; GC: gemcitabine/carboplatin.



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Conclusion: There was a clinically relevant variation of HRQOL during chemotherapy cycles, with increased symptom burden and decreased quality of life the first week following treatment. The timing of HRQOL assessments during chemotherapy may influence the chances of detecting differences between treatment regimens. Assessment schedules based on the expected symptom trajectories can provide more accurate information about the HRQOL experienced by the patients. In the clinical context, increased understanding of patients' symptom burden during chemotherapy cycles may help improve supportive care and thus the deliverance of anticancer treatment.

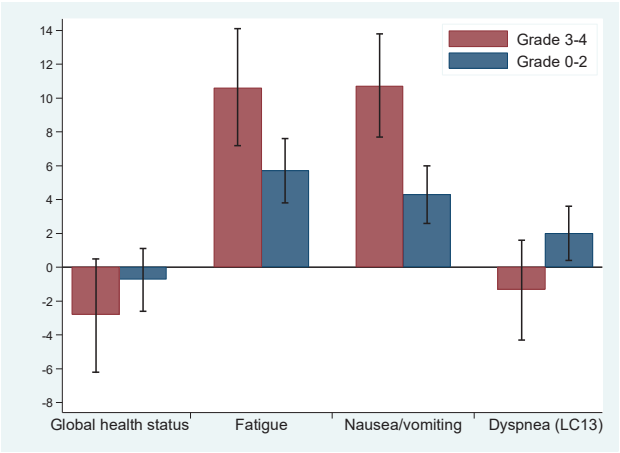
4.2 Paper II

"Associations between hematologic toxicity and health-related quality of life during first-line chemotherapy in advanced non-small-cell lung cancer: a pooled analysis of two randomized trials"

Of the 766 patients with complete data set, 177 (23%) developed severe HT during the first chemotherapy cycle. Severe neutropenia, thrombocytopenia and anemia was observed in 149 (19%), 67 (9%) and 3 (0.4%) patients, respectively.

The mean scores of fatigue and nausea/vomiting increased significantly more in patients with severe HT (10.6 vs. 5.7 points for fatigue and 10.7 vs. 4.3 points for nausea/vomiting; both p=0.01) (Figure 8). There were no significant associations between HT and global quality of life or dyspnea (difference in mean change of 2.1 points; p=0.28, and 3.3 points; p=0.053, respectively). Adjustment for chemotherapy regimen did not alter these results. Among the HRQOL scales not defined as primary endpoints, changes in role functioning, social functioning, alopecia and pain in arm or shoulder were significantly worse for patients that experienced severe HT. Analyses according to type of HT revealed that the association between HT and HRQOL impairment was observed for neutropenia, but not thrombocytopenia. Since only three patients had severe anemia, no separate analyses were performed in this group. The median overall survival was 9.5 months for patients with severe HT and 7.2 months for those without (p=0.03, log-rank test).

Figure 8. Change from baseline to end of cycle 1 in primary HRQOL endpoints for patients with and without severe hematologic toxicity.



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Conclusion: Patients experiencing severe neutropenia during chemotherapy have more negative changes in fatigue, nausea/ vomiting and alopecia, i.e. typical acute side effects of chemotherapy. These patients also have more limitations in social, work and leisure activities. However, the associations were not strong enough to suggest that blood counts can be used to identify patients that need more clinical attention and supportive care during chemotherapy.

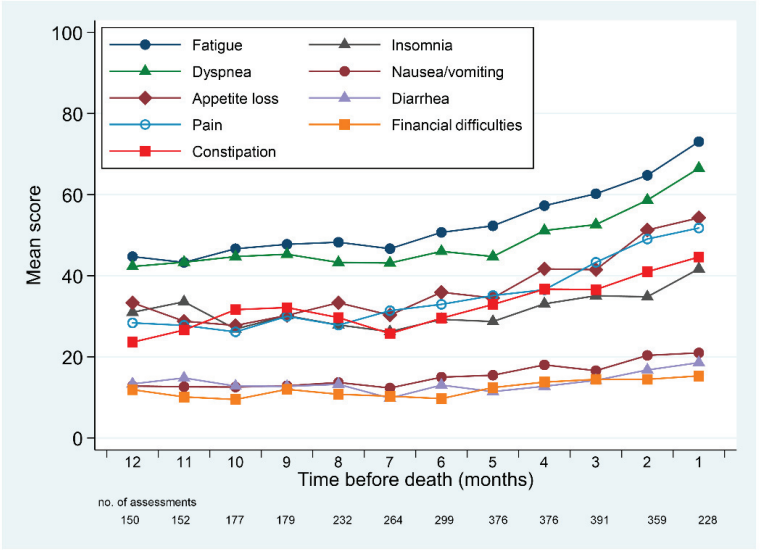
4.3 Paper III

"Health-related quality of life during the last year of life in patients with advanced non-small-cell lung cancer"

Among 767 deceased patients, 730 had completed at least one HRQOL questionnaire during their last year of life and were eligible for inclusion in the present study. Overall, these 730 patients completed 3 183 quality of life questionnaires. The completion rate of expected questionnaires decreased gradually from 96% 12 months before death to 75% two months before death, dropping to 39% in the last month.

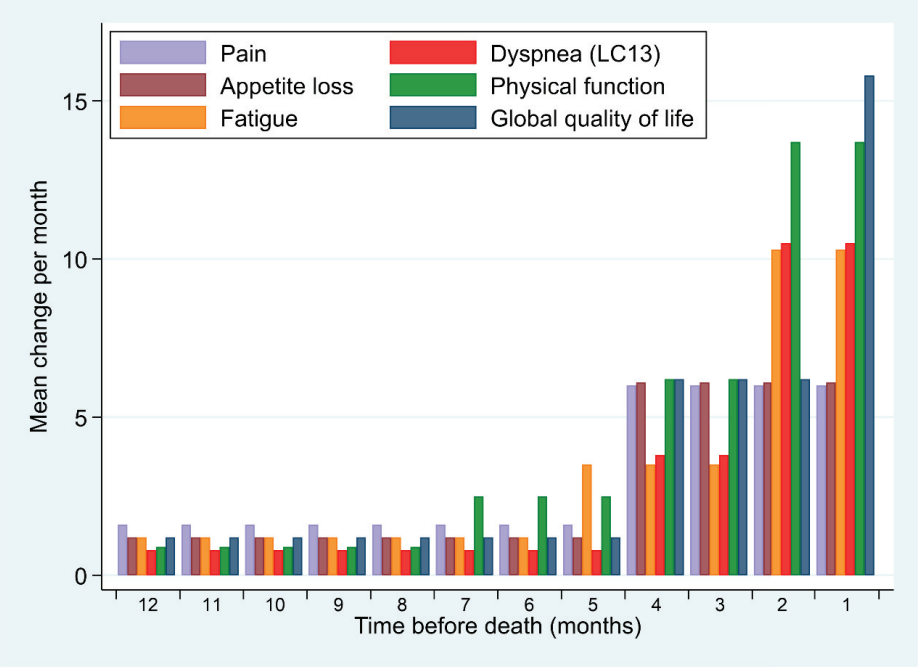
Fatigue, dyspnea, appetite loss and cough were the most pronounced symptoms and significantly worse than the reference population in all phases of the disease trajectory (Figure 9). Notably, mean pain scores were not significantly worse than the reference population up until six months before death but increased substantially thereafter. The ability to carry out physical and social activities was markedly impaired even 9-12 months before death, and then decreased progressively. In contrast, cognitive and emotional functioning was relatively stable during the disease trajectory, and only in the last months of life significantly worse than the reference population.

Figure 9. Mean QLQ-C30 symptom scale scores over time. A high score represents more symptoms. The numbers below data points represent the number of assessments available in given months.



The deterioration rates of global quality of life, physical function and key symptoms pain, appetite loss, fatigue and dyspnea were relatively slow until four months before death (Figure 10). Later, the decline accelerated and for physical function, fatigue and dyspnea there was a very rapid decline in the last two months.

Figure 10. Rate of monthly change in the last year of life for key HRQOL scales, estimated using piecewise linear mixed models. A high value represents a rapid decline.



Conclusion: Patients with advanced NSCLC experience a high symptom burden and significantly impaired quality of life in the last year of life. The degree of worsening increases substantially in the last two to four months of life. Regular symptom measurements may help identify patients with progression before the accelerated deterioration of physical function occurs, and serve as a starting point for decisions about anticancer and symptomatic treatment and discussions about end-of-life care.

5 Discussion

5.1 Main findings

The overall aim of the thesis was to increase the understanding of how chemotherapy and the cancer disease affect health-related quality of life in patients with advanced non-small-cell lung cancer. It was demonstrated that the most severe HRQOL impairment is found in the first week following chemotherapy administration, and that certain symptoms, such as fatigue and nausea/ vomiting, are more pronounced in patients experiencing severe neutropenia. During the last year of life, symptom burden in patients with advanced NSCLC was high and most aspects of HRQOL deteriorated substantially. The degree of worsening for physical functioning and key symptoms increased markedly in the last two to four months.

In the following sections it will be discussed how the findings may contribute to more precise measurements of HRQOL in clinical trials, and improved management of patients in clinical practice.

5.1.1 Measurement of HRQOL in clinical trials

Cancer therapies can affect HRQOL both positively, through alleviating symptoms and slowing or reversing deterioration in functioning, and negatively, through toxic side effects. When studying the effects of treatments that are toxic and cyclic, such as chemotherapy, the timing of HRQOL assessments has particular relevance.

In paper I, we observed that certain scales followed a repeating pattern during the chemotherapy cycles. Global quality of life, nausea vomiting, fatigue, appetite loss and constipation worsened in the first week of the treatment cycle, and the resolved before the next cycle. These results are in line with other investigations of the variation of HRQOL during chemotherapy. In an Austrian study, including 54 outpatients with various cancer types, nine domain scores of the QLQ-C30 were significantly worse one week after treatment (109). The largest differences were observed in fatigue, constipation and appetite loss. In a retrospective analysis of EORTC trials in NSCLC and colorectal cancer, fatigue, appetite loss, social functioning and nausea/ vomiting worsened up to 10 days after chemotherapy administration (108). The consistency of these results with our findings suggest that the observations in paper I are relevant not only for patients with advanced NSCLC, but for a broader range of patients receiving

cytotoxic chemotherapy. To our knowledge, no previous trial has evaluated whether timing of measurement influence comparisons of treatment regimens.

The variation of HRQOL during chemotherapy have implications for how to plan and conduct assessments in clinical trials. First, it is necessary to hypothesize the HRQOL trajectory when scheduling the assessments, to ensure that the measurements are conducted at relevant timepoints. Due to different toxicities and schedules of the drug(s) in use, the HRQOL profiles during treatment might be specific for different interventions. Second, assessments at several timepoints during a treatment cycle are necessary to capture interim toxicities. And third, the results illustrate the importance of following a defined assessment schedule, since deviations from the schedule may affect the results significantly.

In a clinical trial, there are countless opportunities for when patients can complete HRQOL measures. The burden on the patient and the associated data management necessitates some limitation, and the ideal number and timing depend upon the research question (152, 153). In some trials, the goal of HRQOL assessment is to assert that an expected survival benefit does not come at the expense of impaired HRQOL. In these cases, a limited number of assessments (e.g. during treatment, end of treatment and e.g. at 3-month follow-up) can be sufficient to investigate whether there are differences between the trial interventions. However, the goal of HRQOL assessments can also be to capture the patient experience when receiving different treatments, and collect data about treatment effects that can be used to inform future patients. This information can include the frequency and severity of common toxicities, when they typically start and subside, and if and when improvement of disease-related symptoms is observed. In these situations, more frequent assessments are necessary to capture the possible variation in HRQOL over time (e.g. weekly reporting during the first cycles of therapy with reduced frequency thereafter). As demonstrated in paper I, frequent assessments in a population of advanced cancer patients are feasible, even when using a comprehensive questionnaire.

Treatment toxicity has traditionally been registered by clinicians based on the Common Terminology Criteria for Adverse Events (CTCAE). However, approximately 10% of

the adverse event items in the CTCAE are symptoms, like diarrhea, fatigue, nausea and pain (154). Several studies have shown that such symptoms are often missed or underestimated by clinicians (116-121). Moreover, the adverse events reporting offers only information regarding the presence of a symptom at any time, focus on the severe toxicities (grade 3 and 4) and may fail to capture the impact of lower-grade but long-lasting toxicities that can have severe impact on patients` quality of life (155). To improve the precision in the reporting of symptomatic toxicity, patient-reported versions of the CTCAE have been developed, like the PRO-CTCAE in the US (156) and the eRAPID in the UK (157). The systematic assessment of treatment toxicity using PROs may provide additional information that is complementary to CTCAE reports by clinicians.

The use of validated, well-established instrument has been important to standardize HRQOL measurements and obtain high-quality results. The questionnaires used in the studies in this thesis, the EORTC QLQ-C30 and LC13, were developed in an era dominated by intravenous cytotoxic chemotherapy. Today, the therapeutic landscape is dominated by novel therapies, with toxicities that are often unique for different drugs, and not necessarily measured by the traditional instruments. In a review of the PRO collection in 28 registrational trials of checkpoint inhibitors, none of the PRO questionnaires that were used adequately covered all common adverse effects of checkpoint inhibitors (158).

One strategy to keep pace with the treatment advances is updates of standard PRO instruments, such as the LC29 (88), or to develop new instruments for specific therapies, such as the FACT-ICM module for checkpoint inhibitors (159). An alternative to using the standard “static” instruments is a more flexible strategy, such as item libraries that can be added to existing questionnaires or allow researchers to create shorter, more targeted assessments that include only the domains considered most relevant. A standardized, evidence-based hypothesis-driven item selection process is then important to ensure that the data collection is appropriate for the given patient population and treatments being studied (160).

The best solution may be a combination of both assessment strategies: The use of standardized, comprehensive instruments at a few pre-specified and treatment relevant timepoints, and more frequent assessments with shorter instruments adapted to the specific therapies in use. Studies examining the correlation between analogous item in different instruments as the QLQ-C30 and the PRO-CTCAE have found good reliability and consistency (161, 162), indicating that the use of corresponding questions from one instrument can be sufficient and reduce the patient burden. The best way to combine different HRQOL instruments needs to be further investigated and tested in clinical trials.

As shown in paper III, patients with advanced NSCLC experience a high symptom burden. Since the 1980s, assessment of HRQOL has been an important part of the evaluation of new cancer treatments. For targeted therapies (e.g. EGFR TKIs), HRQOL benefits were vital to substantiate the clinical meaningfulness of prolonged PFS, since the first trials of TKIs did not show differences in overall survival (163-168). The findings that PD-L1 inhibitors are associated with benefits in HRQOL compared to chemotherapy alone, reinforced the evidence supporting immunotherapy as first-line therapy for patients without driver mutations (169-171).

Still, HRQOL is not assessed in a considerable proportion of cancer trials. A recent systematic review reported that even in the advanced or metastatic setting, HRQOL was not an endpoint in 40% of phase III trials published between 2012 and 2016 (172). This is problematic, considering the sometimes marginal benefit in OS or PFS outcomes, and the toxicity and cost often associated with new treatments. Clinical trials represent an exclusive opportunity to gain increased insight into the impact of new therapies on patients` lives, and PROs have been described as enabling the health care personnel to "hear the patient voice at a greater volume" (173). As for today, there is a lack of information about how patients experience a specific therapy. When starting a new treatment, clinicians are often unable to adequately answer how many patients using that drug that had improvements e.g. of their cancer-related fatigue or pain, or how many that had symptomatic side effects (174). Considering the costs and potential toxicities of new drugs, it is reasonable that the evaluation of new products includes the patient perspective, and that reasons are given when PROs are omitted.

5.1.2 Measurement of HRQOL in clinical practice

Acknowledging that patients` symptoms often go undetected by clinicians, the aim of paper II was to investigate whether a simple blood test could predict worsening of HRQOL during chemotherapy. Dosing systems of most chemotherapy agents are based on the body surface area (BSA). BSA-based dosing is inaccurate because it does not account for differences in organ functioning and metabolism, leading to high interpatient variability in drug clearance and toxic effects (175). A high grade of hematologic toxicity (HT) may indicate a strong biological effect of myelotoxic drugs.

The results showed that patients experiencing severe HT, and specifically severe neutropenia, had worse changes in fatigue and nausea/ vomiting compared to patients with non-severe HT. Changes in alopecia, pain in arm or shoulder and role and social functioning were also worse for patients with severe HT. The differences in mean change were in the range of 5-10 points, corresponding to a clinically small difference, and it was no difference in global quality of life. Thus, we concluded that blood counts during chemotherapy could not be used as a tool to guide supportive care efforts.

Still, the results of the study give some indications about the relationship between HT/ neutropenia and HRQOL. Among the six scales in which significant differences were detected, three (fatigue, nausea/ vomiting and alopecia) are typical acute side effects of chemotherapy (110). The social and role functioning scales reflect whether the treatment has interfered with social activities and the ability to do work, household or leisure activities. It stands to reason that this ability is lower in patients suffering more from chemotherapy toxicity.

The results of previous studies investigating the impact of chemotherapy-induced neutropenia on HRQOL have been conflicting. Two small US studies found that patients developing severe neutropenia had increased physical symptom distress and declined physical and social functioning (127, 130). In contrast, a large German multicenter study of docetaxel-related toxicities did not find any impact of leukopenia/neutropenia on global quality of life or other QLQ-C30 domains (131). An explanation for these divergent results may be the timing of measurements relative to treatment administration and hematologic nadir. While the US studies measured HRQOL weekly and restricted the analysis to the first treatment cycle, the German

study measured HRQOL every 4 weeks for up to 40 weeks, independent of the timepoint for chemotherapy administration. In paper I, we demonstrated that the most severe HRQOL impairment is found in the first week of the treatment cycle (176). Thus, it is possible that the associations between HT/ neutropenia and impaired HRQOL in paper II would have been stronger if HRQOL had been measured e.g. weekly during the first cycle.

In addition to increased HRQOL impairment, overall survival was significantly longer in patients experiencing grade 3-4 HT in the first treatment cycle. An association between the grade of HT and survival have been reported also in previous retrospective studies, focusing especially on chemotherapy-induced neutropenia (122, 123, 177). Based on these observations it has been proposed that chemotherapy efficacy could be improved by using the level of nadir counts to adjust subsequent doses (either increase or decrease). However, when tested in prospective randomized trials in ovarian cancer (178), early breast cancer (179) and small-cell lung cancer (180), this principle of toxicity-adjusted dosing has failed to improve treatment outcomes.

An alternative strategy to improve care during chemotherapy is to systematically ask the patients about symptoms. Historically, the purpose of HRQOL collection in the research context has been to inform the care of future patients, and the measurements usually had no influence on the treatment of that specific patient. In contrast, the purpose of assessments in clinical practice is to improve the care for the respondent. In this setting, the assessments usually focus on proximal effects (symptoms), and the term PROs is often used rather than HRQOL. Several studies have documented benefits of routine assessment of PROs in clinical practice like improved patient communication (181-183), increased awareness of patients` symptoms and functioning (182, 184), improved patient well-being (181, 185) and possibly improved survival (186, 187).

The findings in paper I have implications for the timing and frequency of PRO measurements in clinical practice. For convenience, symptom questionnaires are often completed when patients attend clinics for treatment administration. However, assessments at this time may underestimate the true symptom burden, since side effects from the previous cycle may have abated. Thus, data collected between hospital visits,

when the patient is at home, could better reflect the true symptom burden. Technological advances have made it possible to collect PRO data electronically, which facilitate assessments between hospital visits and immediate transfer of results to the electronic health record (157, 188-191). Meta-analyses have demonstrated that capturing PROs electronically (ePROS) provide equivalent results as paper-based methods (192, 193). In paper I, the completion rate was 92%, demonstrating that frequent assessments on comprehensive paper questionnaires was possible. This suggests that when using a shorter, and preferably electronic questionnaire, e.g. weekly assessment during treatment should be feasible.

While routine administration of symptom questionnaires has long traditions in palliative care, the use of PROs in routine oncology care is still scarce. The implementation of PRO monitoring in the real-world setting is multifaceted and complex, and several issues are important for its success. First, the purpose of measuring PROs should be thoroughly considered. This should guide the PRO content and the timing and frequency of assessments. Insight into common symptoms and functional problems of the specific patient group, such as provided by the current thesis, is important to tailor the symptom monitoring strategy. Second, the recording of symptoms must be easy for patients and the resulting data accessible for health care personnel, at the point of care. Electronic completion of PROs should be used when patients are willing and able to do so, and the data should preferably be integrated into the existing electronic health record. Third, the collection of PRO data is not enough to improve clinical care, relevant actions need to be taken based on the results. This might include automatic advices to patients for self-care for mild symptoms, and available health staff resources with clear instructions on how to respond to severe symptoms.

Regular symptom assessments can be used not only to identify treatment toxicity, but also to monitor the disease status in periods with or without active treatment. In lung cancer, most relapses are symptomatic and disease progression is usually accompanied with deterioration in HRQOL (132, 194). A French RCT investigated the effect of web-based PRO monitoring in patients with lung cancer (195). The intervention, which consisted of patients weekly self-reporting their weight and 11 symptoms, was compared to routine follow-up with CT scans scheduled every three to six months

(196). In the experimental arm, the oncologist was alerted and asked to contact the patient when symptoms matched predefined criteria. The trial demonstrated prolonged OS in the experimental arm (187), possibly because relapse or disease progression was detected earlier while the patients still were in a good performance status.

Previous studies in patients with various cancer types had suggested that the HRQOL trajectory is characterized by a terminal drop pattern, i.e. a rapid deterioration during the last months of life (138, 139). It was unclear, however, how long before death an accelerated deterioration could be observed. In our population of patients with advanced NSCLC, the deterioration of key scales was relatively slow up to four months before death. Then, increasing decline was seen in physical function, and symptoms like pain and appetite loss. The worsening of physical function accelerated in the last two months, when a rapid increase in fatigue and dyspnea was also observed. Salvage therapies are mainly effective in patients with good performance status (8, 197), and identifying symptoms that may indicate disease progression before the accelerated deterioration in physical function occurs may allow more patients to receive optimal anticancer treatment.

Findings from landmark RCTs demonstrating benefits of routine PRO monitoring are not necessarily generalizable to populations with different cancers or from other geographic regions. Other factors may influence how much time it takes before changes in disease status are discovered in routine follow-up, like how educated patients are about which symptoms that should warrant attention, and the availability for patients to contact the health care team when having new or changing symptoms. Moreover, the effects may be moderated by factors such as age and cognitive functioning (198, 199), and tailored monitoring strategies are needed to meet the unique needs of different subgroups. In the Scandinavian countries, studies of PRO-based follow-up are currently being performed in e.g. breast cancer and gynecologic cancer (200, 201).

Lung cancer is associated with a higher symptom burden than most other cancer types (143-145). We observed that most aspects of HRQOL deteriorate substantially during the disease trajectory, and even 9-12 months before death mean scores for global quality of life and several symptom and functional scales were significantly worse than in the

reference population. This observation support that dedicated attention to the supportive care needs of patients with advanced NSCLC should be a priority during the whole disease trajectory, and not restricted to the end-of-life phase. Systematic monitoring of patients` symptoms could be a key factor to increase the oncology team`s awareness of patients` symptoms and needs, and facilitate early integration of palliative care into routine oncology care.

5.2 Methodological considerations

5.2.1 Study design

The papers in this thesis were based on data from three RCTs. Paper I was the primary publication of the HELIK trial, reporting the results of the research questions it was designed to answer. The objective of the HELIK study was to demonstrate "proof of principle" rather than to conduct a fully powered comparison of the two treatment regimens. Thus, no formal sample size calculation was performed, and the analyses focused on effect sizes and patterns of HRQOL variation during chemotherapy cycles, rather than testing of statistical significance. It was estimated that 25 patients in each treatment group would be enough to provide an indication of whether there were clinically relevant variations in HRQOL during chemotherapy cycles. The small sample size is a limitation, but it was considered that the number of patients was sufficient for an exploratory study.

Paper II and paper III were based on pooled data from the PEG and VG trials (27, 104), and addressed research questions that were not addressed by the original trials. Thus, the data registration was not designed specifically to answer the research questions in this thesis.

The analyses in paper II and III included all eligible patients from the meta-dataset. The main reason for excluding patients in paper II was missing HRQOL data at the end of cycle 1. Although the number was relatively small (n=70, 8%), most of these patients received only one cycle of chemotherapy and their overall survival was poor. HRQOL assessments at several timepoints during the first cycle (e.g. weekly at the same as the blood counts, and not only at the end of the cycle) could have reduced the number of patients with missing HRQOL data. This would also allow us to analyze whether the association between HT and HRQOL impairment was stronger at the time of

hematologic nadir. Moreover, complications could have been registered specifically for the first cycle, and not only summarized for the whole study treatment period. Then it could have been examined whether the grade of HT was associated not only with HRQOL impairment but also with other measures of toxicity, such as infections or hospital admissions.

For paper III, continuing assessments to death (instead of stopping at 12 months) would have resulted in more complete data for the approximately 30% of patients living longer than one year. However, the analyses indicated that the mean score trajectories for the patients living longer than 12 months were similar to those for the patients living less than 12 months. If more detailed data on post-study treatment and cause of death were registered, differences in HRQOL according to status of anticancer treatment and specialized palliative care (controlled for time to death) could have been investigated.

A potential disadvantage of RCTs is that strict eligibility criteria may affect the external validity, i.e. the generalizability of the study results to patients outside the study sample (202). The eligibility criteria of the RCTs in this thesis were broad; patients with PS 0-2 and brain metastases were allowed and no upper age limit was defined. The included patients constituted 20-30% of eligible patients nationwide in the inclusion periods, suggesting that the studies were representative for patients receiving chemotherapy in everyday clinical practice (27, 104). However, only 8% in the HELIK trial had PS 2, compared to 22% and 25% in the PEG and VG trial. We have no data to explain this difference, but it might be that patients with poorer performance status were less willing to complete the frequent HRQOL measurements in HELIK or that health care personnel were less willing to ask them to do so. Patients in poorer condition are more likely to experience chemotherapy side effects (203), and a higher proportion of PS 2 patients in paper I could possibly have resulted in larger variation of HRQOL during the chemotherapy cycles.

The therapies in the RCTs in this thesis did not include targeted therapies or immunotherapy, which is now the preferred first-line treatment for patients with advanced NSCLC. However, many patients receive still receive chemotherapy, either in first-line in combination with immunotherapy, or as salvage treatment after progression

on other therapies. And although up to 25% long-term survivors has been observed in recent studies (39), the majority of patients still progress and die of their cancer. Thus, the results from the thesis is considered relevant also in the treatment landscape of today.

5.2.2 Patient-reported outcomes

Patients` symptoms, functioning and overall well-being are best measured using carefully developed and validated self-reported questionnaires. The psychometric properties of the QLQ-C30 and LC13 have been extensively evaluated, and they are the most frequently used questionnaires in lung cancer trials (204-206).

It is not recommended to do changes on validated questionnaires. Nevertheless, the recall period of the QLQ-C30 and LC13 in the HELIK study was changed from "the past week" to the "last three days" in order to avoid overlapping time intervals. The soundness of this modification was supported by results of a study showing that patients do take into account the stated time frame of the QLQ-C30 (3 or 7 days) (207). However, a concern was whether patients would actually complete the questionnaires at the scheduled day. Since some assessments were only three days apart, deviations from the assessment schedule could influence the results significantly. To facilitate completion at the correct time, research personnel gave the questionnaires to the patients at the hospital visits at day 1 and 8, along with instructions on when to complete them. Overall, as many as 620/693 (89%) of returned questionnaires were completed as scheduled, plus/ minus one day. Sensitivity analyses including only these 620 questionnaires showed similar results as the main analyses.

The EORTC questionnaires use a standardized score ranging from 0 to 100 (147). There are several methods to provide familiarity with scale scores, and indicate whether a certain difference or change is large enough to be considered clinically relevant. Population-based references values are scores from the general population or for various subgroups of patients (151, 208, 209). To facilitate the interpretation of the symptom burden experienced by lung cancer patients, the mean scores in paper III was compared to reference data from the general Norwegian population, adjusted for age and gender (151). As one might expect, HRQOL was considerably worse than the reference population in the last months of life. More interesting, however, was the observation

that several aspects of HRQOL was significantly impaired even 9-12 months before death.

The minimal important differences (MIDs) are the smallest differences or changes in mean HRQOL scores considered to be of clinical relevance, and are estimated by various methods (210). Several studies have evaluated MIDs of the EORTC questionnaires in different cancer populations (148, 149, 211-213). The disease setting should be taken into consideration when defining the MIDs (214). In paper I, intracycle patterns of variation in HRQOL scales was examined. In these within-patient analyses over a short period of time, differences exceeding 5 points were considered clinically relevant (215). The analyses in paper III involved comparisons between mean scores in 3-month intervals up until death. Over such long periods of time, deterioration of HRQOL is expected and it was defined that changes over time and differences relative to the general population should be at least 10 points to be considered clinically meaningful.

During a course of illness and treatment individuals may adapt to symptoms or recalibrate their own internal standards and values. Changes in the criteria of how patients perceive their HRQOL are referred to as "response shift" (216, 217). The response shift can result in an under- or overestimation of the true changes in HRQOL, dependent on its direction. In a meta-analysis, the effect sizes of response shift were found to be relatively small, the largest for fatigue, followed by global quality of life, physical limitation, psychological well-being and pain (218). It is difficult to quantify the impact of response shift, but focusing the analyses in paper I and II on the first cycle of chemotherapy may have reduced its effects. In paper III, some patients reported HRQOL for up to a year, and during this time adaption to symptoms may have influenced the scores.

5.2.3 Missing data and statistical analyses

Missing data means that there exist a meaningful data value which could have been, but was not recorded. Missing data occur in most longitudinal HRQOL studies and may have important consequences (202). First, statistical precision and power is decreased due to reduction in data. Second, and more important, it introduces a potential bias in

the estimation of treatment effects since the reasons for missingness are often related to deterioration in the patients` health status (219).

The mechanisms for missing data are often classified as follows (220):

- Missing completely at random (MCAR): There are no systematic differences between the missing values and the observed values.
- Missing at random (MAR): Any systematic differences between the missing values and the observed values can be explained by differences in the observed data.
- Missing not at random (MNAR): Even after the observed data are taken into account, systematic differences remain between the missing values and the observed values.

The appropriate statistical method for data analysis depends on the research objective and the proportion and assumed mechanism for missing data (90). The mean score plots in paper I, representing the average scores of available assessments at each timepoint, are available case analyses. Unless the data are MCAR, the results from available case (and complete case) analyses will be biased. However, if the proportion of missing data is low, these analyses will provide quite similar results as more complicated statistical methods (221). An alternative way to analyze longitudinal data is to use the linear mixed model for repeated measures (LMM), which can be considered as an extension of the ordinary linear regression model that can be used when data are not independent. LMMs give unbiased results provided that the data are MAR, which is often more reasonable than MCAR, and are also fairly robust to data which are MNAR (202, 222). Other advantages of these models are the possibility to control for covariates and test statistical significance. Their complexity, however, can be considered a disadvantage, and to produce unbiased results the models must be correctly specified (56).

In paper I, differences in HRQOL scores between treatment arms was examined using both available case analyses and LMM. Overall, the resulting plots from these two methods were quite similar (Figure 7). An illustrative exception, however, was the global quality of life scores for VC at day 11 to 22 in cycle 3, where the available case analyses provided higher mean scores than the estimates from the LMM. At these

timepoints, the completion rate of questionnaires in the VC arm was only 65%. Patients feeling unwell may be less likely to complete and return questionnaires (223, 224), meaning the data were not MCAR. Consequently, the available case mean scores were biased, while the estimates from the LMM were more valid.

In paper II, 75 of the 840 patients receiving chemotherapy had missing HRQOL data at the end of cycle 1. It can be suspected that patients who did not complete the follow-up assessment suffered more from treatment side effects, but unfortunately we did not have any data on this. The main analyses included patients who had completed both the baseline and the end-of-cycle assessment. This is analogue to performing a complete case analysis, which could have biased the results and probably lead to an underestimation of the association between HT and HRQOL. However, the proportion of patients with missing HRQOL values was relatively small (75/841; 9%), and sensitivity analyses including also patients with missing data at one of the assessments gave the same results and conclusions as the main analyses.

In paper III, the rate of missing data increased in the last two months, and it can be assumed that those who did not complete the questionnaires were the patients in worst physical condition. This would result in underestimation of the symptom burden. Another limitation is the somewhat arbitrary knots (changes in slope) at monthly intervals in the piecewise regression models of the deterioration rates. The approach was based on previous studies of HRQOL trajectories and visual inspection of the data, which clearly indicated that the deterioration of several HRQOL scales followed a nonlinear slope. Still, the models could have been defined differently, e.g. with knots at other timepoints, which could have resulted in different regression coefficients for the change rates.

6 Conclusion

This thesis has aimed to improve management of patients with advanced NSCLC by contributing to increased understanding of how chemotherapy and the cancer disease affect HRQOL. The thesis includes three papers answering the following research questions:

Paper I:

1. *What is the variation of HRQOL scores during chemotherapy cycles?*

There was a significant variation in mean scores of global quality of life, nausea/ vomiting and fatigue during the chemotherapy cycles. Patients experience the most severe impairments in the week following chemotherapy administration.

2. *Does timing of HRQOL assessments influence the chances of detecting differences between treatment regimens?*

In some HRQOL scales there was a repetitive pattern of cycle-specific differences between treatment regimens. The timing of assessments can consequently affect the chances of detecting differences in treatment effects and potentially influence the overall comparison of treatment regimens.

Paper II:

3. *Do patients who experience severe hematologic toxicity (HT) in their first cycle of chemotherapy report more negative changes in HRQOL than patients with no severe HT?*

Patients experiencing severe neutropenia during the first cycle of chemotherapy have worse changes in fatigue and nausea/ vomiting, but similar global quality of life and dyspnea as patients with no severe HT. Changes in alopecia, pain in arm or shoulder and role and social functioning were also significantly worse. However, the magnitude and clinical relevance of these differences was too small to suggest that blood counts could be used to rank patients according to their projected need for supportive care.

4. *Is there an association between experiencing severe HT and overall survival?*

Overall survival was significantly longer for patients experiencing severe HT compared to those with no severe HT (median OS 9.5 vs. 7.2 months; p=0.03).

Paper III:

5. *What characterizes the HRQOL trajectory during the last year of life in patients with advanced NSCLC?*

Patients with advanced NSCLC experience a significant deterioration of HRQOL in the last year of life. Fatigue, dyspnea, appetite loss and cough were the most pronounced symptoms and significantly worse than the reference population in all phases of the disease trajectory, even 9 to 12 months before death. Mean pain scores were not worse than the reference population until six months before death, but increased substantially thereafter.

6. *When and to what degree does deterioration of symptoms and functioning accelerate towards the end of life?*

The deterioration rates of global quality of life, physical function and key symptoms pain, appetite loss, fatigue and dyspnea were relatively slow until four months before death. Then, the decline accelerated and for physical function, fatigue and dyspnea there was a very rapid decline in the last two months of life.

7 Future perspectives

The development of new therapies has revolutionized the treatment of advanced NSCLC, and 15-25% of patients receiving immunotherapy become survivors at 5 years (39, 225). PROs have been included in most of the landmark trials of these novel drugs, and the collection and analyses of data has been well designed and the results supported their use in clinical practice. Still, there is a potential for clinical trials to contribute to increased insight into how patients are affected by different therapies. More detailed assessments of relevant symptoms and toxicities will improve the understanding of how patients feel and function during treatment.

The use of PROs in routine clinical practice is still fairly modest, but this can change as the patient-centered perspective in health care is becoming increasingly important and the technology advances (226, 227). Electronic capture of PROs through devices like patients` smart phones may allow for real-time monitoring of symptoms, early detection of problems, and prompt clinical interventions (228). Such symptom monitoring could be useful not only for patients receiving systemic therapy, but also for patients receiving radiotherapy or undergoing major surgery.

Systematic registration of PROs could also provide valuable information for future patients. Most information about the efficacy and toxicity of new drugs are derived from RCTs, which often have strict eligibility criteria. Thus, data from real-world patients could provide more generalizable findings for the patient group actually receiving treatment. More research is needed on how to present such results effectively and understandably to patients. For institutions, PROs could be used to evaluate the quality of care, e.g. prevention of nausea during chemotherapy.

In Central Norway, a common electronic health record solution for all levels of the health sector is being developed. At St. Olavs hospital implementation of the system is scheduled to Autumn 2021. This new and modern solution can facilitate the use of ePROs in routine clinical practice, both in primary care and in specialist care. The introduction of such a system also represents an opportunity for research on how PRO monitoring at different levels of the health care system may contribute to improved patient care.

At the time that this thesis is being finalized, the COVID-19 pandemic is affecting most countries in the world. The pandemic has drastically impacted the management of cancer patients (229).To reduce the patient volume visiting the hospitals, outpatient clinics have shifted towards telemedicine and many consultations are now being conducted using video or telephone. My impression is that both patients and clinicians are satisfied over how effective and well-functioning such virtual visits can be. Still, the patient-physician interaction can be challenging when managed remotely. When you are not talking to the patients face-to-face or observing how they look and move, it can be more difficult to use the "gut feeling" to identify issues patients do not report spontaneously. In this situation, systems for real time ePROs would represent a valuable tool to ensure that symptoms are being identified and patients receive the care they need. The pandemic will eventually subside, but hopefully some of the experiences from this crisis can be used to improve the management of cancer patients in the future.

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9 Appendix

Contents

1. EORTC QLQ-C30 version 3.0
2. EORTC QLQ-LC13
3. Paper I
4. Paper II
5. Paper III

EORTC QLQ-C30 (versjon 3.0.)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette en ring rundt det tallet som best beskriver din tilstand. Det er ingen "riktige" eller "gale" svar. Alle opplysningene vil bli behandlet konfidensielt.

Ditt navns forbokstaver: _____

Født (dag, mnd, år): _____

Dato (dag, mnd, år): 31 _____

		Ikke i det hele tatt	Litt	En del	Svært mye
1.	Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	1	2	3	4
2.	Har du vanskeligheter med å gå en lang tur?	1	2	3	4
3.	Har du vanskeligheter med å gå en kort tur utendørs?	1	2	3	4
4.	Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	1	2	3	4
5.	Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	1	2	3	4

I løpet av den siste uken:

		Ikke i det hele tatt	Litt	En del	Svært mye
6.	Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	1	2	3	4
7.	Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	1	2	3	4
8.	Har du vært tung i pusten?	1	2	3	4
9.	Har du hatt smerter?	1	2	3	4
10.	Har du hatt behov for å hvile?	1	2	3	4
11.	Har du hatt søvnproblemer?	1	2	3	4
12.	Har du følt deg slapp?	1	2	3	4
13.	Har du hatt dårlig matlyst?	1	2	3	4
14.	Har du vært kvalm?	1	2	3	4

Bla om til neste side

I løpet av den siste uken:

		Ikke i det hele tatt	Litt	En del	Svært mye
15.	Har du kastet opp?	1	2	3	4
16.	Har du hatt treg mage?	1	2	3	4
17.	Har du hatt løs mage?	1	2	3	4
18.	Har du følt deg trett?	1	2	3	4
19.	Har smerter påvirket dine daglige aktiviteter?	1	2	3	4
20.	Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	1	2	3	4
21.	Har du følt deg anspent?	1	2	3	4
22.	Har du vært engstelig?	1	2	3	4
23.	Har du følt deg irritabel?	1	2	3	4
24.	Har du følt deg deprimert?	1	2	3	4
25.	Har du hatt problemer med å huske ting?	1	2	3	4
26.	Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	1	2	3	4
27.	Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	1	2	3	4
28.	Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	1	2	3	4

Som svar på de neste spørsmålene, sett en ring rundt det tallet fra 1 til 7 som best beskriver din tilstand

29. Hvordan har din helse vært i løpet av den siste uken?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uken?

1	2	3	4	5	6	7
Svært dårlig						Helt utmerket

EORTC QLQ - LC13

En del pasienter opplever av og til at har noen av følgende symptomer eller problemer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene eller problemene i løpet av den siste uka. Sett en ring rundt det tallet som best beskriver din tilstand.

I løpet av den siste uka:	**Ikke I det hele tatt**	**Litt**	**En del**	**Svært mye**
31. Hvor mye har du hostet ?	1	2	3	4
32. Har du hostet blod ?	1	2	3	4
33. Har du vært tungpustet i hvile ?	1	2	3	4
34. Har du vært tungpustet når du har gått ?	1	2	3	4
35. Har du vært tungpustet når du har gått i trapper ?	1	2	3	4
36. Har du vært sår i munnen eller på tungen ?	1	2	3	4
37. Har du hatt svelgeproblemer ?	1	2	3	4
38. Har du hatt prikking (stikking) i hendene eller i bena ?	1	2	3	4
39. Har du hatt håravfall ?	1	2	3	4
40. Har du hatt smerter i brystet ?	1	2	3	4
41. Har du hatt smerter i arm eller skulder ?	1	2	3	4
42. Har du hatt smerter i andre deler av kroppen ?	1	2	3	4
Hvis ja, hvor har du hatt vondt ? _____				
43. Har du brukt smertestillende medisiner ?				
1. Nei **2. Ja**				
Hvis Ja, hvor mye har det hjulpet ?	1	2	3	4

Paper I

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