Kari Röhrl

Symptoms and quality of life
during chemotherapy
in patients with colorectal cancer

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Foreword

Meeting educated, passionate professionals when one is most vulnerable is an unconditional requirement for patients with a life threating cancer diagnose. Outpatients with cancer spend most of their time outside the hospital environment between treatment cycles, which means that the time allocated for professional support is often limited to the days of chemotherapy. It is one of my tasks as a nurse to help patients "stay on track" and to help relieve severe or distressing symptoms experienced during treatment. It is challenging for the health professional to support and follow up each individual patient in a busy outpatient clinic. Patients must be seen and heard, and be met with dignity and respect for their individual needs. It is important to remember that the patient represents more than the disease and is an entire human being.

Alle har et medfødt menneskeverd som man ikke skal tulle med

Per Fugelli

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<center>

"Work hard, play hard"
Jeg elsker dere! I love you! Ich Liebe Euch!

</center>

Publications included in this thesis

I   Röhrl K, Guren MG, Miaskowski C, Cooper BA, Diep LM, Rustøen T. No differences in symptom burden between colorectal cancer patients receiving curative versus palliative chemotherapy. *Journal of Pain and Symptom Management*. 2016;52(4):539–547.

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Abbreviations

BMI	Body mass index
CINV	Cancer-induced nausea and vomiting
CRC	Colorectal cancer
CTX	Chemotherapy
DPD	Dihydropyrimidine dehydrogenase
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ	EORTC Quality of Life Questionnaire
ESAS	Edmonton Symptom Assessment System
5-FU	5-Fluorouracil
HRQoL	Health-related quality of life
KPS	Karnofsky Performance Status
LMM	Linear mixed model
MCAR	Missing completely at random
MCS	Mental Component Summary
MNAR	Missing not at random
MSAS	Memorial Symptom Assessment Scale
NGICG (-CR)	Norwegian Gastrointestinal Cancer Group (Colorectal)
OUS	Oslo University Hospital
PCS	Physical Component Summary
PhD	Doctor of philosophy
PRO-(M)	Patient-reported outcome (Measure)
QoL	Quality of life
REC	Regional Committees for Medical and Health Research Ethics
RT	Radiotherapy
SCQ-19	Self-administered Comorbidity Questionnaire-19
SD	Standard deviation
SF-12/36	Short-Form 12/36
TNM	Tumor–node–metastases
TOUS	The middle range theory of unpleasant symptoms
TSM	Theory of symptom management
VEGF	Vascular endothelial growth factor

Summary in English

Background

Patients with colorectal cancer (CRC) experience multiple co-occurring symptoms as a result of the disease, treatment, or comorbidity. Surgery is the standard curative treatment for CRC and is often combined with additional treatment as radiotherapy and/or chemotherapy. In patients with metastatic disease, chemotherapy is the main treatment modality. Chemotherapy for CRC patients is commonly administered in an outpatient setting. Cancer treatment is demanding and can lead to distressing physical and mental symptoms, and side effects, which affect the patient's quality of life (QoL).

Aims

The aim of this thesis was to evaluate the symptom burden, in terms of occurrence, frequency, severity, and distress before the start of chemotherapy and throughout 6 months of chemotherapy in CRC outpatients. Additional aims were to measure QoL over the same period and to identify the demographic and clinical variables and symptoms associated with symptom burden and QoL.

Methods

This study included 120 patients diagnosed with CRC and starting a new chemotherapy regimen. Multiple symptoms and QoL were assessed using detailed self-reported questionnaires from the start of chemotherapy (enrolment), during the first two cycles, and thereafter for 6 months. The questionnaires were administered at eight times: enrolment, 3 and 7 days after the initiation of chemotherapy, before the second chemotherapy cycle, 3 and 7 days after initiation of the second chemotherapy cycle, and 3 and 6 months after enrolment. The Memorial Symptom Assessment Scale (MSAS) was used to assess the multidimensionality of symptoms with addition of the MSAS subscores physical and mental symptoms. The Short Form 12-item Health survey (SF-12) was used to assess QoL, the Self-Administered Comorbidity Scale (SCQ-19) was used to identify comorbidity, and the Karnofsky Performance Status (KPS) scale was used to evaluate performance status. Descriptive statistics were used to present the occurrence and dimensions of the symptoms. Binary logistic regression and ordinal regression analyses were conducted to compare symptoms between subgroups before the start of chemotherapy. Linear mixed-model analyses were used to evaluate the symptoms and QoL, and their potential associations with demographic and clinical variables over time.

Results

The most frequently occurring symptoms at enrolment were worrying (65%), lack of energy (59%), feeling drowsy (54%), feeling bloated (53%), pain (51%), and difficulty sleeping (50%). The symptom with the highest severity and distress score at enrolment was problems with sexual interest. No significant difference in symptom burden was revealed between curative and palliative patients at enrolment. Lack of energy, nausea, and numbness/tingling (oxaliplatin-treated group) increased significantly in severity in the days and week following chemotherapy and returned towards the enrolment levels by the day of the next chemotherapy administration. Physical and mental QoL scores were lower than those in the general population at all assessment points throughout the 6 months of chemotherapy. The symptom burden was associated with diminished QoL over the whole assessment period. Numbness/tingling was associated with impaired physical QoL. Being a woman, being younger, and having problems with sexual interest were associated with impaired mental QoL.

Conclusion

Patients with CRC experience co-occurring symptoms throughout the entire chemotherapy trajectory, and these negatively affect their QoL. The most frequently occurring symptoms were not always those that were the most severe or distressing. Patients experienced increased severity for several symptoms between the chemotherapy administrations (when patients were at home) compared with the day of chemotherapy administration. Patients experienced fluctuations in QoL throughout the treatment trajectory.

Clinical importance

Clinicians can use these results to inform patients about the expected symptoms and QoL during treatment. Understanding the factors associated with increased symptom burden and impaired QoL will be helpful for identifying those patients who are more at risk. The use of self-reported questionnaires is recommended for the early detection of severe or distressing symptoms and for improved communication and symptom control.

Sammendrag på norsk

Bakgrunn

Pasienter med tykk- og endetarmskreft (kolorektal kreft) opplever mange symptomer samtidig som følge av sykdom, behandling eller komorbiditet. Standard kurativ behandling for kolorektal kreft er kirurgi, men ofte med tilleggsbehandling som stråling og kjemoterapi. Hos pasienter med metastatisk sykdom, er kjemoterapi hovedbehandlingen. Kreftbehandling er krevende og kan bidra til plagsomme fysiske og psykiske symptomer og bivirkninger med negativ innvirkning på livskvaliteten. Kjemoterapi for kolorektal kreft blir oftest gitt poliklinisk. Dette resulterer i at plagsomme symptomer og bivirkninger fra sykdom og behandling ofte kan bli en utfordring i pasientenes hverdag i tiden mellom kjemoterapi behandlingene.

Mål

Hovedmålet med denne studien var å evaluere symptombyrde, tilstedeværelse, hyppighet, hvor kraftig symptomet var, og grad av bekymring/plagsomhet av symptomer før oppstart av kjemoterapi hos pasienter diagnostisert med tykktarm eller endetarmskreft, og følge disse gjennom et halvt år med poliklinisk kjemoterapi. I tillegg var målet å undersøke livskvaliteten hos disse kreftpasientene over samme tidsperiode, og se hvilke faktorer som påvirker symptombelastningen og livskvaliteten.

Metode

Totalt 120 polikliniske pasienter med kolorektalkreft ble inkludert. Et utvalg av selvrapporterte spørreskjemaer ble fylt ut før de startet med kjemoterapi, etterfulgt av hyppige målinger gjennom de to første kjemoterapi syklusene og deretter over 6 måneder, totalt 8 ganger. Spørreskjemaene ble administrert ved inklusjon, 3 og 7 dager etter oppstart av kjemoterapi, før 2. kjemoterapi syklus, 3 og 7 dager etter start av 2. kjemoterapi syklus, deretter 3 og 6 måneder etter inklusjon. Memorial Symptom Assesment Scale (MSAS) ble brukt for å måle enkelt-symptomer, i tillegg til MSAS subskår for å måle fysiske og psykiske symptomer. Short Form-12 (SF-12) ble brukt for å måle livskvalitet, SCQ-19 ble brukt for å måle komorbiditet og Karnofsky Performance Status (KPS) for å måle ytelsesstatus. Deskriptiv statistikk ble brukt for å beskrive forekomsten av symptomene, og dets dimensjoner. Binær logistisk regresjon og ordinal regresjons analyser ble brukt for å sammenlikne symptomene mellom ulike grupper før oppstart av kjemoterapi. Linear Mixed Models ble brukt for å undersøke assosiasjoner mellom symptomer, livskvalitet og utvalgte faktorer over tid.

Resultater

De hyppigste forekommende symptomer før oppstart av kjemoterapi var bekymring (65%), mangel på energi (59%), søvnig/mye trøtt (54%) oppblåsthet (53%), smerte (51%) og søvnvansker (50%). Problemer med seksuell lyst/aktivitet hadde høyest symptomskår i både hvor kraftig symptomet var og hvor plagsomt/bekymringsfullt symptomet var før de startet opp med behandling. Ingen forskjell i symptombelastning ble funnet mellom de kurative og palliative pasientene ved oppstart av kjemoterapi. Etter oppstart av kjemoterapi opplevde pasientene at følgende symptomer økte i kraft; mangel på energi, økt kvalme og neuropati (oxaliplatin gruppen) i dagene etter kjemoterapi. Symptomene ble mindre kraftig og nærmere baseline verdier på dagen for neste kjemoterapibehandling. Neuropati var assosiert med lavere fysisk livskvalitet, mens det å være kvinne, yngre og ha problemer med seksuell lyst hadde negativ innvirkning på den mentale livskvaliteten over tid. Den fysiske/mentale livskvaliteten var lavere enn den generelle befolkningen på alle målte tidspunkter.

Konklusjon

Pasienter med kolorektalkreft kan oppleve mange plagsomme symptomer samtidig, som også kan ha negativ innvirkning på livskvaliteten. Symptomene som var hyppigst forekommende eller kraftige var ikke alltid de som var mest bekymringsfulle/plagsomme. Pasientene oppleede økt intensitetsgrad (kraft) i flere symptomer i dagene etter kjemoterapi. Livskvaliteten fluktuerte over tid.

Klinisk betydning

Helsepersonell kan bruke resultatene fra disse studiene til å informere pasienter om forventet behandlingsforløp, med tanke på symptomer, symptombelastning og livskvalitet. Kunnskap om assosierte faktorer som kan påvirke symptombelastningen og livskvaliteten negativt, kan bli brukt til å identifisere og ha fokus på pasienter som er mer utsatt. Systematisk kartlegging ved bruk av selvrapporterte spørreskjemaer er anbefalt for lettere og tidligere å oppdage symptomer som er kraftige og bekymringsfulle/plagsomme for pasienten, og for å forbedre kommunikasjonen og få kontroll på symptomer.

Introduction

Colorectal cancer (CRC) is one of the most common cancer diagnoses in the world and affects both males and females.[1,2] Since the introduction of chemotherapy in 1957 for CRC patients,[3,4] the survival rate has increased.[4,5] During the last several decades, additional improvements in new chemotherapy agents and more advanced surgery techniques, screening, and radiotherapy have improved survival rates even further.[6,7] Despite the improvements in treatment, and high survival rates,[8] the incidence of CRC has increased, and Norway has one of highest incidence rates of CRC in the world.[9] Today, around 30,000 people live with the disease in Norway.[10] The risk of developing CRC increases with age, and given the increasing aging population, the number of patients is expected to increase further.

Patients living with a life-threatening illness face problems in physical, psychological, and social function that impact negatively on the quality of life (QoL).[11] Knowledge of a patient's symptom burden is essential for offering effective health services and achieving good health outcomes. The presence of symptoms is often what brings patients to seek health care and can be the first indication of a disease or the reason that patients are unable to function normally in daily life. To identify patients at particular risk for adverse outcomes, it is important to understand more about the science of symptom management.

Despite the high incidence rates in Norway, there is limited understanding of how the disease and treatment affect a CRC patient's life and ability to function in everyday life during chemotherapy. Living with a CRC diagnosis is unpredictable and involves a complex health situation for many patients and their next of kin, environment and social network,[12] throughout the treatment trajectory toward survivorship or death. To address the needs of CRC patients and improve the quality of supportive care, research is needed to understand patients' symptom burden and QoL during all treatment phases.[13]

During 20 years as a nurse, I have met many cancer patients who struggle with side effects and symptoms. I have found that "face-to-face" time spent with outpatients on the day they receive chemotherapy is an important aspect of nursing interventions to alleviate side effects or symptoms and distress. However, time is often limited [12] because of the busy environment and lack of rooms or facilities. Patients often expressed concern about reporting symptoms; that is, they did not want to bother the nurses, they were afraid to interrupt, and they were thankful

to receive treatment. As a result, patients' problems could be missed because of the lack of time, and this seemed to become another burden for patients in addition to living with a life threatening disease.

It is essential to strengthen those parts of the patients that remain healthy by stimulating the use of each patients' own resources, providing patients with self-management strategies, involving patients in treatment decisions and care, and focusing on how they can manage their situation. Outpatient involvement is essential because they spend most of their time outside the hospital. In addition, helping patients reduce their symptom burden might positively affect their QoL and provide benefits such as increased survival.[14]

> *"Tell me and I forget. Teach me and I remember. Involve me and I learn."*
> *Benjamin Franklin*

The present study is part of a larger longitudinal cohort study for people with diverse cancer diagnoses called "Advancing the science of symptom management and support for cancer patients and their caregivers".[15] The substudies described in this thesis included patients with CRC from this larger study. Several decisions regarding study design and data collection had been taken before I started this PhD project.

The study aim of this thesis is to provide deeper insight into CRC patients' self-reported experience of living with the disease before the start of chemotherapy and throughout the continuum of chemotherapy and until 6 months of treatment. The studies focused on symptoms, symptom burden, multidimensionality of symptoms, and factors associated with symptom burden and QoL.

Background

Colorectal cancer

Cancer is a wide group of diseases characterized by an unregulated growth of cells. Colon cancer originates in the large intestine (colon), and rectal cancer in the rectum. (Fig. 1). The large intestine's main functions are to absorb water and vitamins and to convert digested food into feces. Right-sided cancers occur most often in the cecum and ascending colon, and left-sided cancers in the descending and sigmoid colon (Fig. 1). The rectum's main function is the storage of feces before the nerves located in the rectum walls give signals to defecate. Right-sided colon cancers often present with diffuse symptoms such as anemia, whereas left-sided colon-and rectal cancers more often present with changes in defecation.[16,17] Tumors may present with obstructive symptoms. Symptomatic CRC is often diagnosed at a late stage, and 20–30% of patients present with metastatic disease at the time of diagnosis.[18,19]

CRC develops mainly from polyps called adenomas,[20] and about 20% of people aged >60 years have adenomas,[20] but only a small percentage of these transform to cancer. To detect and remove precancerous polyps before they turn into cancer, screening programs have been widely established.[21] Screening aims to improve survivals rates,[22] although there are differences in the preference for screening tests.[21] A national screening program is planned to be established in the public health system in Norway in 2019.[23] As a first step, patients aged ≥55 years will be invited and offered screening testing for blood in feces or colonoscopy. In case of a positive fecal test, colonoscopy will be offered.[23]

Despite the anatomical differences between the colon and rectum, the disease is often referred to as CRC. Treatment of metastatic disease does not differ between colon and rectal cancer. In this thesis, colon and rectal cancer is presented as one entity and called CRC.

Disease stages

The tumor–node–metastasis (TNM) classification system provides important information about the tumor stage and is used when making decisions about treatment and prognosis (Table 1). Tumor (T) describes the extent of the tumor growth and is classified as T1–T4. Node (N) indicates whether the tumor has spread to the lymph nodes and the extent of lymph node involvement (N0–N2). Metastasis (M) indicates whether the tumor has metastasized to other organs; M0 means no metastases and M1 denotes metastases. Based on the TNM classification,

CRC is categorized into four stages (I–IV). Stage I is limited to the bowel wall. Stage II includes T3–4 tumors without lymph node metastases. Stage III includes any T stage when lymph node metastases are present. Stage IV comprises distant metastases (Fig. 1).[24] The most common sites for metastases are the liver, lungs, and peritoneum.[1] Metastases in bone and the brain are less frequent.[25]
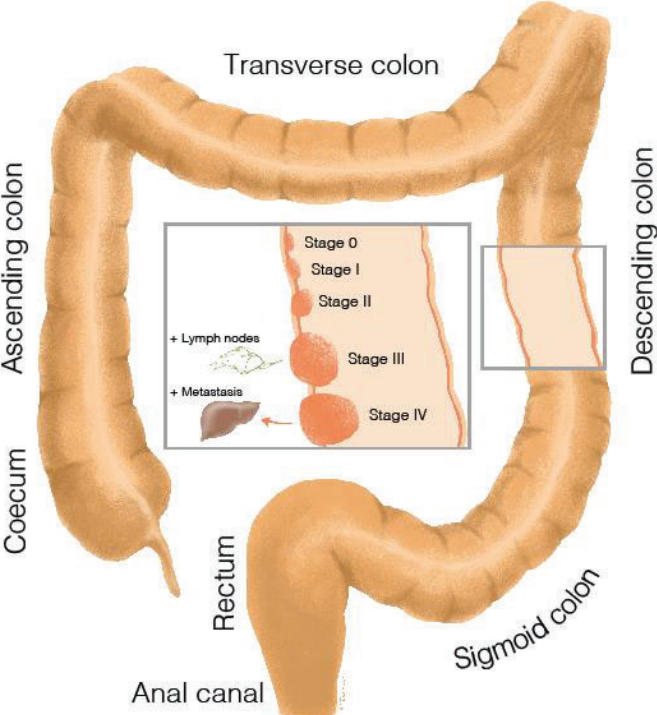

Fig. 1. Anatomy of the large intestine and rectum

Reprinted with permission from Hellevik Studio.[26]

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Table 1 International Union Against Cancer (UICC) Tumour–Node–Metastasis (TNM) classification of Malignant Tumours, 8th Edition.[27]

AJCC stage	TNM stage	TNM stage criteria for colorectal cancer
Stage 0	Tis N0 M0	Tis: Tumour confined to mucosa: cancer-in-situ
Stage I	T1 N0 M0	T1: Tumour invades submucosa
Stage I	T2 N0 M0	T2: Tumour invades muscularis propria
Stage II-A	T3 N0 M0	T3: Tumour invades subserosa or beyond (without other organs involved)
Stage II-B	T4 M0 M0	T4: Tumour invades adjacent organs or perforates the visceral peritoneum
Stage III-A	T1-2 N1 M0	N1: Metastasis to 1–3 regional lymph nodes, T1 or T2
Stage III-B	T3-4 N1 M0	N1: Metastasis to 1–3 regional lymph nodes, T3 or T4
Stage III-C	Any T, N2 M0	N2: Metastasis to 4 or more regional lymph nodes, any T
Stage IV	Any T, any N, M1	M1: Distant metastases present, any T, any N

Treatment

Cancer treatment in CRC patients in Norway is standardized and based on the latest Norwegian guidelines for CRC patients.[16] These guidelines have been developed to assist in the treatment and management, and are based on the available evidence. The treatment of CRC is often multimodal and may involve combinations of surgery, radiotherapy, oral or intravenous chemotherapy, and antibody treatment.[18]

Surgery

Surgical resection is the main curative option for CRC patients.[18] Surgery for colon cancer is often performed as a right- or left-sided hemicolectomy. For rectal cancer, most patients undergo low anterior resection, often with a temporary stoma, and others undergo abdominoperineal resection with a permanent stoma. Surgery may be a treatment option for resectable metastases, most often in the liver, but sometimes in the lung or peritoneum. Advancements in surgical techniques have made it possible to take a curative approach for patients with liver metastasis, who were previously not curable, and often in combinations with chemotherapy.[18,19,28,29] This has made the categorization of curative and palliative patients more complicated and "blurred".[19]

Radiotherapy

Neoadjuvant radiotherapy, often with concomitant chemotherapy, is commonly used before surgery in rectal cancer patients to reduce the tumor volume or extent (called "downsizing/downstaging") and to prevent local recurrence.[30] Radiotherapy is also used for symptom relief, for example, for painful bone metastases or for pelvic tumors.[18,31]

Chemotherapy

Adjuvant chemotherapy may be warranted to eliminate potential micrometastatic disease after surgery. In Norway, chemotherapy is recommended for patients after surgery for colon cancer stage III and high-risk stage II. Chemotherapy should be started 4–6 weeks after surgery. For patients aged <70 years with stage III colon cancer, combination treatment with oxaliplatin and 5-fluorouracil (5-FU) is recommended. The recommended total treatment time is usually 6 months.[19] Chemotherapy can be given as intravenous infusion (FOLFOX, Nordic FLOX) every second week. It can also be given with iv oxaliplatin combined with oral capecitabine (CAPOX/XELOX) every third week.[18] Patients aged >70 years or those with high-risk stage II disease are usually offered monotherapy with 5-FU or capecitabine.

Patients treated with palliative intent have more options for combination chemotherapy. In addition to oxaliplatin/5-FU or 5-FU monotherapy, patients may receive a combination of irinotecan/5-FU (FOLFIRI/Nordic FLIRI) every second week. For selected patients regorafenib or TAS-102 may be considered.[16] The treatment duration depends on the treatment efficacy and tolerability. Patients may continue treatment until progression or have treatment breaks. This treatment is often individualized.

There is no rigid age limit for receiving chemotherapy, although special attention is given to older patients and those with reduced physical or psychological capacity or comorbidity. Patient preference is also important.[18] Chemotherapy in CRC patients is commonly administered in an outpatient setting. Today, over 60 years after the first introduction to chemotherapy, 5-FU is still the cornerstone in the treatment of CRC.

Targeted therapy

The emergence of targeted drugs has improved survival. Epidermal growth factor receptor (EGFR) inhibitors such as cetuximab or panitumumab may be considered for patients with *RAS* wild-type tumors.[18] Common side effects are skin toxicity of varying degrees.[18,19] The use of the vascular endothelial growth factor (VEGF) inhibitor-targeting antibody bevacizumab

[18] is well established. Bevacizumab is often well tolerated, but side effects can include hypertension and proteinuria, and, rarely, increased risk of thromboembolism and intestinal perforation.[18] Targeted agents are usually given in combination with chemotherapy.

Supportive and palliative care

Supportive care is used to prevent or treat physical and mental symptoms and side effects. It might also address the social and spiritual aspects during rehabilitation of cured cancer survivors, irrespective of the treatment intention.[32] Supportive care, or symptom management, focuses on symptom relief and stabilization of QoL, [33] should be integrated early in the treatment phase, and should continue throughout the treatment trajectory until the end of life.[32]

Palliative care focuses on patients with a life-limiting disease with the aim to provide care and symptom relief, however is important not only in dying patients, but during the entire palliative treatment phase.[34]

Symptoms and signs in colorectal cancer patients

The word symptom is derived from a Greek word meaning "a departure from normal function or feeling which is noticed by a patient".[35] Rhodes et al [36] defined a symptom as, "A subjective phenomenon regarded by an individual as a deviation from that which is normal in the aspects of function, sensation or appearance." A symptom is therefore subjective and reflects the experience of a change from normal functioning or feeling, as appraised by the patient. A sign is an objective observation, and can be assessed by others.

Symptoms in cancer patients are often underestimated and undertreated,[37] and this can negatively affect outcomes e.g., impaired QoL The provision of effective symptom management requires knowledge about the symptoms experienced by CRC patients throughout the entire treatment period. Knowledge about these symptoms in CRC patients allows health practitioners to identify the specific areas for symptom management needed to provide symptom control and improve outcomes, QoL, and survival.[38,39]

The CRC disease itself, treatment, and comorbidities present with a diversity of symptoms, signs, and side effects (see below). In addition, side effects caused by supportive therapies,[40]

such as obstipation caused by analgesic or antiemetic drugs, are common. The symptoms can be primary (e.g., pain from the tumor) or secondary (e.g., side effects of treatment) in nature.

Symptoms originating from the CRC disease are often diffuse in the early stage.[41] Symptoms such as abdominal pain, changes in bowel habits, perianal hemorrhage symptoms, and anemia are common in the later phase of the disease.[41-44] Fatigue, loss of appetite and weight, and nausea are other common symptoms.[44] Surgical emergencies resulting from obstruction, bleeding, or perforation by the tumor occur in 15–20% of CRC patients.[44,45]

Previous cancer treatment involving surgery, radiotherapy, and/or chemotherapy may produce late effects after treatment.[46-52] Surgery of the colon usually does not have a major effect on other organs. Some patients have colostomy, and some patients experience fear of e.g., leakage.[53] By contrast, rectal surgery is performed closer to other organs and nerves, which might increase the risk for later adverse effects involving the bladder, bowel, or sexual organs.[54] This includes the risk of fecal and urinary incontinence and sexual dysfunction.[46,52,54,55] Abdominal pain after surgery is also common.[52,56]

Radiotherapy can produce short-term side effects such as lack of energy, nausea, diarrhea, urinary problems,[56] rectal skin irritation around the anus, and painful defecation.

Prolonged late effects after radiotherapy with dyspareunia (painful intercourse) and vaginal dryness in women [49] and reduced erectile function and overall dissatisfaction with their sex life in men are reported.[50] Late effects of radiotherapy might also include fatigue, diarrhea, anorectal dysfunction such as fecal incontinence and altered bowel frequency, urinary problems[57] and pelvic micro fractures.[58]

Patients who undergo chemotherapy for CRC commonly experience nausea, vomiting, lack of energy, and numbness/tingling.[59-61] 5-FU may cause specific symptoms such as running eyes and nose, nausea, and diarrhea.[16] In rare cases, patients may have a deficiency in dihydropyrimidine dehydrogenase (DPD); this occurs in 0.3–1.5% of patients.[18] If present, it results in serious 5-FU toxicity that appears as mucositis, enteritis, and bone marrow deficiency. Patients receiving either irinotecan or oxaliplatin are at risk of neutropenia.[18,19] The most common side effect from oxaliplatin is peripheral neuropathy, and the risk increases with cumulative doses.[18,19,62-64] These symptoms can occur shortly after oxaliplatin

administration and appear as symptoms such as numbness/tingling in the fingers, toes, or pharynx, and increased sensitivity to cold exposure. Neurotoxicity is a common dose-limiting toxicity of oxaliplatin.[64,65]

Adverse side effects and QoL are often assessed in clinical studies. However, the time frame between each assessment is often too long to detect the short-term side effects of chemotherapy.[59,60] Despite the high prevalence of CRC, there is limited evidence-based literature on CRC patients' self-reported multiple symptoms and symptom dimensions during chemotherapy from longitudinal studies.

Multiple symptoms

CRC patients rarely present with a single symptom, but commonly experience multiple symptoms,[35,66-68] which may occur together (co-occurring) and in clusters.[35,69] Symptom clusters have been defined as two or more symptoms that are related and may or may not share a common etiology.[69] Multiple symptoms can have a multiplicative effect on each other. The experience of multiple symptoms at the same time can make the patient feel worse than when experiencing each symptom. The management of one symptom might then have a role in the management of other symptoms. The effects of these multiple symptoms on patients is termed the "symptom burden",[35] which includes both the patient's perceived severity and distress caused by the symptoms.[35]

Symptoms may often change over time, and the use of a longitudinal study design is essential to detecting these fluctuations.[47,60,70,71] Untreated, multiple symptoms can create a vicious cycle and may be an additional burden for cancer patients, which might negatively affect their functioning, rehabilitation, and QoL.[35] Only a limited number of studies with a longitudinal design had assessed multiple symptoms and symptom dimensions in CRC patients before the initiation of this study. The relevant studies published before the initiation of this thesis are listed in Table 2.

Self-reported symptoms

The use of patients self-reported symptoms is important to understanding the complex symptoms experienced by CRC patients throughout the daily chemotherapy trajectory.[72] The term patient-reported outcome measures (PROMs) refers to "any report coming directly from patients about a health condition and its treatment" using self-reported instruments or

questionnaires.[73] PROMs are essential in clinical patient decision-making, research, and political health decisions.[74] Symptom monitoring by the use of PROMs might improve clinicians' attention to symptoms, safety, and patient satisfaction with care.[75]

Quality of life in colorectal cancer patients

Aristotle described the nature of QoL in the fourth century BC as a good life and *eudaimonia* (happiness). In 1946, the World Health Organization defined health as "a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity." Health or health status is closely related to QoL.[76] Common terms used to describe health include *disease* (objective measure of health), *sickness* (the community perception of health), and *happiness* or *life satisfaction*.[77]

The concept of QoL was introduced to research in the 1970s [78]; however, there remains inconsistency in how to interpret and define QoL in medical research, and several definitions and measures of QoL are available.[78] "Despite the lack of a common universal definition, health-related quality of life (HRQoL) covers the subjective perceptions of the positive and negative aspects of a cancer patient's symptoms', including physical, emotional, social, and cognitive functions and disease symptoms and side effects of treatment."[79-81] HRQoL is a measure of self-perceived health status and is a multidimensional concept in the way the disease, symptoms, or treatment affects the physical (e.g., performance status), mental (e.g., worrying), social (e.g., cohabitation), and cognitive ("chemobrain") dimensions and their relationship to health.[35,81,82] The terms QoL and HRQoL are used interchangeably.[83] Both terms refer to QoL in this thesis.

Previous studies on QoL in CRC patients during chemotherapy before the initiation of this study [79] varied in study design and were cross-sectional [61,84,85] as well as longitudinal.[59,60,86] Selected relevant studies assessing only patients diagnosed with colon or rectal cancer receiving chemotherapy, and or focused on symptoms published before the initiation of this thesis, are listed in Table 3.

Demographic and clinical factors associated with symptoms and QoL

Assessment of both symptoms and QoL provides valuable information in the clinical setting. However, identifying which factors are associated with worse symptoms and QoL in CRC

patients is complex because the symptoms themselves can be associated with a worsening of other symptoms. Previous studies assessing CRC outpatients have examined factors associated with high symptom burden in CRC patients, including depression,[87] financial difficulties,[87,88] disease status,[89] reduced performance status,[87] comorbidity,[90] type of treatment,[60,65,87,91] gender,[89] and suburban residence.[89] It is unclear whether age ≥60 years is associated with worse symptoms.[89] High symptom burden is associated with a body mass index (BMI) <18.5 kg/m^2 compared with BMI in the normal range (18.5–25 kg/m^2).[89]

Improving QoL requires identification of the risk factors associated with impaired QoL. Symptoms can directly or indirectly affect the QoL of patients. One example is pain,[88] which has direct negative effects on QoL, in addition to indirect effects by interfering with the performance of daily activities. Other symptoms found to affect QoL include depression,[61,88,92-94] insomnia,[60] fatigue,[60,88,94] nausea and vomiting,[60] anxiety,[61,92,93] dyspnea, anorexia,[94] and distress.[93] Other common factors associated with impaired QoL in CRC patients include having a stoma,[93] more self-reported comorbidities,[94] being a woman,[94,95] and being younger.[88,95] Having more severe disease (higher disease stage) does negatively affect QoL.[93]

Patients receiving a curative treatment might accept a reduced QoL for a shorter period of time to increase their chance of survival. In studies with a curative aim, progression-free or overall survival is often the primary end point, and QoL is a secondary end point.[96] In palliative patients, prolonged survival is often an important endpoint, with QoL and symptom relief often as secondary endpoints.

The theoretical framework of symptom management

The present study is part of "Symptom Clusters in Cancer Patients and Their Caregivers — a Longitudinal Study," which used the theory of symptom management (TSM) as the theoretical framework. [97] The TSM was first introduced in 1994 at the University of California, San Francisco School of Nursing.[98] The TSM model comprises three concepts: symptom experience, symptom management strategies, and symptom status outcomes. One limitation of this theoretical framework is the lack of integration of symptom dimensions and time. Given these limitations, the middle range theory of unpleasant symptoms (TOUS) – an update [99]

was used as the theoretical framework and for guidance in this thesis to understand the symptom complexity in CRC patients. This framework was selected after the planning of the main study.
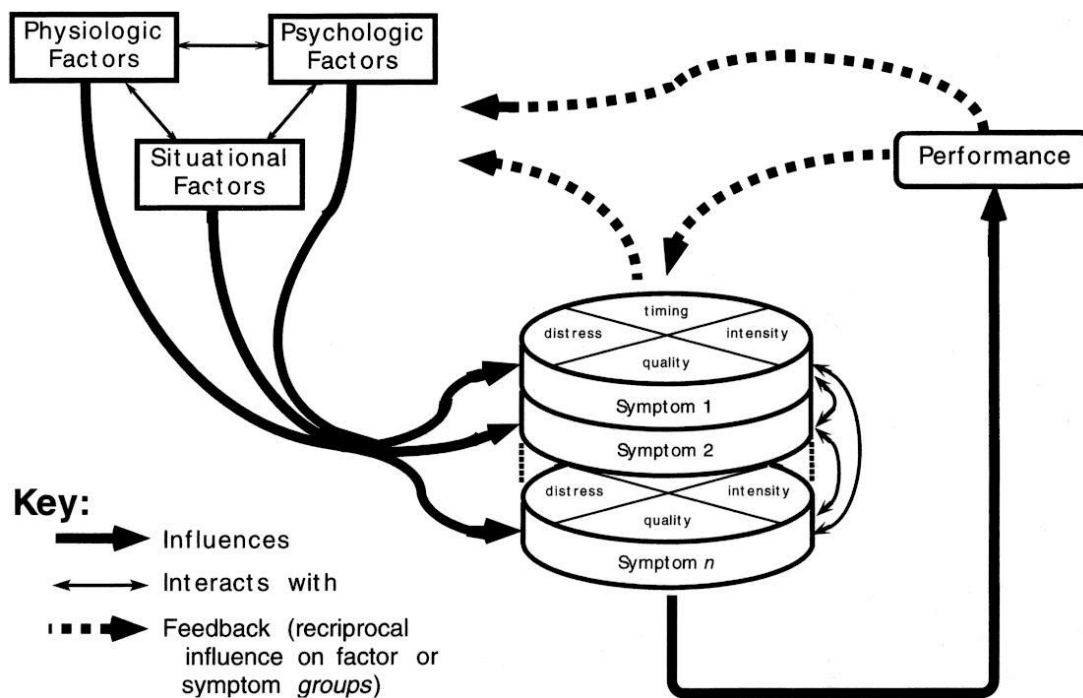
Fig. 2. The model of the middle range theory of unpleasant symptoms – an update.

The TOUS was developed against the background of existing knowledge on symptoms and how they interact.[99] The purpose of this model is to illustrate how symptoms interact with each other in diverse contexts. The TOUS focuses on the experience, multidimensionality, and co-occurrence of symptoms. The TOUS emphasizes that managing one symptom has a role in the management of other symptoms. The TOUS has three main components: 1) the patient's experience of symptoms; 2) factors influencing the symptoms; and 3) outcomes. Lenz et al stated that these components interact and influence each other, and that the dimensions are separable but related.[99]

TOUS component 1. The patient's experience of symptoms
Symptom management is a multidimensional process, as illustrated in Fig. 2. *Timing* refers to the appearance of symptoms at different times and how symptoms can vary in their occurrence

and frequency over time. The symptom dimensions might also vary depending on the timing of a symptom's occurrence (e.g,, the CRC patients experience of increased pain during toilet visits). Furthermore, the duration of symptoms, can be both acute and/or chronic. The use of a longitudinal design in this thesis allowed to assess the variations in symptoms throughout the chemotherapy cycles over time. The *distress* component refers to the effects of the symptoms on the patient and the emotional burden, and to how much this burden bothers the patients. Symptom *intensity* refers to the severity or strength of the patient's experience of a symptom. Finally, *quality* refers to the patient's experience or feeling of having the symptoms. The self-reported Memorial Symptom Assessment Scale (MSAS) questionnaire [100] includes all of these symptom dimensions and was used to measure symptom burden in all three papers in this thesis.

When symptoms are experienced at the same time, the effect can be experienced as worse than if the symptoms are experienced separately. The TOUS emphasizes that managing one symptom has a role in the management of other symptoms.[99]

TOUS component 2. Factors influencing symptoms

As shown in Fig. 2, Lenz et al described three factors that can influence the experience of symptoms. First are the *physiologic factors*, which refer to the physiological, illness, and treatment-related variables; examples include age, gender, type and duration of treatment, comorbidity, and stage of disease. Second are the *psychologic factors*, which refer to the mental state and how the patient reacts to illness, for example, by worrying or feeling sad. Third are the *situational factors*, which are factors within the patient's social and physical environment such as educational level, marital status, social support, or outpatient setting. The relevant clinical and demographic information is presented in all three papers included in this thesis. In addition, in Paper III the MSAS physical (MSAS PHYS) and psychological (MSAS PSYCH) subscales were used.

TOUS component 3. Outcomes (performance)

Performance is the outcome concept in this model and illustrates the consequence of symptoms for the patients, for example, how the effects of the symptoms on physical, mental, or social functioning are experienced by patients. The performance concept reflects the patient's ability to perform daily activities, for example, activities with family, within the social network, and at work. This thesis measured the symptom burden using the MSAS and QoL using the Short

Form 12-item Health Survey (SF-12) as the outcomes. However, the TOUS does not include explicit measures of QoL.

Table 2 List of selected published studies that investigated symptoms in homogeneous groups of colorectal cancer patients.

Author(s)	Year	Design	Sample	Measure	Findings
Alacacioglu et al [61]	2010	Cross-sectional	110	EORTC-QLQ C30, STAI, BDI	Depression was reported in 23.6% of the patients. Anxiety levels were higher than in the normal population.
Borjeson et al [68]	2012	Qualitative	13	Interview	The most frequently experienced symptoms were fatigue, nausea, changed bowel habits, impaired mental well-being, loss of appetite, and neurological problems.
Foltran et al [47]	2014	Case-crossover	229	Retrospective	The highest risk for hospitalization occurred 15–21 days after treatment. The most frequent complaints were pain, fatigue, and anorexia. Ten percent of the unplanned visits resulted in hospital admission.
Hung et al [59]	2013	Longitudinal	134	MSAS/FACT-C, VAS	Female and stage IV patients had more severe physical symptoms. Stage II and IV patients had worse psychological symptoms over time. Pain improved over time.
Lam et al [67]	2008	Descriptive	256	MSAS	The most prevalent symptoms were worrying (59%), dry mouth (54%), and lack of energy (54%).
Pettersson et al [66]	2014	Cross-sectional		MSAS	The mean number of symptoms was 10.3 (±7.7). The most prevalent were numbness/tingling (64%), lack of energy (62%), feeling drowsy (49%), and nausea (45%). Symptoms with highest frequency, severity and distress were lack of energy, difficulty sleeping, numbness/tingling in hands/feet.
Spichiger et al [101]	2012	Qualitative	19	Interview	Increased knowledge about fatigue did not encourage patients sufficiently to discuss fatigue with their physicians or nurses. Fatigue was strongly related to their individual life and illness situation.
Tofthagen et al [102]	2011	Descriptive	33	CIPNAT	The most prevalent symptoms were cold sensitivity and tingling/numbness in the hands. The severest were cold sensitivity, nerve pain, and trouble with balance. These symptoms interfered with numerous activities.
Walker et al [60]	2012	Longitudinal	182	PCM, MSAS	Patients receiving bevacizumab reported lower symptom burden than those receiving cetuximab.

Abbreviations: BDI = Beck Depression Inventory; CIPNAT = Chemotherapy-Induced Peripheral Neuropathy Assessment Tool; EORTC-QLQ C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-C = Functional Assessment of Cancer Therapy–Colorectal; MSAS = Memorial Symptom Assessment Scale; PCM = Patient Care Monitor survey; STAI = State–Trait Anxiety Inventory; VAS = visual analog scale.

Footnote: Data search limitations: year of publication 01/01/2002–31/12/2014; >18 years of age; in English, German, or Scandinavian language.

Table 3 List of selected studies investigating the quality of life in homogeneous groups of colorectal cancer patients.

Author(s)	Year	Design	Sample	Measure	Findings
Alacacioglu et al [61]	2010	Cross-sectional	110	EORTC-QLQ C30, STAI, BDI	Anxiety and depression were strongly associated with poor QoL.
Byrne et al [79]	2007			Report	To bridge the gap between HRQoL research and clinical practice, a checklist for evaluating HRQoL outcomes is recommended.
Carlsson et al [103]	2010	Longitudinal	57	SF-36	Symptoms included fatigue, pain, and limited HRQoL. The presence of a stoma was not a major problem during the recovery period.
Conroy et al [82]	2003	Review	n/a	n/a	Assessing HRQoL is essential to identifying the optimal treatment strategies. Baseline QoL predicts survival in metastatic disease. QoL improves with time.
Dunn et al [13]	2003	Systematic review	n/a	n/a	This study found inconsistent QoL over time and an inconsistent relationship with survival. There is a need for large-scale, longitudinal population-based studies of QoL in CRC patients. Measurement of and adjustment for potential confounding factors are needed.
Farkilla et al [88]	2013	Cross-sectional	508	EORTC-QLQ-30	HRQoL is fairly good in CRC patients. Fatigue, pain, age, and financial difficulties can negatively affect HRQoL.
Graca Pereira et al [92]	2012	Cross-sectional	114	HADS, QOL-CA2	The main predictors for impaired QoL were anxiety and depression. Recurrence of CRC increased the levels of traumatic symptoms. Anxiety and depression can interfere with e.g., patients functioning, compliance with cancer treatment and follow-up examinations.
Gray et al [94]	2011	Descriptive	497	EORTC-QLQ-30	Fatigue, anorexia, dyspnea, and depression are symptoms that can affect QoL. Beliefs about illness can also affect QoL.
Hung et al [59]	2013	Longitudinal	134	MSAS/FACT-C, VAS	Patients with stage IV cancer, previous surgery, and concurrent chemoradiation therapy have the worst HRQoL compared to

Author	Year	Type	n	Instrument	Findings
					those with less comprehensive disease, no previous surgery or chemoradiation therapy.
Marventano et al [93]	2013	Review	n/a		There are various determinants of QoL in CRC; the most common are physical problems linked to symptoms and surgical procedures such as bowel problems and stoma.
Sanoff et al [104]	2007	Systematic review	n/a	n/a	Many patients experience a decline in physical function immediately after surgery and have an increased need for supportive services. Little information is available on the effect of chemotherapy in elderly patients.
Sun et al [86]	2012	Descriptive	56	EORTC-QLQ-30	The patient barriers to pain and fatigue are related to their attitudes and beliefs about addiction and tolerance, and that fatigue is part of cancer and its treatments.
Tau et al [95]	2011	Systematic review	n/a	n/a	Depression, distress, and bowl problems affect QoL.

Abbreviations: BDI = Beck Depression Inventory; EORTC-QOQ-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; FACT-C = Functional Assessment of Cancer Therapy–Colorectal; HADS = the Hospital Anxiety and Depression Scale; SF-36 = Short Form Health Questionnaire;STAI = The State—Trait Anxiety Inventory; QOL-CA2 = Quality of Life Scale for Cancer; VAS = visual analog scale.

Footnote: Data search limitations: year of publication 01/01/2002–31/12/2014; >18 years of age; in English, German, or Scandinavian language

Aims of the thesis

The aim of the thesis was to assess the multidimensionality of common cancer-related symptoms and QoL in CRC outpatients at the start of chemotherapy, in the days immediately following chemotherapy, and after 6 months. Additional aims were to identify the demographical and clinical characteristics and symptoms associated with symptom burden and QoL.

Aim I

The aim was to examine the multidimensionality (occurrence, severity, and distress) of multiple symptoms in CRC patients before the start of chemotherapy. Also, to investigate differences in occurrence, severity and distress between patients starting treatment with curative or palliative intent (Paper I).

Aim II

The aim was to identify changes over time in the occurrence and severity of common cancer- and treatment-related symptoms in patients with CRC during two chemotherapy cycles, and at 3 and 6 months after enrolment. Additional aims were to investigate differences in symptom trajectories between chemotherapy groups and to determine whether selected demographic and clinical characteristics were associated with symptom severity throughout the treatment trajectory (Paper II).

Aim III

The aim was to assess physical and mental quality of life during 6 months of chemotherapy in CRC patients. An additional aim was to investigate whether demographic and clinical variables and selected symptoms were associated with physical and mental QoL (Paper III).

Materials and methods

Inclusion and exclusion criteria

Patients diagnosed with CRC were eligible for inclusion if they were ≥18 years, able to read, write, and understand Norwegian, and if they were scheduled for their first or a new type of chemotherapy in an outpatient setting. Patients with brain metastases or diseases affecting their cognitive ability were excluded.

Design

This was a prospective longitudinal study of patients diagnosed with CRC. The current study is a substudy of a larger study (Clinicaltrials.gov, NCT00769301) that involves oncology outpatients (n = 534) and caregivers (n = 278). The main study was based on patients with one of four cancer diagnoses receiving either radiotherapy or chemotherapy. Their caregivers were also recruited.[105] Patients who received radiotherapy for breast cancer [106-108] and head and neck cancer, [109-111] were included. Patients diagnosed with ovarian cancer [112] or CRC (Papers I, II, III) receiving chemotherapy were also included. This thesis includes the data about the patients with CRC. The CRC patients completed the questionnaires eight times during the 6-month treatment trajectory. These questionnaires were self-reported and assessed symptoms and QoL. Blood samples for genetic testing were taken with routine samples at enrolment before the patients began treatment. The results of the genetic testing have not yet been published and are not part of this thesis.

To capture the symptom burden as it relates directly to treatment, the assessment time points of the questionnaires were based on the perceived clinical importance and followed the chemotherapy cycles for this patient group. The patients were assessed at enrolment, before initiation of either their first or a new chemotherapy regimen (T1), 3 days after the start of chemotherapy (T2) and 7 days after the start of chemotherapy (T3), before the following treatment cycle (T4), 3 days after the second treatment (T5), and 1 week after the second chemotherapy (T6). At T2, T3, T5, and T6, the patients were at home. The last assessments were performed at 3 months (T7) and 6 months (T8) after enrolment (Fig. 3).
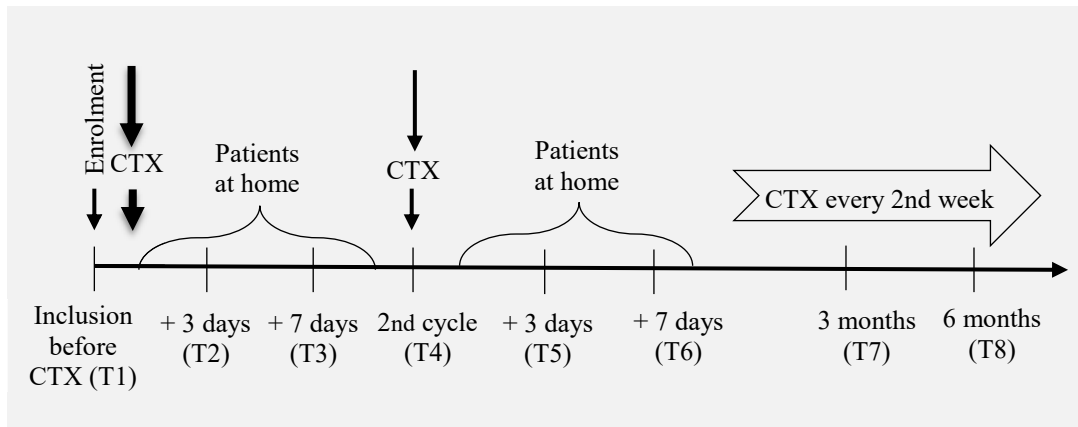
Fig. 3. Timeline of data collection over the 6-month chemotherapy trajectory

Abbreviations: CTX = chemotherapy; T1 = at enrolment; T2 and T3 = 3 days and 7 days after initiation of the first chemotherapy cycle, respectively; T4 = before the second chemotherapy cycle; T5 and T6 = 3 days and 7 days after initiation of the second chemotherapy cycle, respectively; T7 = 3 months after enrolment; T8 = 6 months after enrolment.

Study procedures and follow-up

The patients diagnosed with CRC were recruited at the outpatient clinic of the Department of Oncology, Oslo University Hospital, Ullevål, between October 2009 and December 2010. The nurses in the clinic identified eligible patients for the study and provided information about the study to patients who were interested. The nurses were trained to give patients information about the study. One study nurse was responsible for the inclusion and follow-up of patients who were interested. The patients received oral and written detailed information about the study from the research nurse before signing an informed consent form. The included patients were given a unique study identification number.

The first set of questionnaires was given to the patients to be completed before their first chemotherapy treatment. The questionnaires for the next five measurements were given to the patients to bring home. The last two sets of questionnaires (at 3 and 6 months) were mailed the patient's home address with a prepaid addressed return envelope. The patients were given a contact phone number in case they had any questions about the study questionnaires (e.g., something was unclear). Patients who did not complete the first questionnaires were excluded from the study. The study nurse made a telephone call to remind patients before the time points T2–T6. If a patient did not return a questionnaire, one reminder was sent by post at each

21

measurement point. Patients who found it difficult to return the questionnaires by post were given the option to bring the completed questionnaires to the hospital on their next visit.

Demographic and clinical characteristics

The patients provided information on demographic characteristics including gender, age, marital status (married, partnered, divorced, widowed, or unmarried), cohabitation (living alone or with someone), daily responsibility for children (number), level of education (primary school, secondary school, or college/university), and employment status (part- or full-time work, sick leave/disability benefit, retired, unemployed, or other).

The research team obtained information from the medical records about the time of diagnosis, height and weight, disease status (primary, recurrent, or progression), sites and number of metastases, previous treatment (surgery, radiotherapy, chemotherapy or antibody treatment), presence of a stoma, and the treatment goal. BMI was calculated.

The oncologist in the research group classified the patients into the curative or palliative phase based on the treatment intent.[18] Patients who had received surgery for colon cancer with pathological lymph node metastases stage III received adjuvant chemotherapy with curative intent. Patients with resectable or potentially resectable metastases (mainly in the liver) receiving neoadjuvant chemotherapy before liver resection were treated with curative intent. These patients were registered as having present liver metastasis. Adjuvant and neoadjuvant chemotherapy were classified as curative treatment intent, and chemotherapy for nonresectable metastatic disease was classified as palliative intent. Information regarding previous treatments received in other hospitals was retrieved when applicable.

After 6 months (T8), at the last measurement point, information regarding the patients' status of disease (disease-free, alive with metastases, dead from cancer, or dead from another cause) was obtained from medical records. Information regarding treatment of metastases (surgery, chemotherapy, antibody treatment, or radiotherapy) was also retrieved.

Pilot study

To determine the feasibility of the main study protocol, a pilot study was performed before the study began. Ten patients were included: six women and four men. Patients diagnosed with CRC, head and neck, breast, or ovarian cancer, or malignant lymphoma were included. The time needed to complete the questionnaires ranged from 8 to 35 minutes.

Data collection

A range of assessment tools are available to assess symptoms and QoL; however, there is no "gold standard" [113] for assessment timing (e.g., the best time, duration, and frequency) and knowledge about whether digital or paper versions should be used. [114] In this thesis, several self-reported questionnaires were given to the patient at multiple time points during the study period (Table 4).

The times of assessment were chosen to correspond to the times of clinical attendance (before they received their chemotherapy) and between the treatment cycles (when the patients were home) (Fig. 3). Only the enrolment data were used in Paper I (cross-sectional design). The MSAS, SCQ-19, and KPS questionnaires were used in all three papers. Data from all eight measurement points were used in Papers II and III (longitudinal design) with main focus on repetitive measures during the two first chemotherapy cycles .

The tools frequently used to measure self-reported symptoms are the Edmonton Symptom Assessment System (ESAS) [115] and MSAS.[100] There are three main groups of QoL instruments.

- Generic instruments are used to measure health in general (e.g., SF-36,[116] SF-12) [117] in patients with various conditions.[74,117] These instruments may be used to compare different groups of patients with the general population. The SF-12 generic questionnaire is a short version of SF-36 and was used in this thesis.[117]

- Disease-specific instruments are more specific and focus on specific populations or a certain disease (e.g., cancer). One example of a disease specific instrument is The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life of Cancer Patients, a 30 item instrument (QLQ-C30).[71,118,119]

- Diagnose-specific questionnaires can be used for specific patient groups (e.g., those with CRC). The Functional Assessment of Cancer Therapy–Colorectal (FACT-C) [120] and the EORTC module for CRC, QLQ-CR29) [121] are often used. These questionnaires provide more detailed information about a specific population compared with generic instruments.

Table 4 Questionnaires and assessment time points for each instrument over the 6 months of treatment

Concepts measured	Instruments	Patient measurement points in months								Number of questions
		T1	T2	T3	T4	T5	T6	T7	T8	
Demographics	Demographics	✓	-	-	-	-	-	-	✓	7
Multiple symptoms	MSAS	✓	✓	✓	✓	✓	✓	✓	✓	32 (+3)
Comorbidity	SCQ-19	✓	-	-	-	-	-	✓	✓	16 (+3)
Performance	KPS	✓	✓	✓	✓	✓	✓	✓	✓	1
Quality of life	SF-12	✓	✓	✓	✓	✓	✓	✓	✓	12
Total (open questions)		✓	✓	✓	✓	✓	✓	✓	✓	68 (+6)

Abbreviations: CTX = chemotherapy; KPS = Karnofsky Performance Status; MSAS = Memorial Symptom Assessment Scale; SCQ-19 = Self-Administered Comorbidity Scale; SF-12 = Short Form-12 Health Survey, version 1; T1 = at enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at the second cycle, assessed before chemotherapy; T5 = 3 days after the second chemotherapy; T6 = 7 days after the second chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment.

Memorial Symptom Assessment Scale

The MSAS is a multidimensional self-reported questionnaire to assess cancer-related or treatment-related symptoms and comprises 26 questions about physical symptoms, six about psychological symptoms, and three optional questions about other symptoms.[100] The MSAS is available as shorter versions: The MSAS Short Form (32 symptoms with one dimension), the Condensed MSAS (14 symptoms with one dimension),[100] and a version for children aged 7–12 years. The initial version of the MSAS included outpatients diagnosed with colon cancer.[100] However, the long version was selected to assess all dimensions of each symptom.

For each symptom, patients reported whether they had experienced the symptom during the past week (i.e., occurrence). If they had experienced the symptom, they were asked to rate its frequency, severity, and distress on 4–5-point Likert scales. Using 4-point scales, symptom frequency was rated as 1 = rarely, 2 = occasionally, 3 = frequently, and 4 = almost constantly, and severity was rated as 1 = slight, 2 = moderate, 3 = severe, and 4 = very severe. Symptom distress was rated using a 5-point scale as 0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much.

Paper I presents the occurrence of all 32 symptoms. The most common symptoms that occurred in more than 30% of the patients were presented with severity and distress scores. The mean numbers of all symptoms were summed to provide a total number of symptoms. Paper II includes all 32 symptoms along with the symptom dimension occurrence with a focus on the severity of five specific symptoms. Paper III reports the subscale physical symptoms (MSAS PHYS) and psychological symptoms (MSAS PSYCH).[100] The MSAS PHYS provides the average of the dimension frequency, severity, and distress of 12 prevalent physical symptoms (lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness). The MSAS PSYCH provides the average of the dimensions frequency, severity, and distress of the six most prevalent psychological symptoms (feeling sad, irritable and nervous, worrying, difficulty sleeping, and difficulty concentrating).

The patients completed the MSAS eight times during their chemotherapy trajectory (Table 4). Various symptom dimensions were included in the analyses in the thesis and are reported as occurrence, severity, and distress (Paper I), occurrence and severity (Paper II), and the subscores MSAS PHYS and PSYCH (Paper III). Patients were coded as having the symptom if any of the three boxes were checked (i.e., occurrence, frequency, severity, distress). Missing items were interpreted and coded as if the patient did not have the symptom. The reliability and validity of the MSAS are well established in cancer outpatients,[100] and the MSAS is used in cancer patients in Norway.[105-110,112,122]

Short Form-12 Health Survey

The Short-Form 12-item Health Survey (SF-12) (version 1), developed by the Medical Outcomes Study,[117] is a 12-item short form used to assess QoL. The SF-12 is a shorter version of the 36-item SF-36 and was developed to reduce the potential burden of too many questions. The SF-12 is a generic instrument to assess general health status or in specific populations. It comprises 12 questions, whose answers are used to create physical (PCS) and mental health (MCS) summary scores. The PCS and MCS were scored using norm-based data from the 1998 U.S. general population (n = 2329), because of the research collaboration with the U.S. on the main study, using a computer based scoring algorithm.[123] The scores were transformed to a mean of 50 (standard deviation [SD] 10). A higher PCS or MCS indicates better QoL than the mean U.S. population. Similar cutoff scores have been reported by a study that included nine European countries, in which the mean scores for the Norwegian population were 50.3 (SD 8.8) for the PCS and 50.6 (SD 9.9) for the MCS.[124]

The questions are related to eight domains of general health perceptions, role limitations related to physical and emotional problems, bodily pain, physical and social functioning, vitality (e.g., energy levels and fatigue), general mental health, psychological distress, and psychological well-being. The recall period, which influences the accuracy or completeness of recall of past experiences, ranges from right now to the past 4 weeks. The SF-12 has well-established validity and reliability [124] and takes about 2 minutes to complete.[117] In this thesis, the patients completed the SF-12 questionnaire at all eight measurement points (Table 4).

Karnofsky Performance Status

The Karnofsky Performance Status (KPS) scale is used to assess patients' performance status.[125] The KPS score ranges from 0 (death) to 100 (normal activities) in 10-point increments (Table 5). Because outpatients were assessed in this thesis, the range of 40 (i.e., disabled, requires special care and assistance) to 100 (i.e.; normal no complaints, no evidence of disease) was used. The KPS scale has well-established validity and reliability.[125] The Norwegian version has been used in previous studies in cancer patients.[106,109] An equivalent scale to the KPS commonly used in clinical settings is the Eastern Cooperative Oncology Group scale [27] (Table 5).

Table 5. Comparison between the Karnofsky Performance Status (KPS) scale and Eastern Cooperative Oncology Group (ECOG)

KPS Grade		ECOG Grade	
100	Normal, no complaints	0	Fully active, able to carry on all pre-disease performance without restriction
90	Able to carry on normal activities. Minor signs or symptoms of disease	1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
80	Normal activity with effort		
70	Care for self. Unable to carry on normal activity or to do active work	2	Ambulatory and capable of all self-care, but unable to carry out any work activities; up and about more than 50% of waking hours
60	Requires occasional assistance, but able to care for most needs		
50	Requires considerable assistance and frequent medical care	3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
40	Disabled. Requires special care and assistance		

The Self-Administered Comorbidity Questionnaire -19 (SCQ-19)

The Self-Administered Comorbidity Questionnaire (SCQ-19) [126] comprises 16 common and three additional comorbidities. For each comorbidity, the patients were asked whether they had the comorbidity. If yes, they were asked whether they had received treatment for it. To capture the burden of the symptom, the patients were asked if the comorbidity limited their activities. The total SCQ-19 with all dimensions score ranges from 0 to 57. The total score to assess only the number of comorbidities ranges from 0 to 19.

A patient who answered "yes" to either or both of the questions (if they received treatment and had a limitation of activities) was coded as having the comorbidity even if he/she had answered "Do not have the comorbidity." A higher total score indicates a more severe comorbidity profile. The SCQ is used in Norwegian cancer patients [106,112,127,128] and has well-established validity and reliability in patients with cancer and other chronic conditions.[126,129]

Procedure for and validation of the translation into Norwegian
The procedure for the translation of the MSAS into Norwegian has been described in detail.[107] The SF-36 has been translated into Norwegian and validated in patients with rheumatoid arthritis,[130] and has been used in both international and Norwegian studies assessing cancer patients.[103,131] The SF-12 has been validated in a Norwegian general population.[124]

Sample size calculation
The power calculations had been performed for the main study for the main outcome.[105]. Therefore, sample size calculations was not performed specifically for this thesis; retrospective power calculations are not recommended.[132]

Data management and review
All questionnaires and case report forms were scanned electronically using the MedInsight® system. In the case of boxes left empty, marks between two boxes, or marking of several boxes, the scanner stopped and the question was marked as a missing item.

In this thesis, errors were detected in the items "reason for treatment" (primary, recurrent, or progression). To ensure the quality of the data and reduce the risk of random errors, all questionnaires were double-checked manually against the medical records for previous treatment, reason for treatment, history of or presence of metastases, and cancer diagnoses (colon or rectal).

Statistical analyses

Categorical data are presented as proportions and percentages, continuous variables with normal distribution are presented as means and SDs, and data with a skewed distribution are presented as medians and ranges. To evaluate possible differences between patients who did and did not complete the study, Student's t tests and chi-squared tests were used. The items comprising subscores for symptoms as assessed by the MSAS PHYS and MSAS PSYCH [100] and for QoL, as assessed by the PCS and MCS,[117] were scored according to the developer's description of each instrument. For all tests, p-values <0.05 were considered to be significant, and all tests were two-sided. The analyses were performed using SPSS versions 22–24 (SPSS IBM Corp., Armonk, NY) and Stata Version 13 (StataCorp LLC, College Station, TX). Fig. 1 in Paper II was designed using Adobe Illustrator CC, (Adobe Inc, San Jose, California, USA), and Fig. 2 in Paper III was designed using Microsoft Office Excel (Microsoft Corporation). To ensure the quality of the statistical analyses, all statistical analyses were performed in close collaboration with statisticians.

Mixed-model analyses

Linear mixed models (LMMs), also called multilevel models, were used to analyze the effect of time (longitudinal data) in Papers II and III, and to estimate the effects of covariates on the outcomes (symptoms and QoL) during the treatment trajectory. LMMs were analyzed using SPSS versions 23–24 (SPSS IBM Corp.). Possible within-patient dependency was accounted for using an unstructured covariance matrix when estimating the statistical models in both Papers II and III because of the varying length of time between the measurement points. The LMM allows one to enter both fixed (explanatory variables such as curative and palliative patients) and random effects (because of individual differences).

To ensure sufficient statistical power, a minimum of four assessment points is required in LMM analyses with moderate sample sizes.[133] These assumptions were met as we had eight assessment points in studies comprising this thesis. The instruments used in this thesis were scored according to the scoring manual for each instrument and included the method for handling of missing data.

LMM analyses are robust because they do not require complete datasets and all available data can be analyzed. This makes the LMM incredibly flexible. However, attrition such as the loss of patients during the course of a study can lead to a loss of statistical power. The best solution is to prevent attrition from occurring. However, including severely ill and older patients increases the risk of attrition related to factors such as mortality [134,135] or missing assessment points because of hospitalization or other events. It is crucial that there is no bias occurring because of missingness; that is, there should not be any underlying reason for the missingness such as patients being too sick or not interested in the study or living too far from the hospital to participate. Such missing values are either missing completely at random (MCAR) or missing at random (MAR). Both cases represent an ignorable nonresponse. However, where some information is lost in missingness, missing points are called missing not at random (MNAR). In practice, it is not possible to determine the type of missingness in the analyzed data, and the researcher can only assume. All statistical models rely on the MAR assumption. It is impossible to check this assumption, which means models that do not require complete datasets are preferable. When using mixed models, no imputation is needed as all available data can be used, regardless of some values being missing at one or several assessment time points. LMMs are robust because the analyses use all available data despite incomplete datasets (e.g., due to missing values or attrition), thus limiting the issue of selection bias. This increases the generalizability because the data from all participants are used. However, the acceptable rates of attrition are difficult to define.[136]

The selection of the included covariates was guided by TOUS [99] and based on clinical considerations and previous research. The LMM model was used for repeated measures with all covariates entered as fixed effects for the analyses in Papers II and III. LMMs for repeated measures were used to model both the effects of selected covariates and of time (e.g., possible changes over time) on the outcome variables.

Only covariates that reached $p<0.05$ in the univariate analyses were selected for inclusion in the multivariate models with addition of age and gender. To reduce the risk for collinearity between the different instruments (questionnaires), testing for possible correlations before fitting the LMMs was performed. A correlation coefficient >0.5 was used as a cutoff when fitting the multivariate models.

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Paper I analyses

Continuous data that were normally distributed are presented as means and SDs, and categorical data as frequencies and percentages. The independent-sample t test and chi-squared test were used to identify differences in demographic and clinical characteristics between the curative and palliative patients. For some symptoms, the occurrence rates were low, and the most common symptoms that occurred in ≥30% of the study sample were included and evaluated using binary logistic regression models because the outcome was categorized as having as opposed to not having a given symptom. To compare the differences in symptom dimensions (severity and distress) between the curative and palliative patients, ordinal logistic regression analysis was performed. In all analyses, $p<0.05$ was considered to be significant, and all tests were two-sided.

Paper II analyses

Descriptive statistics are used to present the demographic and clinical characteristics of the study sample. Normally distributed variables are expressed as means and SDs, and continuous variables with skewed distribution are presented as medians and ranges. Categorical data are described as proportions and percentages.

To identify differences between the selected treatment groups and the outcomes (occurrence and severity of worrying, lack of energy, numbness/tingling, nausea, and pain) over time, LMMs for repeated measures were used. To model the statistical dependencies within the same patient at different measurement points and to accommodate for the different length of time between each measurement, an unstructured covariance matrix was used. Individual differences in clinical and demographical characteristics at enrolment were accounted for by a random intercept parameter. To control for possible confounders, the covariates measured at enrolment were adjusted for based on previous research and their clinical importance. p values <0.05 were considered statistically significant, and all tests were two-sided.

Paper III analyses

Descriptive statistics are used to present the demographic and clinical characteristics of the study sample. Normally distributed variables are expressed as means and SDs,

and continuous variables with skewed distribution are presented as medians and ranges. Categorical data are described as proportions and percentages.

Data were analyzed using LMMs with an unstructured covariance matrix because of the different length between each measurement point. LMMs allow-to model within-patients dependencies as each individual patient is measured at several time point. The time variable was treated as a categorical variable and enrolment level as a reference category when reporting the effect of possible changes over time.

To reduce the risk for collinearity between the different instruments, two LMM models were fitted separately for the physical and mental domains. Statistical model 1 (Physical) was used as follows. Because of the high correlations between the physical SF-12 (PCS) and physical symptom score (MSAS PHYS) (correlation coefficient 0.67) and KPS (correlation coefficient 0.67), the physical symptom score and KPS were omitted. Statistical model 2 (Mental) was used as follows. Because of high correlations between the mental SF-12 (MCS) and mental symptom score (MSAS PSYCH) (correlation coefficient 0.70), the MSAS PSYCH score was omitted.

To control for potential confounders, KPS, SCQ-19, MSAS PHYS, and MSAS PSYCH were included in the multivariate model. Covariates that did not correlate with the outcome variable in the univariate analyses were not included in the multivariate analyses, except for age and gender. In addition, the MSAS subscores do not include all 32 symptoms from the MSAS questionnaire. It was therefore important to include numbness/tingling because of the high risk of this symptom in patients receiving oxaliplatin and sexual problems because this was the symptom with the severest and most distressing symptom score at enrolment with potential effect on patients' well-being (QoL). *p* values <0.05 were considered to be significant, and all tests were two-sided.

Validity and reliability

Psychometric properties refer to the reliability and validity of the instruments.[76,137] Validity comes from the Latin word *validus*, which means strong, and refers to the extent to which the evidence supports that the inference is true or correct.[138] The

main type of validity is construct validity, which indicates the extent to which an instrument measures what it is intended to measure or investigate (accurate). Another type of validity is content validity, which indicates the extent to which the questions cover all dimensions of the phenomenon intended to be measured. A third type of validity is criterion validity, which reflects an instrument's ability to predict accurately what it is supposed to predict.[139] In addition, an instrument's ability, or sensitivity, to detect differences between patients or groups of patients is important; an example is the ability to detect changes occurring over time (responsiveness). Validity, reliability, sensitivity, and responsiveness are interrelated, although each of these characteristics is important individually.[76]

Internal validity refers to whether the study findings or outcomes are 'real' and not caused or confounded by external factors. Internal validity can be defined further according to the extent to which the study reduces the risk for systematic error (e.g., bias). A major threat to internal validity is the occurrence of bias because of confounders or selection or measurement errors. It is essential to consider possible biases to make valid conclusions; for example, including only the healthiest cancer patients increases the risk of selection bias.[139] A covariate is a variable such as age, gender, or education that may or may not be related to the outcome(s). A covariate that is related to both the exposure/risk factor and the outcome becomes a confounder. To reduce the risk of confounding, the TOUS theoretical framework [99] was a helpful guide for selecting the covariates which might have acted as confounders for our variable of interest in this thesis.

External validity is defined by Campbell and Stanley *"to what population, settings, and variables can this effect, be generalized."*[138] Possible threats to the external validity are high attrition and/or low response rates. Studies with high attrition and/or low response rates may have a higher risk of a study sample being identified as different from the original patient population, and the results may not be generalizable.

A major methodological problem in longitudinal studies is the high rate of dropouts, and the longer the follow-up, the higher the risk.[135] The risk of dropouts is especially high in longitudinal studies involving very ill or frail patients, cancer patients, and older people with a higher risk of mortality.[134] In a study that assessed

patients with diverse types of cancer, a high symptom burden at the baseline in addition to high symptom distress, fatigue, dyspnea, and poor performance status increased the risk of attrition.[140] Attrition bias can contribute to selection bias, underpowered studies, and that risk that the sample is not representative.[140] In addition, missing data can lead to biased results. Questions about sexual problems are often left unanswered, which increases the number of missing values.[66,76]

Reliability is used to describe and assess repeatability.[76] To test for reliability, a test–retest analysis, in which measurements are repeated over time, is often used when the scores are expected to be constant. One measure of internal reliability (internal consistency) is Cronbach's alpha coefficient,[76] which assesses the degree to which the items of a questionnaire are interrelated. Acceptable values for psychometric scales are Cronbach's alpha >0.8.[76]

Ethical considerations

The Regional Committee for Medical and Health Research Ethics (REC) (2009/1451), the Privacy Protection Committee at the hospital (08/1194), the Norwegian Directorate of Health (08/6788) (biobank), and the institutional review board at Oslo University Hospital (OUH) approved this study. This study followed the ethical principles in the Helsinki Declaration.[141,142]

To check for long-term symptoms, the research team applied for approval by the REC for a study period of 12 months. This request was rejected based on the potential burden for the patient, and a study period of 6 months was accepted. Eligible patients were asked by the nurses at the ward if they were interested in the study, and those who were interested received information regarding the study. If they were interested, the study nurse was contacted, and performed the inclusion. All included patients signed an informed consent form before enrolment. The invited participants/patients were given the opportunity to consider participation for more than 24 hours before signing the informed consent form. Participants could withdraw from the study without giving any reason at any time during the study period. To ensure confidentiality, each patient was assigned a unique number without any personal data that could be identified. The codebook with all study identification numbers was stored

and secured in a separate locker. The data files were stored on a secure research server at Oslo University Hospital.

Literature searches

The literature searches were performed in collaboration with librarians at the medical library at Oslo University Hospital. The databases included Ovid Medline, PubMed, Cochrane Library, Embase, Up to Date, and BMJ Best Practice. In addition, manual searches and 'snowball" searches' were performed. The search criteria were studies involving patients aged ≥18 years and published in English, German, or a Scandinavian language.

The search strategies identified articles that had the following words in the title, abstract, or text: "colon," "rectal," "colorectal neoplasm(s)," "symptoms," "multiple symptoms," "associated factors," and "predictors." The subject search was linked to the specific search terms for each scientific paper as follows:

#1: Prior to/before/at enrolment/initial/

#2: Longitudinal/treatment trajectory/

#3: Longitudinal/chemotherapy/(health-related) quality of life/

Results

Demographic and clinical characteristics

The demographic and clinical characteristics of the study cohort at enrolment are presented in Table 6. A total of 134 patients who had been diagnosed with CRC were eligible for inclusion, and 120 completed the questionnaires at enrolment and were included in the analyses (Fig. 4). Most patients were men (61%), the median age was 65 years, and 44% were retired.

A number of 57% of the patients were scheduled for curative treatment; 28% of the total cohort had received previous chemotherapy, 78% had undergone surgery, and 15% had received radiotherapy. The patients received 5-FU monotherapy (17%), irinotecan in combination with 5-FU (23%), and most received oxaliplatin in combination with 5-FU (60%). Three of the patients in the irinotecan treatment group received cetuximab or bevacizumab in combination with irinotecan. In the SCQ-19, the patients reported no comorbidity (25%), 1–2 comorbidities (42%), or ≥3 comorbidities (32%) at enrolment. Hypertension (31%) was the most commonly reported comorbidity. Depression was reported by 7.5%, and 2.5% reported that they had received treatment for depression at enrolment.

Table 6 Demographic and clinical characteristics at enrolment (n = 120)

	Median	Range
Age, years	64.7	33–80
Physical functioning KPS (60–100)	90	60–100
Number of comorbidities (0–19)	2.0	0–8

Characteristics	n	%
Sex		
Male	73	61
Female	47	39
Cohabitation		
Living alone	38	32
Living with someone	81	68
Education		
Primary/secondary	68	58
College/university	50	42
Occupation		
Part/full-time work	9	8
On sick leave	51	47
Retired	48	44
Previous treatment		
Surgery	93	78
Chemotherapy	34	28
Radiotherapy	18	15
Site of primary tumor		
Colon	86	72
Rectum	33	28
Treatment intent		
Curative	68	57
Palliative	52	43
Metastasis present at enrolment [a]	69	58
Metastasis site		
Liver only	24	20
Lung only	3	3
Lymph nodes only	3	3
Peritoneum only	2	2
Multiple sites	37	31
Type of chemotherapy		
5-FU monotherapy	20	17
Irinotecan/combination 5-FU	28	23
Oxaliplatin/combination 5-FU	72	60
Patients with stoma (temporary/permanent)	19	16

Abbreviations: 5-FU = 5-fluorouracil; KPS = Karnofsky Performance Status
[a] Metastasis could be present at more than one site; some frequencies do not total to the complete sample size of 120 because of missing values.

Symptoms at enrolment (Paper I)

The most frequently occurring physical symptoms reported at enrolment were lack of energy (59%) and feeling drowsy (54%). The most frequently occurring mental symptoms were worrying (65%) and difficulty sleeping (50%). The most severe and most distressing symptom score reported by the total patient group was problem with sexual interest (Table 7). The frequencies of these assessed symptoms did not differ significantly between the curative and palliative patients, although a few symptoms were scored differently between the patient groups. Sweats was rated among the seven most frequently occurring symptoms by the curative patients, but was not rated among the seven most frequently occurring symptoms by the palliative patients. The palliative patients rated nausea among the top seven most frequently occurring symptoms, but this was not one of the most frequently occurring symptoms among the curative patients. Problems with sleeping was among the severest and most distressing symptom in palliative patients, whereas the curative patients did not report this as being one of the severest or most distressing symptoms. The discrepancies between the different symptom dimensions and the range of the symptoms demonstrates that the most frequently occurring symptoms are not always the severest or most distressing.

Table 7 Symptom occurrence, severity and distress assessed with Memorial Symptom Assessment Scale at enrolment in colorectal cancer patients (n = 120)

Symptom dimension	Occurrence	Severity		Distress	
MSAS Physical symptoms	%	Mean	SD	Mean	SD
Lack of energy	59.2	2.0	0.7	1.4	1.0
Feeling drowsy	54.2	1.9	0.8	1.0	1.0
Feeling bloated	53.3	2.1	0.8	1.2	1.1
Pain	50.8	1.9	0.6	1.6	0.9
Problems with sexual interest	34.2	3.0	1.0	2.0	1.4
Lack of appetite	34.2	2.2	0.7	1.6	1.1
Dry mouth	33.3	1.8	0.6	0.7	0.7
Sweats	30.8	1.9	0.8	1.2	0.9
Nausea	28.3	1.8	0.7	1.3	1.1
Weight loss	25.8	2.3	1.0	2.0	1.4
Diarrhea	25.0	1.9	0.7	1.6	1.1
Cough	23.3	1.4	0.6	0.7	0.9
Numbness/tingling in hands/feet	22.5	1.6	0.6	0.9	0.9
Constipation	22.5	2.3	0.8	1.9	1.1
Shortness of breath	21.7	2.0	0.7	1.2	1.0
Dizziness	20.8	1.7	0.6	1.1	0.6
Itching	19.2	1.9	0.6	1.1	0.8
Change in the way food tastes	18.3	2.0	0.8	0.8	1.0
Changes in skin	14.2	2.0	0.8	1.5	1.1
Problems with urination	12.5	2.4	1.0	1.6	1.2
Hair loss	10.0	2.0	0.8	1.6	1.3
Swelling of arms or legs	8.3	1.8	0.7	0.8	1.0
Vomiting	7.5	1.7	0.8	1.0	1.1
Difficulty swallowing	5.0	2.8	1.0	1.8	1.6
Mouth sores	4.2	2.0	1.4	1.0	1.7
MSAS Mental symptoms					
Worrying	65.0	1.9	0.7	1.4	1.0
Difficulty sleeping	50.0	2.1	0.8	1.3	1.0
Feeling nervous	42.5	1.8	0.8	1.5	1.1
Feeling sad	41.7	2.1	0.7	1.4	1.0
Difficulty concentrating	37.5	1.7	0.5	1.1	0.9
Feeling irritable	20.8	2.0	0.6	1.3	0.8
"I don't look like myself"	10.0	2.4	0.8	1.9	1.0

Abbreviations: SD = standard deviation

Symptoms during chemotherapy (Paper II)

The patients became less worried over time. At the last assessment point 6 months after enrolment, lack of energy was the most frequently occurring symptom (53%). Lack of energy was high at enrolment and increased in severity in the days after chemotherapy administration during the two first cycles. Lack of energy remained severe, as shown by scores >60% throughout the following six assessment points, and did not return to the enrolment level before the last assessment point (Table 8). The palliative patients reported a significantly more often severe lack of energy than the curative patients over time; similar patterns were observed for younger compared with older patients and in women compared with men. Nausea was not among the most frequently occurring symptoms at enrolment, but it increased in severity from the start of chemotherapy. The severity of nausea increased in the days and week (3 and 7 days) after chemotherapy administration, but it declined towards the day of chemotherapy (T4). Being a woman, being younger, and having lower performance status was associated with more severe nausea. Pain did not change significantly over time, but more severe pain was associated with palliative treatment intent and lower performance status. The total number of symptoms remained stable at 8–11 throughout the 6-month study period (Table 9).

Table 8 Symptom occurrence rates assessed with the Memorial Symptom Assessment Scale (MSAS) in CRC patients (n = 120) over 6 months of chemotherapy

Assessment time	T1	T2	T3	T4	T5	T6	T7	T8
Study population (n)	120	116	112	110	108	103	98	88
MSAS Physical symptoms								
Lack of energy	59.2	71.7	65.8	60.8	65.0	63.3	64.2	53.3
Feeling drowsy	54.2	65.8	58.3	51.7	55.8	56.7	59.2	44.2
Feeling bloated	53.3	55.8	50.0	44.2	49.2	47.5	40.0	39.2
Pain	50.8	49.2	45.0	37.5	35.8	35.0	34.2	33.3
Problems with sexual interest	34.2	40.8	35.0	28.3	34.2	31.7	38.3	31.7
Lack of appetite	34.2	49.2	45.8	35.8	40.0	42.5	26.7	25.0
Dry mouth	33.3	41.7	40.8	40.8	38.3	43.3	43.3	35.0
Sweats	30.8	35.8	26.7	25.0	27.5	20.0	25.8	21.7
Nausea	28.3	61.7	52.5	35.8	51.7	54.2	43.3	29.2
Weight loss	25.8	30.0	30.0	25.8	26.7	30.0	14.2	18.3
Diarrhea	25.0	34.2	37.5	34.2	35.0	36.7	35.0	26.7
Cough	23.3	31.7	30.0	30.0	21.7	26.7	22.5	16.7
Numbness/tingling in hands/feet	22.5	40.8	35.0	30.8	45.8	46.7	43.3	48.3
Shortness of breath	21.7	27.5	27.5	21.7	25.8	26.7	28.3	21.7
Dizziness	20.8	32.5	28.3	23.3	28.3	27.5	27.5	24.2
Itching	19.2	20.8	15.0	19.2	17.5	20.8	11.7	15.0
Change in the way food tastes	18.3	32.5	32.5	23.3	35.8	41.7	35.8	29.2
Changes in skin	14.2	16.7	15.8	17.5	21.7	24.2	22.5	22.5
Problems with urination	12.5	17.5	13.3	11.7	12.5	13.3	9.2	10.8
Hair loss	10.0	6.7	8.3	11.7	13.3	16.7	26.7	21.7
Swelling of arms or legs	8.3	7.5	8.3	5.8	9.2	9.2	9.2	7.5
Vomiting	7.5	12.5	10.0	8.3	19.2	17.5	14.2	6.0
Difficulty swallowing	5.0	15.0	12.5	10.0	15.8	14.2	13.3	6.7
Mouth sores	4.2	12.5	17.5	16.7	19.2	26.7	15.8	15.8
MSAS mental symptoms								
Worrying	65.0	55.8	52.5	47.5	49.2	48.3	35.8	35.8
Difficulty sleeping	50.0	48.3	47.5	41.7	44.2	40.0	38.3	35.0
Feeling nervous	42.5	38.3	33.3	30.8	30.0	31.7	20.8	22.5
Feeling sad	41.7	49.2	45.0	34.2	40.8	37.5	36.7	25.0
Difficulty concentrating	37.5	44.2	45.8	37.5	40.0	41.7	37.5	35.8
Feeling irritable	20.8	25.8	26.7	21.7	24.2	21.7	18.3	18.3
"I don't look like myself"	10.0	15.8	14.2	15.0	21.7	17.5	17.5	14.2

Abbreviations: CRC = colorectal cancer; T1 = At enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle, assessed before chemotherapy; T5 = 3 days after second chemotherapy; T6 = 7 days after second chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

Table 9 Quality of life and total MSAS scores at selected time points during chemotherapy in CRC patients

Assessment time	T1	T2	T3	T4	T5	T6	T7	T8
Study population (n)	120	116	112	110	108	103	98	88
	Mean	Mean	Mean	Mean	Mean	Mean	Mean	Mean
Total SF-12 PCS	43.5	43.3	44.4	45.8	43.3	44.5	43.4	44.2
Total SF-12 MCS	46.2	46.0	47.4	46.7	47.5	46.8	48.0	48.6
Total MSAS (SD)	9 (6)	11 (7)	10 (7)	9 (7)	10 (8)	10 (8)	9 (7)	8 (8)

Abbreviations: CRC = colorectal cancer; SD= standard deviation; SF-12 MCS = Short Form 12-item Health Survey mental subscore; SF-12 PCS = Short Form 12-item Health Survey physical subscore; T1 = at enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle, assessed before chemotherapy; T5 = 3 days after second chemotherapy; T6 = 7 days after second chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment.

Symptoms and QoL over time (Paper III)

The physical QoL was lower in the CRC patients than in the general population at all measured time points (Table 9). The total SF-12 PCS and MSC scores are presented in Table 9. Physical QoL increased on the day of the second chemotherapy administration, but did not change significantly from enrolment to the other time points. Mental symptom symptom burden was significantly associated with physical QoL; that is, impaired physical QoL was reported by those with higher mental symptom burden compared to those with lesser metnal symptom burden. Numbness/tingling was associated with impaired physical QoL.

The mental QoL was lower in the CRC patients than in the general population at all measured time points. Mental QoL increased significantly at T5 and 3 months (T7), but not at any other time point. The physical symptom burden was negatively associated with mental QoL. Being female or younger and having problems with sexual interest were associated with impaired mental QoL.

The burden of physical and mental symptoms was associated with impaired QoL in these CRC patients. In addition, the symptoms of numbness/tingling and problems with sexual interest were both of importance in the way they were associated with impaired QoL.

Disease and mortality status at the last measurement point (6 months)

At the last measurement time point (6 months (T8)), 88 (73%) of the 120 patients completed the last set of questionnaires. An overview of the patients, instruments, and compliance at each measurement point is presented in Fig. 4 and Table 10. None of the demographic or clinical characteristics differed significantly between those who did and did not complete the questionnaires at the last measurement point. Of the patients assessed at 6 months, 47 were still alive with no evidence of disease, 62 were still alive with disease, five had died, and two had been diagnosed with brain metastases and thus excluded from the last assessment point. Information was not available for four patients.

Recruitment and compliance

Fig. 4. Flowchart of patient recruitment and compliance
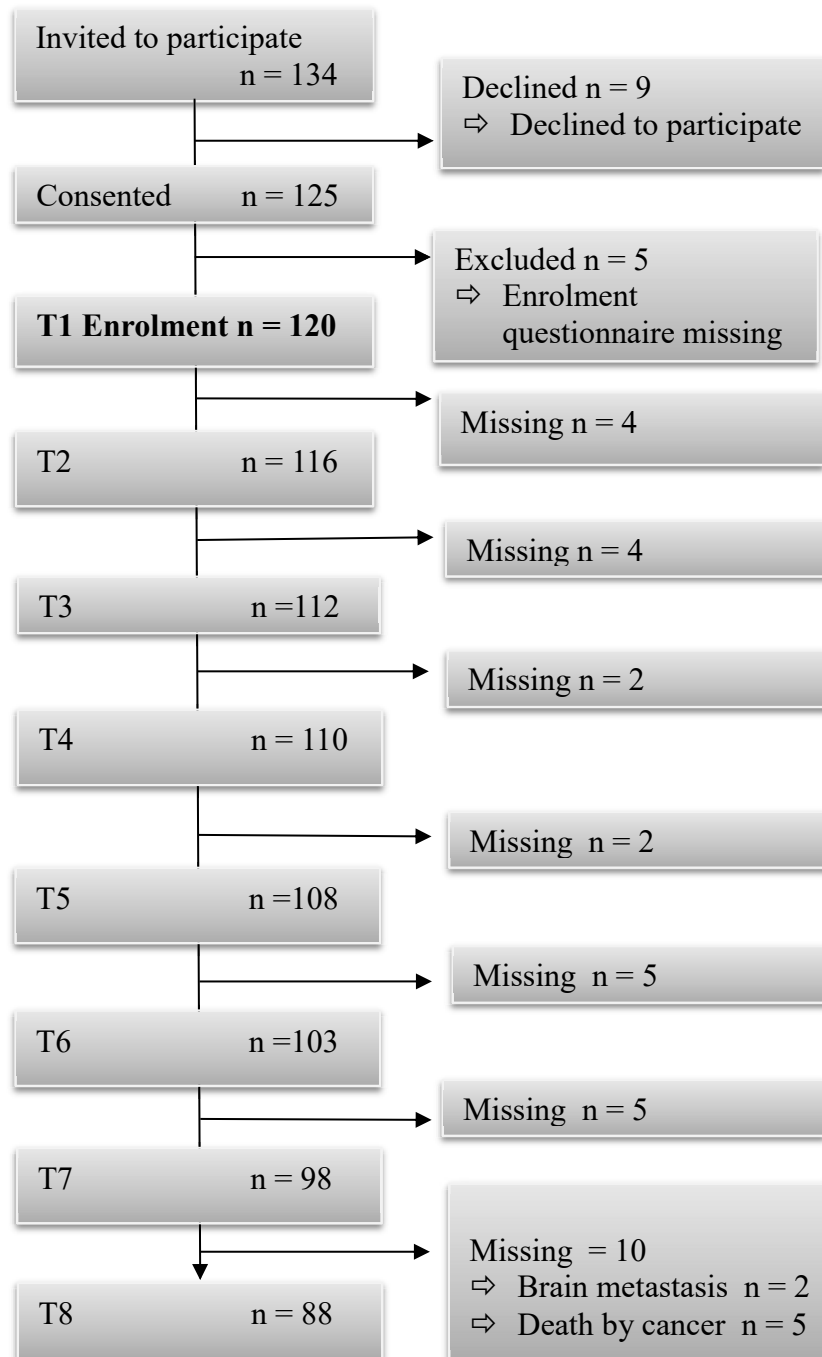
Abbreviations: T1 = at enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle, assessed before chemotherapy; T5 = 3 days after second chemotherapy; T6 = 7 days after second chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

Table 10 Total number of patients and completed instruments at the eight measurement points

Time	T1	T2	T3	T4	T5	T6	T7	T8
MSAS	120	116	112	110	108	103	98	88
SF-12 PCS	119	114	109	105	102	102	96	85
SF-12 MCS	118	113	106	108	97	101	96	85
KPS	118	115	111	109	107	102	98	88
SCQ-19	117	N/A	N/A	N/A	N/A	N/A	–	–

Abbreviations: KPS = Karnofsky Performance Status; MSAS = Memorial Symptom Assessment Scale; N/A = not available; SF-12 MCS = Short Form 12-item Health Survey mental subscore; SF-12 PCS = Short Form 12-item Health Survey physical subscore; SCQ-19 = Self-Administered Comorbidity Questionnaire 19; – = not calculated

T1 = at enrolment; T2 and T3 = 3 days and 7 days after initiation of the first chemotherapy cycle, respectively; T4 = before the second chemotherapy cycle; T5 and T6 = 3 days and 7 days after initiation of the second chemotherapy cycle, respectively; T7 = 3 months; T8 = 6 months after enrolment;

Summary of papers

Paper I

No differences in symptom burden between colorectal cancer patients receiving curative versus palliative chemotherapy

In this longitudinal prospective study, enrolment data were analyzed. This study investigated occurrence, severity, and distress in CRC patients before they initiated chemotherapy or a new chemotherapy regimen. This study also explored differences between patients scheduled to receive curative or palliative chemotherapy.

A total of 120 CRC outpatients were included; 57% were treated with curative and 43% with palliative intent. The patients reported a mean of nine co-occurring symptoms at enrolment in the study. Worrying (65%), lack of energy (59%), feeling drowsy (54%), feeling bloated (53%), pain (51%), and difficulty sleeping (50%) were the most frequently occurring self-reported symptoms. Despite the high occurrence rates, these symptoms did not have the highest severity or distress scores. The severest and most distressing symptom reported by this cohort was problems with sexual interest, and the scores were in the moderate to high range. The groups receiving chemotherapy with curative or palliative intent did not differ significantly on any of the 13 most common symptoms in terms of symptom occurrence, severity, or distress. Despite the lack of significant differences between the curative and palliative patients, the range of the symptoms differed between the groups. In conclusion, these patients experienced several co-occurring symptoms at the start of chemotherapy, and the most frequently occurring symptoms were neither the severest nor most distressing ones.

Paper II

Symptoms during chemotherapy in colorectal cancer patients

In this longitudinal prospective cohort study, self-reported questionnaires were used to investigate common cancer- and treatment-related symptoms in CRC patients undergoing chemotherapy. The patients were assessed at six defined time points during two chemotherapy cycles and at 3 and 6 months after the start of chemotherapy. The assessment points were selected to reveal possible changes in symptoms throughout the course of chemotherapy and at 6 months after.

The study focused particularly on the occurrence and severity of worrying, lack of energy, numbness/tingling, nausea, and pain. Differences in symptom experience between the chemotherapy groups were investigated, and the factors associated with more severe symptoms were identified.

In total, 120 patients were included before the start of chemotherapy. Nausea increased in severity 3–7 days after chemotherapy administration, and women experienced worse nausea than men. In the days after chemotherapy, numbness/tingling (oxaliplatin group) increased in severity, and being male and having a lower educational level were associated with greater severity of this symptom. Lack of energy increased in severity in the days following chemotherapy. By contrast, worrying became less severe over time. A more severe lack of energy and worrying were associated with female gender. Palliative patients reported more severe pain than curative patients. Reduced performance status was associated with more severe symptom experience in all aforementioned symptoms except for numbness/tingling.

In conclusion, symptoms fluctuated during the chemotherapy cycles, and the severity of a lack of energy, nausea, and numbness/tingling (in those receiving oxaliplatin) worsened in the days following chemotherapy. Female gender was associated with more severe nausea, lack of energy, and worrying.

Paper III

High symptom burden is associated with impaired quality of life in colorectal cancer patients during chemotherapy – A prospective longitudinal study

In this longitudinal prospective cohort study, 120 CRC patients were included, and their PROMs were assessed at defined time points throughout 6 months of chemotherapy. The SF-12 and MSAS questionnaires were used to assess QoL and symptoms, respectively. Associations between QoL and demographical and clinical data were also assessed.

The physical and mental QoL scores were lower in CRC patients than in the general population at all eight measurement points. Impaired physical QoL was significantly associated with a higher mental symptom burden ($p<0.01$) and numbness/tingling ($p<0.01$). Impaired mental QoL was significantly associated with a higher physical symptom burden ($p<0.01$), female gender, younger age, and problems with sexual interest.

In conclusion, patients with high symptom burden were at higher risk for diminished physical and mental QoL throughout the treatment trajectory. In addition, the specific symptom numbness/tingling was associated with impaired physical QoL, and the symptom problems with sexual interest was negatively associated with impaired mental QoL throughout the treatment trajectory.

Discussion

The discussion section contains two main parts: first, a methodological discussion and second, a general discussion with a focus on the main findings in this thesis.

Methodological considerations

Study design

A prospective longitudinal design with repetitive measures throughout chemotherapy treatment was used in the thesis. The six assessment points were selected to capture symptoms and QoL at several times during two chemotherapy cycles T1–T3 (cycle 1) and T4–T6 (cycle 2), early in the treatment phase (Fig. 3). The time points at 3 (T7) and 6 months (T8) were selected to capture the long-term effects of chemotherapy.

It is important to examine changes in outcomes (multiple symptoms, symptom dimensions, and QoL) over time from the time of pretreatment throughout the chemotherapy treatment. Such changes have been shown to be important in previous studies of patients with lung cancer [72] and diverse cancer diagnoses [71]; however, they have been studied less in CRC patients.[47] The timing of the assessment points during the chemotherapy cycle is important because various side effects of chemotherapy can occur at different times,[72] and be present for a shorter time period, which means that there is a risk of missing some by infrequent assessments during the course of chemotherapy or only on the day of chemotherapy.[71,72] Assessments after 3 and 7 days provided information about the most acute side effects of chemotherapy, through the chemotherapy cycle, in this cohort. These changes in symptoms may be missed when assessments are conducted only on the day of next chemotherapy administration.[71,72]

The time of enrolment in this cohort cannot be defined as a true baseline for measuring the effects of chemotherapy. About one-quarter (28%) of the sample had received chemotherapy before the initiation of the study (T1). This "blurred" the enrolment data because of the lack of a clear pretreatment time point, and made it difficult to draw conclusions about whether symptom burden and QoL assessed at enrolment was associated with previous cancer treatment. However, it is considered to be representative for patients with CRC starting a new chemotherapy regimen. The symptom burden, physical symptoms (MSAS PHYS) or mental symptoms (MSAS

PSYCH), physical QoL (PCS), and mental QoL (MCS) did not differ significantly (*p*>0.05) between patients who had and had not received previous chemotherapy. In addition, comorbidity and performance scores at enrolment did not differ significantly between patients who had and had not received previous chemotherapy. To impose a clearer baseline, the inclusion of patients with no previous chemotherapy could have been an option.

In this study, the recall time ranged from the preceding week to the last 4 weeks [100,117] depending on the questionnaire used. Because frequently repeated measures were used, one risk is that overlapping assessments may have occurred, reducing the opportunity to capture the experience or changes in symptoms and QoL during the two first chemotherapy cycles. However, the information about how symptoms change in CRC patients receiving chemotherapy obtained in this thesis provides additional important information to clinicians because symptoms caused by chemotherapy [143,144] may occur during treatment or may develop later, after the patient leaves the hospital (days after chemotherapy).[47,71,72] The frequent assessments during the two first chemotherapy cycles might have been an extra burden for the patients. However, this allowed us to obtain important clinical information at a time when the patients are not seen directly by clinicians. This information may help to improve communication by increasing clinicians' awareness of symptoms experienced by CRC patients while receiving chemotherapy in the clinic.

Demographic and clinical characteristics

Patients were recruited at the outpatient clinic at OUH, one of the largest outpatient cancer clinics in Norway. Recruitment and inclusion at only one hospital might have affected the generalizability of the research because there are geographic inequalities in socioeconomic status and health conditions in Norway.[145,146] On the other hand, OUH is responsible for medical oncology treatment for CRC for a majority of the Oslo population (around 600,000 people). The inclusion of patients from a large university hospital of consecutive patients who met the inclusion requirements, and the use of the same study nurse to include all patients, may have reduced the risk for selection bias and thus strengthen the external validity and generalizability of these results to other CRC patients in the same treatment setting.[147]

The demographical and clinical characteristics e.g., age, gender, of the cohort were similar to Norwegian CRC cancer patients, which might reduce the risk of selection bias. The patient cohort was heterogeneous: age ranged from 33 to 80 years (median age 65 years), patients were of different educational levels and civil statuses, and both men and women were included. In addition, the median age in this sample was similar to the median (60–71 years) and mean (65–66 years) reported for other studies of CRC patients.[66,68,143,148] CRC patients usually receive their diagnosis at age >70 years, but few older patients are included in clinical studies of CRC patients.[149] In the present study, also older patients were included, which increases the generalizability to older patients. We believe that the present cohort are representative and can be generalized to other CRC patients with similar characteristics.

In this cohort, 99% were Caucasians, which means that other ethnic groups were underrepresented, even though Oslo has a large immigrant population. One possible reason is that patients with poor Norwegian fluency were excluded because the questionnaires were in Norwegian. Information about socioeconomic status was not included, but educational level, a proxy for socioeconomic status, was recorded.[150] QoL and symptoms might have different meanings depending on patients' culture or religious beliefs.[151]

Representativeness, compliance, and attrition

The patients received a comprehensive package of 10 questionnaires, five of which were used for analyses in this thesis (see Appendix). The pilot study showed that the time required for completion of the total package of questionnaires was 8–35 minutes. By including cancer patients, there is always a risk of not including the most vulnerable or sick patients (selection bias); however, surprisingly few patients declined to participate (Fig. 4). Several patients expressed gratitude about being able to contribute to the project. Despite the comprehensive package of questionnaires, a participation rate of 89.6% was achieved. This participation rate is consistent with that of other studies of CRC patients, where this rate ranged from 72% to 90%.[148,152-154] The patients who declined to participate reported spontaneously that they felt too fragile and vulnerable and lacked energy. Not including the most vulnerable patients might have led to underestimation of the symptom severity, distress, and QoL scores and, in turn, might have limited the groups that these results could be generalized to. However,

considering that few patients declined to participate, we assume there was minimal risk of a significant effect on the outcomes and that the 10 questionnaires used in this thesis are feasible. Patients seem to be willing to report their symptoms even when older, sick, or close to death.[155,156]

Longitudinal studies in palliative oncology always carry a risk for attrition (dropouts).[157] We do not have information about the reason for drop-out; however, a few patients gave their reasons spontaneously. Four patients complained about the comprehensive package of questionnaires, two patients reported feeling too tired or burdened by the situation, and one did not wish to receive any more chemotherapy. In addition, five patients died during the study period. To reduce the risk for dropouts or missing values, the patients were given the phone number for the study nurse in case they had questions or problems with the questionnaires.

Of the 120 patients included at enrolment, 88 (73%) completed the last set of questionnaires. Two patients were excluded from the study at the last measurement point (T8) because of brain metastases. The completion rate is consistent with that of a previous longitudinal study of lung cancer patients that used HRQoL as the end point.[72] In the cohort included in this thesis research, the demographic and clinical data did not differ significantly between patients who completed or did not complete the final questionnaires at 6 months. Therefore, the results may be considered as representative of the intended patient population. Moreover, both patient groups (curative and palliative) were equally distributed at the last measurement point.

Moreover, the instruments used in this study were scored according to the scoring manual for each instrument, which included instructions for the handling of missing data. The choice of modeling strategy did not require full data sets. The LMM uses all available data in the dataset, despite randomly missing values for one or more assessment items, to estimate the covariance structure and model the within-patient dependencies, in addition to the estimates for the included covariates.

Questions about sexual issues can have higher missing values than those about other symptoms.[66] In this thesis, 9.2% of the study sample did not answer the question about "problems with sexual interest/activity" at enrolment. Incomplete questionnaire

answers or barriers to reporting issues about sexuality have been reported as a problem in previous studies.[66-68,158] One explanation is that talking about sexual issues can be difficult,[68] possibly because of cultural issues. Previous studies have also suggested that some patients believed that if they were sexually inactive they did not need to answer the questions, whereas other felt the questions to be too sensitive,[66,67,158] or felt that their sex life was not that important.[68]

This thesis research used paper versions of the questionnaires, which increases the risk of errors and loss of information because of the many steps required for documentation and data entry.[159] Returning questionnaires by mail might be complicated and time-consuming, and may increase the risk of missing data. To reduce this risk, the patients were allowed to bring the completed questionnaires to the hospital at their next treatment. Electronic systems represent an alternative to the paper versions that allows the patient to report symptoms in real time, and have been reported to increase patient compliance compared with paper versions.[159] In addition, electronic systems for symptom assessment can increase early responsiveness to patients' symptoms and may thereby prevent worsening of symptoms.[14,114] When using electronic systems, it is essential to assure patients' security and privacy, which may be one barrier to their implementation in hospitals.[160] Despite the increasing use of electronic devices, their use might be challenging for elderly patients.[160]

Categorization of curative and palliative patients

In the study described in Paper I, it was hypothesized that the curative patients would have a lower symptom burden than the palliative patients. Dichotomization of the patients into the two groups was performed by an oncologist. The categorization of all assessed symptoms did not differ significantly between the curative and palliative groups at enrolment. One explanation for the lack of difference is that the categorization of patients into either curative or palliative is complicated because the difference between these two groups has become more "blurred".[161] The liver is the predominant metastatic site in CRC patients, but patients previously categorized as palliative because of limited liver metastasis might today be regarded as curative if they have a good response to chemotherapy and can undergo surgery.[162] Regarded as the only chance for a cure, liver resection has become possible with recent progress in surgery techniques. The categorization of CRC patients into two groups may no

longer be the most appropriate way to classify patients receiving treatment in clinical studies.[161] A recent study reported increased overall survival in patients diagnosed with nonresectable liver-only metastases after liver transplantation.[163] The results of this thesis show that both curative and palliative patients are burdened with symptoms.

Selection of covariates

One of the main aims of this thesis was to identify changes in symptoms and QoL over time and associations between selected covariates and the outcomes. The TOUS [99] was used to guide the selection of covariates in Papers II and III, in addition to discussions within the research group, important clinical considerations, and previous research. Even though several covariates were included to test for possible confounders, unobserved factors might have influenced the results. However, we believe that these results identify some of the most important risk factors for severe and distressing symptoms and impaired QoL in CRC patients.

Palliative patients with BRAF-mutated tumors have a worse prognosis and poorer QoL,[148] although this was not adjusted for in this thesis research. Histories of smoking and alcohol use have also been shown to be predictors of worse QoL,[164] but were not included as covariates in this study. Information about the presence of a stoma was collected from medical records; however, because it was not significant in the univariate analyses, this covariate was not included in the final model.

In the study described in Paper III, covariates that reached the level of significance ($p<0.05$) in univariate analyses were included in the multivariate analyses. It is customary to use $p<0.1$ for this type of analysis, but the threshold was reduced to <0.05 to adjust for multiple testing. Multiple testing increases the risk of Type 1 errors, and we assumed that using $p<0.05$ would reduce the risk of Type 1 errors in this study. It was important to include the specific symptoms numbness/tingling and problems with sexual interest as covariates because these are not included in the MSAS subscales. The rationale for including numbness/tingling was that it has been shown that this variable affects QoL.[165] Further, the rationale for including problems with sexual interest was that our data in Paper I revealed that this variable had the highest severe and distress scores.

Psychometric properties of the instruments used

An important criterion determining the methodological quality of a study (reliability and validity) is the use of well-constructed instruments.[76,137] The questionnaires selected for assessing the psychometric properties in this thesis research (MSAS, SF-12, KPS and SCQ-19) have all been shown to have satisfactory reliability and validity.[100,117,124-126] These questionnaires have been used in previous studies of cancer patients in Norway.[106-109,166]

The MSAS is a comprehensive questionnaire for assessing cancer symptoms for both clinical and research use.[113] A pilot study was performed in the "Cluster study" to detect any problems before patient inclusion such as questionnaire layout, and to test the different combinations of instruments and the Norwegian version of the MSAS. One limitation is that the instruments included in the thesis research were selected from the main study.[15] The questionnaires were not selected specifically for CRC patients, and the diagnoses of specific symptoms such as anorectal function and stoma-related symptoms might have been missed. However, we assume that the content validity (i.e., the MSAS covers relevant items) [76] is good because the MSAS contain 32 symptoms and three open questions, and the comprehensive questionnaires cover symptoms that are important to patients with various types of cancer, as well as those with CRC.[66,167]

Cronbach's alpha is the most common test for internal consistency (internal reliability). However, in papers included in this thesis research, Chronbach's alpha was not calculated for the MSAS, SF-12, KPS, or SCQ-19 questionnaires. The MSAS and SCQ-19 cover different symptoms, and these questionnaires are not intended to correlate with each other. The SF-12 comprises the two components physical and mental, which are weighted differently.[123] The KPS has only one item, and thus, it is not possible to calculate Cronbach's alpha.[76] One option for testing for internal consistency or stability is to test–retest, but this is possible only if scores are expected to remain stable over an adequate time span (10–14 days),[168] which was not expected in the pilot and thesis research studies.

The risk for recall bias depends on the length of the recall period and is higher in studies using self-report. In this thesis research, self-report questionnaires involved a

recall period that varied from "right now" to the "last 4 weeks," and this may have increased the risk for recall bias, which could be a threat to internal validity. However, during the first two cycles, the assessments were often repeated, and we suggest that this reduced the risk of recall bias because the patients may have ignored the time frame. Similar results have been reported in a study of patients with diverse types of cancer, which found that the 7-day recall version of the MD Anderson Symptom Inventory [169] was as sensitive as the 24-hour recall version. Those authors concluded that, "the choice of a suitable recall period should depend on the specific purpose of the trial, the characteristics of the disease, and the treatment to be tested."[169]

One challenge with longitudinal studies is the risk of response shift, which refers to the recalibration by patients of their QoL expectations and adjustment to their new life situation, or in other words, how patients accommodate to the disease and treatment and quantify their QoL over time.[170] The patients in this thesis research were assessed over a short period of time, and we believe that the risk of an effect on the results because of a response shift was small.

Measuring symptoms with the MSAS

The MSAS is a disease-specific questionnaire for patients with cancer.[100] However, the MSAS may miss symptoms specific to CRC patients because it does not include symptoms or side effects of chemotherapy specific to CRC patients, such as gritty, watery, or sore eyes (lacrimation and dacryostenosis) related to the chemotherapy drug 5-FU.[171] Lack of fecal control [46,84,172,173] is often seen as a late side effect after radiotherapy and surgery, and four patients added problems with leaking feces or blood from the rectum in their answers to the open-ended questions in the MSAS. In patients with a stoma, leaking is a reported problem,[53] but this was not added by any of the patients.

The MSAS includes the symptoms worrying and sadness, but not depression,[174] which affects QoL.[94,175] To assess depression, the SCQ-19, which contains the question "Are you depressed?" and information regarding medical treatment for depression, was used in the thesis research. In this sample, 7.5% of the patients reported depression and 2.5% had received treatment for depression at enrolment.

Information about the use of antidepressants or other medications that could affect the symptoms experienced or depression [176] was not collected in this study. To obtain more detailed information about depression in the present cohort, the Center for Epidemiologic Studies Depression Scale, which was included in the main study (see Appendix), could have been used.

Even though some diagnosis-specific symptoms are not included in the MSAS, it covers the most important symptoms related to cancer and treatment.[11] Another strength of the MSAS is that it includes the symptom dimensions occurrence, frequency, severity, and distress. The MSAS may be valid for use with CRC patients because the additional three open-ended questions allow patients to add symptoms not included in the questionnaire.

Measuring QoL using the SF-12

The SF-12 is a generic questionnaire that provides information about health status in general and specific populations.[93] CRC patients can experience diagnosis-specific symptoms that can affect QoL, and a disease-specific questionnaire such as the EORTC QLQ-C30 or the diagnosis-specific questionnaire for CRC such as the EORTC QLQ-CR29 are alternatives.[177,178] However, there is no gold standard for assessing QoL, [179,180] and the choice of a generic questionnaire was made because this study was part of a larger study including several cancer diagnoses and treatments.

The SF-12 assesses health status [117] and how the disease affects a person's functioning, but not the person's feelings about functioning.[170] There is a difference between health status and QoL.[170] In addition to health status, QoL assesses to what extent a patient is bothered by the limitations.[170] One might then question whether the term QoL is used correctly in this thesis, even though the SF-12 has been used in other studies to assess HRQoL in CRC patients.[144,164,181]

Another limitation is that we scored the PCS and MCS subscales using the 1998 U.S. general population normative values. The reason for using the U.S. population as a normative value was that the main "cluster study" was based on an international collaboration with The School of Nursing, University of California, San Francisco in the U.S, aiming to compare different patient populations in the "cluster study". This

might not be appropriate because Norway and the U.S. are quite different countries. However, cutoff scores similar to those in the U.S. population (e.g., PCS 50.3 [SD 8.8] and MCS 50.6 [SD 9.9]) have been reported for the Norwegian population.[124] Gandek et al [124] concluded that the differences between the countries are small, and recommended using the standard (U.S.) scoring of the SF-12 summary measures when comparing and interpreting results between countries. This justifies the use of the U.S. normative values in the thesis research.

Another limitation is that the normative values were published about 20 years ago, in 1998.[124] These old normative values are a limitation because the U.S. and Norwegian populations have changed; for example, both life expectancy and numbers of immigrants have increased, which has resulted in more diverse and older populations.[146] However, despite changes in the Norwegian population over the past two decades, QoL has remained stable in the general Norwegian population.[146]

Measurement of physical functioning

The KPS is a widely used questionnaire to assess performance status or physical functioning in cancer patients.[125,144,182,183] The KPS is commonly administered by clinicians, but was self-reported in the studies in this thesis. Self-report was part of the study design to allow the patients to assess themselves at home. A previous study has reported a correlation between clinicians' assessments and patients' self-assessments,[184] which justifies the use of the KPS for self-report in the thesis research. Another option besides self-report is to obtain information in interviews, which might provide more reliable information about patients' functional status [125] and reduce the risk of information bias. Even though the KPS is a standardized, reliable, and validated questionnaire in cancer patients,[125] it was apparent that some patients found the questions unclear and sometimes replied with more than one answer. In such cases, the highest score was selected. The patient cohort was in fairly good physical condition at inclusion, with a median number of comorbidities of two and a mean KPS score of 90. However, selecting the highest value for such cases may have led to overestimation of the total physical functioning. Nonetheless, only a few patients answered with more than one option (<5 at each assessment point), and we assume that the KPS scores accurately reflect these patients' physical functioning.

Measurement of comorbidity

The SCQ-19 [126] was used to measure the patients' self-reported comorbidity. This questionnaire is short and easily completed and has three options for adding additional comorbid conditions. One limitation with self-reporting is that patients may have different understandings of their medical conditions. One relevant SCQ-19 question is, "Do you have a bowel disease?" In total, 30.8% answered "yes" to this question at enrolment. These results are difficult to interpret as some patients might have ticked yes as they referred to their colon or rectal disease. However, the SCQ-19 is valuable for assessing a number of comorbidities and as a valuable complement to the MSAS, for example, to assess depression. The studies in this thesis used only the total number of comorbidities. Comorbidity is important because it is a risk factor for greater symptom burden [174,185,186] and impaired QoL [93]; however, comorbidity was low in the cohort included in the thesis studies.

Discussion of the main results

Side effects from chemotherapy can occur at different time points during treatment. To be able to offer symptom management at the right times, it is important to understand which symptoms appear during the different chemotherapy phases.[72] Symptoms can vary between different types of cancer and treatment,[72,90,187] and it is important to assess symptoms within the context of specific cancer diagnoses such as CRC. Assessing symptoms with questionnaires can be bothersome for patients, however self-reported questionnaires provide important and unique information from the patients' perspective for identifying those most at risk and their symptoms.[66,167] In addition, the use of self-reported questionnaires allows clinicians and researchers to capture multiple symptoms. Once symptoms are identified, symptom management strategies can be initiated and interventions with symptom management can be offered.[11,87,94,167] To report symptoms directly to health care providers, allows clinicians to offer immediately help. To capture symptoms with paper or electronically based questionnaires are important in order to systematically collect information on the group level. Improved symptom management may reduce the need for hospitalization,[47,188,189] help stabilize or improve QoL,[93,94] and improve the patient's capacity for well-being throughout treatment.[190]

Symptoms at enrolment

This patient cohort experienced psychological burden at enrolment, as shown by the occurrence rate of 65% for worrying. Confrontation with a life-threating disease, which implies accommodation to a new life situation, the need for starting or altering chemotherapy, may help explain this finding.[191] Other symptoms with high rates of occurrence at enrolment were lack of energy (59%) and pain (51%). Lack of energy or fatigue and pain commonly co-occur in cancer patients.[182,190] Fatigue is one of the most common symptoms reported early in the treatment phase in CRC patients,[66,68] whose occurrence rates range from 24% to 62% [66,89,192] depending on the assessment method. In a longitudinal study of CRC patients [192] and another study of patients with diverse cancer diagnoses,[193] the severity of fatigue at baseline was a predictor of persistent fatigue.[192,193] In these studies, persistent fatigue predicted fatigue in the year after completion of treatment.[192,193]

Cancer patients rarely experience symptoms in isolation; rather, multiple symptoms can occur simultaneously, and this combination can have an additive effect (Paper I).[60,66,99,133,153,167] According to Lenz et al,[99] management of one symptom can contribute to the treatment of other symptoms. For example, in a randomized trial, nurse-led interventions, exercise, and antidepressants improved depression and anxiety in cancer patients.[194] In-depth understanding of single symptoms is good, but methods to assess and treat multiple symptoms is less developed.[35] To assess the patient's symptom status in the early treatment phase is therefore important because early responsiveness to adverse symptoms may prevent worsening of the symptoms [14] and reduce the risk of developing other symptoms [99] and negative long-term outcomes.[195] Symptom control might also reduce the need for emergency department visits, hospitalization,[133] and negative effects on functional status and activity.[35] Functional status is an important criterion in the decision about the use of chemotherapy.[18] Thus, untreated symptoms might delay or terminate important treatment.[35]

Changes in symptoms and QoL over time

The choice of time points for assessing symptoms and QoL is important when investigating the effects of chemotherapy.[72] Frequent assessments with few days between measurements increases the ability to describe variations in the symptom pattern.[196] Previous research has shown that the lowest levels of symptoms occur before patients receive chemotherapy,[71] whereas chemotherapy can increase the need for unplanned hospital visits in the days following chemotherapy because of side effects.[47] The thesis findings are consistent with those of previous studies showing that CRC patients experience a variety of severe and distressing physical and psychological symptoms. In this cohort, these symptoms, especially nausea, fatigue, and numbness/tingling (oxaliplatin group), co-occurred throughout the study period and increased in severity 3–7 days after chemotherapy. The risk of unplanned emergency admissions increases after chemotherapy, as does that for impaired performance status and greater symptom burden (e.g., pain, fatigue, and anorexia–cachexia syndrome).[47]

The increased and delayed severity of nausea in the days after chemotherapy is concerning because these patients had received a preventive antiemetic for low to

moderate emetogenic chemotherapy.[18,197,198] These patients seemed not to have been treated optimally. In these studies, nausea and vomiting were assessed separately. Cancer-induced nausea and vomiting (CINV) is commonly assessed as one entity,[72,90,143,148,199] even though nausea and vomiting sometimes are experienced differently.[66,200,201] Cancer patients sometimes experience higher levels of nausea than vomiting,[11,66,152] (Paper I) and the level of nausea may be underestimated if nausea and vomiting are assessed as one entity. In this cohort, nausea increased during the first and second cycles, and 62% of patients reported nausea compared with 19% reporting vomiting. Assessing CINV with one question increases the risk of overestimating vomiting rates and underestimating nausea rates if CRC patients are more bothered by nausea than by vomiting.[66]

Failure to obtain nausea control during the first 24 hours after chemotherapy has been shown to predict delayed emesis in the same cycle.[202] Vomiting in a previous cycle is a predictor of emesis in the following cycle.[197] Nausea control early in the treatment phase is most effective when used prophylactically; thus, it is important to reduce the risk of both delayed nausea [197,202] and anticipatory emesis.[203] It is also important to exclude other causes of nausea, which may be related to the use of opioids or other medications.[198] Pain and the use of medications were not examined in depth in the thesis studies, and the percentage of patients reporting nausea may have been influenced by the use of opioids. Patient inclusion in the present study occurred during 2009–2011, following guidelines for nausea and vomiting,[204] but new guidelines for nausea and vomiting were published in 2017.[197] Only limited research has been published about prophylaxis to prevent both acute and delayed nausea and vomiting since the previous guidelines.[204] However, one difference from the previous guidelines is that dexamethasone may be given for 2–3 days to patients receiving oxaliplatin.[197] To prevent acute and delayed nausea, the combination drug; netupitant and palonosetron)[205] in combination with dexamethasone has shown positive effects in preventing nausea.

The patients in this cohort experienced co-occurring psychological symptoms. This cohort reported high occurrence of sleep disturbance (>40% throughout the first two cycles (T1–T6)) and high occurrence of fatigue (>50% at all measurement points) (Table 8). It is important to identify patients with sleep disturbance because daytime

sleep can lead to difficulty sleeping at night, which increases the risk of fatigue.[206] The patients in the present study also had high rates of worrying at enrolment (Paper I), but this improved over the following months in terms of both occurrence and severity (Paper II). To reduce the effects of psychological stressors experienced during chemotherapy treatment, important tasks for the oncology nurse are to provide patients with evidence-based information and to guide patients in self-management techniques. Self-management techniques, such as information seeking, have been reported as an effective coping strategy in CRC patients.[207]

The importance of symptoms (Papers I–III) and the association with physical and mental QoL (Paper III) support previous findings in CRC patients.[88,94] Gray et al [94] found that the symptoms with most effect on QoL were fatigue, anorexia, dyspnea, and depression. The nonsignificant difference in QoL (Paper III) between the curative and palliative patients suggests that attention to symptoms is important in both patient groups. In a cross-sectional study of CRC patients (n = 508), curative patients experienced a good QoL, whereas older patients, those with cancer-related symptoms (e.g., fatigue and pain), and those with financial difficulties had an poorer QoL.[88] This thesis research did not assess financial aspects, although the patients were followed for only 6 months, during which time, they were usually covered by sickness benefits from the Norwegian government. A longer follow-up period is needed to assess the effects of cancer on financial status in CRC patients.

Numbness/tingling worsened over time (in patients receiving oxaliplatin) and was associated with impaired physical QoL in Paper III. This is consistent with previous reports on a cumulative increase in severity in numbness/tingling [208] in the feet over time for 1 year after enrolment.[154] In the latter study, numbness/tingling in the hands peaked after 3 months of treatment and decreased by 1 year after enrolment.[154] The MSAS does not differentiate between numbness/tingling in the hands and feet, however it captured the peripheral neuropathy associated with oxaliplatin treatment.

Addressing patients' perceived severe and distressing symptoms might provide valuable information for clinicians to assist and improve QoL outcomes. When the symptoms remain underdiagnosed and undertreated, they might have a negative impact on QoL.[188] Symptoms are often modifiable, and providing interventions

aiming to improve symptoms might positively improve QoL. Problems with interest in sex were also associated with impaired mental QoL in the present study. Intimate relationships have an important role in reducing the risk of depressive symptoms.[209] Psychological distress can adversely affect sexual activity and body image.[210] Despite the reduced levels of worrying over time, the psychological symptom burden (MSAS PSYCH) was associated with impaired physical QoL throughout the treatment trajectory. Providing patients with coping strategies to manage long-term stressors, e.g., physical exercise and mindfulness, might help them adjust better psychologically.[211]

Co-occurring symptoms might trigger other symptoms negatively, impact negatively on functional performance, cognitive status, and QoL,[190] and interfere with daily life.[212] Symptom management in cancer patients is challenging, as the symptoms are most often influenced by one another and present in clusters.[99,190] Fatigue, has previously been found in an emotional cluster with depression.[153] In addition to fatigue, sleep disturbance, and pain has been described as a symptom cluster.[213] For patients in the outpatient setting, only focusing on one single symptom at a time might increase risk of other symptoms developing or worsening because of the prolonged time between every clinical visit.[99] The complexity of the symptoms makes it challenging to achieve symptom control and provide effective interventions [190] in the outpatient setting.

Symptom burden and QoL and associated factors

Younger patients were more at risk of severe worrying, lack of energy, and impaired mental QoL than older patients (Paper III). An explanation for these age differences can be that younger cancer patients may experience their disease differently than older cancer patients.[214] Younger patients might have worse financial problems and more limitations in their social and role functioning.[149] Greater symptom burden among younger patients is supported in another recently published study assessing newly diagnosed cancer patients.[186] Another explanation for the age differences is the likelihood that younger patients might receive more aggressive treatment. They might be responsible for children, or in a stage in life where life-threating disease is not expected to occur which results in uncertainty with the future.

Gender differences were also observed, and women were at greater risk of worrying, nausea, and impaired mental QoL than men. Increased prevalence of nausea in women has been observed in previous studies in CRC patients.[199,215] In a recently published study assessing diverse cancer patients, higher symptom scores were found among women in almost all assessed symptoms compared with men,[186] with the addition of the cross-sectional study in adjuvant CRC patients with more severe symptoms in women compared with men.[89]

Reduced performance status, as shown by the KPS, was associated with greater severity in worrying, lack of energy, nausea, and pain in this thesis research. However, it is unclear whether the symptoms impaired the performance status or vice versa. Previous research has shown that poorer performance status results in poorer QoL outcomes,[175] greater psychological distress, anxious preoccupation and hopelessness.[211] When previous findings and those of this thesis are summed up, they suggest that attention should be given to patients with reduced performance status to help to control their symptoms and improve their QoL.

Chemotherapy might be associated with poorer QoL in CRC patients.[175] However, a significant association was observed in this cohort only in patients receiving oxaliplatin, who also reported more severe numbness/tingling. Patients' experience of numbness/tingling was associated with impaired physical QoL. These findings are consistent with those of previous research showing that numbness/tingling was associated with functional impairment and reduced QoL,[68,154,216,217] which interfered with daily activities [102] and reduced enjoyment of life.[218] Given the lack of effective treatment for numbness/tingling, it is important to assess this symptom and its severity systematically and to modify the chemotherapy dose when needed (dose limitation).[208,219]

Symptom dimensions
One strength of the MSAS is the comprehensive characterization of a symptom assessed according to several dimensions. Symptom dimensions are important in the comprehensive symptom assessment in clinical setting [100] and provide information about symptoms that are important to patients.[220] The most frequently occurring symptoms are not always the severest or those causing patients the most distress[66];

for example, problems with interest in sex observed in the present study. The same patient might also respond differently to the same drugs used in different chemotherapy cycles, and the MSAS adds important information about how severity and/or distress changes over time. The MSAS does not differentiate (weight) the importance of the 32 symptoms. However, symptoms can mean different things to different patients and can affect life differently. For a patient working as a neurosurgeon or pianist, a severity score of 2 for numbness/tingling may be very distressing and have a greater effect than other symptoms such as hair loss. Difficulty sleeping might be distressing for patients who do not have the opportunity to rest during the day. Each symptom dimension correlates differently with QoL,[100] and distress is the symptom dimension that provides the most information about the relationship between symptoms and QoL.[100]

Self-report in the clinical setting

To capture the patients' real experience of a symptom, PROMs provide clinicians with valuable information from the patients' perspective.[14,114,188] Use of PROMs is the standard method for finding out about patients' experiences, which is helpful for alleviating symptoms,[221] to prioritize patients' needs,[191] and perhaps to improve survival in cancer patients.[188] Self-report of symptoms also contributes positively by improving communication [155,221] and the experience, efficiency, and outcomes of care by engaging patients during their treatment.[188] Self-report has also been shown to improve patient satisfaction.[221] It seems that the process of self-assessment has a positive effect on QoL.[222]

Patient-reported outcome measures can be used to examine the effectiveness of interventions. A number of validated symptom assessment tools are available to evaluate multiple symptoms. The ESAS is a tool commonly used in clinical settings,[223] and is a "simple and useful method for the regular assessment of symptom distress in the palliative care setting" because it assesses symptoms "right now". [224] Given the lack of a standardized tool, other PROMs used in studies of CRC patients include the EORTC QoL questionnaires, [143,148,211,225,226] the MSAS,[66,105,200] and SF-12.[144,164,227] However, the use of PROMs in the clinical setting is not useful without follow-up strategies. It is important to use methods

that can ensure an easy and quick response to, and management of, symptoms,[14] to allow both patients and their caregivers access to the results.[114]

To reduce symptom severity and distress, it is suggested to provide the patients with greater confidence in coping, communication, and managing their daily activities, personal lives, and self-efficacy.[89] Self-efficacy is strongly associated with reduced symptom severity and distress. Self-efficacy in turn, is an important factor because it influences the patients to self-manage their symptoms.[89]

Theoretical framework of the study

The TOUS theoretical framework was used to guide the development of research questions and hypotheses in the present study.[99] The TOUS focuses on self-reported symptoms, how symptoms interact, and how factors influence the symptom dimensions. This model was useful because it clearly shows the complexity and consequences of symptoms. This model was useful for selecting covariates for analysis in the studies included in this thesis. However, the model is not helpful for identifying the most important symptoms or which ones should be prioritized for management.

The CRC patients experienced co-occurring symptoms, and the TOUS shows that, when patients experience multiple symptoms at the same time, "the effect can be more powerful than the sum of the separate symptoms".[228] According to this model, symptoms have a synergistic multiplicative relationship, which means that the occurrence of one symptom can provoke other symptoms. This could explain why treating only one symptom (e.g., difficulty sleeping) is not necessarily effective when the patient is burdened with other symptoms such as pain. In addition, the most frequently occurring symptoms were not always the most distressing in the thesis studies; therefore, it is important to focus on the dimensions of the symptoms shown clearly by the TOUS. The TOUS does not include arrows indication interactions between the different dimensions. Nevertheless, Portenoy et al [100] suggested that the symptoms dimensions are correlated.

Faith or spiritual well-being is not specified as a specific influencing factor in the TOUS, although it has been shown to decrease the level of anxiety and depression and improve QoL in cancer patients.[229] For palliative patients in particular, existential

issues and faith (or spirituality) [220] become more prominent when there is no longer a chance of a cure.[230] Another factor in the TOUS is the patient's coping skills and resources when living with cancer, which can influence performance (outcomes). QoL was selected as an outcome variable in Paper III, although the TOUS does not include QoL as an outcome measure. To conclude, the TOUS has several advantages and was useful for clarifying the complexity of symptom management. Despite its advantages, theories are never static.[147]

Ethical considerations

Research involving cancer patients has ethical considerations. [142] Ethical challenges found in the present thesis are acknowledged here as follows:

- A comprehensive package of 10 questionnaires
- Frequent measurements during the two first chemotherapy cycles
- Many (eight) repetitive measures over a long period of time (6 months)
- Systematic symptom assessment but no systematic follow-up of severe or distressing symptoms
- Use of paper versions of the questionnaires, which required return by post and may have increased the patient burden.

The comprehensive package and frequent measurements over a long period of time might have been an extra burden for the patients. However, evidence suggests that cancer patients are willing to respond to questionnaires despite their high symptom burden and advanced disease.[156] The questionnaires were paper based, meaning that they had to be returned by post, which might have been an additional burden. The patients' responses to the questionnaires were anonymous, and the nurses at the outpatient clinic did not receive any reports or alerts about those patients reporting severe or distressing symptoms. This might have reduced the opportunity to provide symptom management.[188]

Conclusions and clinical implications

The results presented in this thesis may help clinicians identify CRC patients at risk of greater symptom burden and diminished physical and mental QoL throughout the chemotherapy trajectory. The patients included in the present studies had a high

symptom burden the start of chemotherapy. CRC patients have multiple co-occurring symptoms, which underlines the importance of focusing on multiple instead of single symptoms.[99] To detect multiple symptoms experienced by CRC patients, the systematic use of validated questionnaires is essential. In addition, to identify more vulnerable groups of patients, understanding the factors associated with poor QoL throughout the chemotherapy trajectory might be helpful. The observed increase in symptoms after chemotherapy administration is an important finding and suggests the importance of symptom assessment between hospital admissions.

MAIN FINDINGS

- CRC patients experience co-occurring symptoms throughout treatment.
- The most frequently occurring symptoms are not always the severest or most distressing.
- CRC patients experience increased severity of symptoms such as lack of energy, nausea, and numbness/tingling in the days between chemotherapy administrations.
- High symptom burden is associated with impaired physical and mental QoL.
- Being female and younger are both independently associated with higher symptom burden and impaired QoL.
- To achieve optimal care and improve QoL, symptoms should be assessed throughout the continuum of care with the systematic use of self-reported questionnaires.

Clinical implications of this work

This thesis provides clinicians with knowledge based on CRC patients' self-reported symptom burden and QoL during the first weeks of chemotherapy. Facilitating early symptom control might increase patients' ability to complete the treatment without unnecessary postponements and with less detrimental effects on QoL. The self-reporting questionnaires directly involve patients, which might improve their experience and the efficiency of patient care.[188] QoL is an important aspect of health

and life, and assessment of QoL provides valuable information that helps clinicians identify and evaluate the harms caused by treatment.

Outpatient or ambulatory treatment allows patients more time at home and less at the hospital. However, compared with inpatient treatment, with outpatient the responsibility for symptom management transferred to the patients and their family. The results presented here show the need for accessible supportive care services, both inside and outside of the hospital, including home care cancer and supportive services that focus on e.g., nutrition, physical activity, mental health, and social support. Strengthening the collaboration between specialist and different health professions involved in primary care, both within and between the different levels of care in the hospital and at home, is important for ensuring high-quality health care support.[32]

Future areas of research

The results of these studies show the importance of monitoring symptoms that appear during the entire chemotherapy cycle in both curative and palliative outpatients. Even though health-care providers such as doctors and nurses are vital resources for patients with CRC, they are present for only a limited time in the outpatient's life. More detailed knowledge about how best to support outpatients is needed to allow the patient to be an active participant during cancer treatment.

The Norwegian National Cancer Strategy for 2018–2022 is "To live with cancer." The results of this research show that better understanding is needed to find the best ways to organize health care around patients and to strengthen outpatient care during the entire chemotherapy cycle. Oncology health professionals strive to reduce the symptom burden for each patient as much as possible in order to maintain or even increase QoL. However, the symptom burden can increase when patients are home. Intervention studies may identify the best methods to empower patients to take a more active role during their treatment to improve symptom control.[32,231] A previous study has shown that empowerment [232] strengthens patients' self-efficacy, which is important for the coping process.[211]

There is also a need for more studies to understand how to facilitate early implementation of systematic self-reported symptom assessment in a busy outpatient

setting with the aim of being able to identify patients at higher risk for adverse outcomes. This will require studies to identify the most appropriate predictors and indicators of adverse outcomes in CRC patients undergoing outpatient treatment. Also, more explorative studies are needed for further knowledge about how co-occuring symptoms affect each other and to identify symptoms that occur in clusters. Furthermore, intervention studies are needed to identify the best ways to treat multiple symptoms simultaneously.

Another important area is the need to develop and test methods for capturing self-reported information and for providing feedback about this information, especially symptoms, to health professionals, with the aim of improving the management of symptoms and outpatient outcomes.[188] Electronic/digital devices have been recommended for this task,[188] and this may allow health professionals to respond earlier to patients' symptoms to prevent "adverse downstream consequences."[14] One challenge to the use of such technology is the ability to ensure the confidentiality of patients.

Finally, a range of supportive services are now available for cancer patients in Norway; e.g., 'Montebello senteret',[233] free physical fitness studios in "Pusterommet", and "Vardesenteret," which offer courses for symptom management and advice in areas such as nutrition. Despite this range of supportive services and the high number of cancer patients, these services seem not to be fully exploited. Studies are needed to explore the reason for the underuse of these services and whether these valuable resources could be organized differently. Patients often express their resistance to entering the hospital if they do not have to. An interesting and successful concept developed in England is "Maggie's Centre," which offers free, practical emotional and social support to cancer patients close to, but outside, the hospital environment.[234]

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Forkortelser for type rettelser:

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Celtf – endring av sidelayout eller tekstformat

Side	Originaltekst	Type rettelser	Korrigert tekst
xiv	Pasientene opplevede økt intensitetsgrad (kraft) i flere symptomer i dagene etter kjemoterapi.	Corr-korrektur: «opplevde»	Pasientene opplevde økt intensitetsgrad (kraft) i flere symptomer i dagene etter kjemoterapi.
61	Confrontation with a life-threating disease, which implies accommodation to a new life situation, the need for staring or altering chemotherapy, may help explain this finding.	Corr-Korrektur: "starting"	Confrontation with a life-threating disease, which implies accommodation to a new life situation, the need for starting or altering chemotherapy, may help explain this finding.
68	Self-efficacy is strongly associated with reduced symptom severity and distress Self-efficacy in turn, is an important factor because it influences the patients to self-manage their symptoms	Corr-Korrektur: Punktum	Self-efficacy is strongly associated with reduced symptom severity and distress. Self-efficacy in turn, is an important factor because it influences the patients to self-manage their symptoms

II

ORIGINAL ARTICLE

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Symptoms during chemotherapy in colorectal cancer patients

Kari Röhrl[1] · Marianne Grønlie Guren[2] · Milada Cvancarova Småstuen[3,4] · Tone Rustøen[1,5]

Abstract

Purpose Colorectal cancer (CRC) patients experience several physical and psychological co-occurring symptoms, but little is known about symptom variation during chemotherapy cycles. Therefore, the aims were (1) to assess the occurrence and severity of frequently occurring symptoms (worrying, lack of energy, numbness/tingling, nausea, and pain) at multiple time points during chemotherapy, (2) to investigate differences in symptom trajectories between chemotherapy groups, and (3) to determine whether selected patient and clinical characteristics are associated with symptom severity throughout the treatment trajectory.

Methods In total, 120 CRC patients receiving chemotherapy with curative or palliative intent completed the Memorial Symptom Assessment Scale (MSAS), Self-Administered Comorbidity Questionnaire (SCQ-19), and Karnofsky Performance Status (KPS) scale eight times, during two cycles of chemotherapy and 3 and 6 months after enrolment. Data were analyzed using linear mixed models for repeated measures to assess the effects of selected variables on outcomes over time.

Results The patients experienced greatest symptom severity in the days following the administration of chemotherapy; these were *lack of energy*, *numbness/tingling* (oxaliplatin group), and *nausea*. Palliative patients reported significantly higher *pain* scores compared with curative patients over time, whereas the severity of *worrying* decreased over time in both treatment groups. Age, sex, educational level, performance status, treatment intent and type of chemotherapy were significantly associated with symptom severity throughout the chemotherapy trajectory.

Conclusion Clinicians can use these findings to identify and inform patients about risk for more severe symptom burden, in order to offer supportive care at the right time during the chemotherapy treatment.

Keywords Colorectal neoplasm · Chemotherapy · Symptoms · Trajectory · Longitudinal · Memorial Symptom Assessment Scale

Introduction

A significant number of people are living with colorectal cancer (CRC), which accounts for the third most frequent cancer diagnosis worldwide [1]. CRC patients experience a high symptom burden already early in the treatment phase [2, 3] followed by a range of physical and psychological co-occurring symptoms during the chemotherapy trajectory [4]. Co-occurring symptoms are reported to catalyze each other [5], however without systematic symptom assessment with Patient-Reported Outcome Measures (PROMs) during the chemotherapy cycles, symptoms are at risk of not being detected [6, 7]. Previous research has shown that patients report lowest levels of symptoms at the day of chemotherapy [7] whereas chemotherapy triggers the need of unplanned visits to the general practitioners or hospital in the days following chemotherapy [8].

Treatment for CRC includes surgery, which is the mainstay of curative treatment and is often supplemented with radiotherapy or chemotherapy. Patients operated for colon cancer stage III are recommended adjuvant chemotherapy, either 5-fluorouracil (5FU)-based therapy or in combination with oxaliplatin [9, 10]. Patients receiving palliative chemotherapy for stage IV disease usually receive combination regimens with 5FU and oxaliplatin or irinotecan, or 5FU monotherapy,

✉ Kari Röhrl
  Kari.rohrl@medisin.uio.no

1 Department of Nursing Science, Institute of Health and Society, Faculty of Medicine, University of Oslo, P.O.Box 1130, Blindern, Oslo, Norway

2 Department of Oncology and K.G. Jebsen Colorectal Cancer Research Centre, Cancer Medicine, Oslo University Hospital, Oslo, Norway

3 National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital, Oslo, Norway

4 Faculty of Health Sciences, Oslo Metropolitan University, Oslo, Norway

5 Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway

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often combined with targeted therapy, and often several lines of chemotherapy until disease progression or toxicity [11].

Chemotherapy is commonly given in cycles, which compromises the days of chemotherapy administration (often over 1–3 consecutive days) followed by a period without treatment (at home) before the next cycle. Insight into the self-reported symptoms and their severity are of importance to give the best supportive care during treatment [12, 13]. Knowledge about the symptoms occurrence and severity during and between chemotherapy cycles is almost non-existing in CRC outpatients.

Each chemotherapy regimen has a distinct toxicity profile. A well-known side effect of oxaliplatin is peripheral neuropathy [10, 14, 15] which increases with cumulative dose [16], is often dose-limiting, and may persist after treatment cessation [15, 16]. Irinotecan and 5FU can cause gastrointestinal toxicity such as diarrhea [10]. Other common side effects of chemotherapy include neutropenia, nausea, difficulty sleeping [2, 17, 18], cognitive impairment of attention and memory [19], and lack of energy [2, 20–22]. The disease itself may also cause pain [3, 21, 23].

Frequent symptom assessments during treatment increase the chance of capturing symptom fluctuations [6, 7, 24]. In a review of multiple co-occurring symptoms in CRC patients receiving chemotherapy, only five studies used a multidimensional symptom assessment instrument [21]. Of these, one studied CRC patients receiving second-line palliative chemotherapy with a longitudinal design and found that moderate to severe fatigue was the most common symptom, whereas pain and nausea improved slightly over time [18]. Symptom burden at enrolment was reported to be a predictor of symptom burden during chemotherapy; however, no specification of assessment times were reported [18]. Other longitudinal studies of CRC patients have assessed few or single symptoms and have reported increasing fatigue and depression [22] and decreasing level of anxiety [15, 25] over the course of chemotherapy, and persisting neuropathy after chemotherapy [15]. Small study samples and assessment of only a single or few symptoms [15, 22, 25] limit the conclusions about symptom experience that may be drawn from these studies. In a recently published longitudinal study of gastrointestinal cancers, the symptoms varied across the course of chemotherapy [4]. However, the time of assessment did not follow the chemotherapy cycle and therefore does not demonstrate possible symptom severity between the chemotherapy cycles [7, 8].

Based on the knowledge gap of multiple symptoms during, and in the days following chemotherapy administration in CRC outpatients, the aims of the present study were (1) to assess prospectively the occurrence and severity of symptoms (worrying, lack of energy, numbness/tingling, nausea, and pain) at multiple time points during two chemotherapy cycles, and at 3 and 6 months; (2) to investigate the differences in symptom trajectories between the chemotherapy groups (patients receiving 5FU, irinotecan/5FU, or oxaliplatin/5FU); and (3) to determine whether selected demographic and clinical characteristics are associated with symptom severity during the chemotherapy trajectory.

Methods

Study procedures

The present study is part of a larger longitudinal study of symptom clusters and quality of life (QoL) in oncology patients ($N = 534$) (Clinicaltrials.gov, NCT00769301) [3, 26]. Patients with CRC who were scheduled to receive outpatient chemotherapy at Oslo University Hospital were included in the present study ($n = 120$). Eligible patients received information about the study from the research nurse, and informed consent was obtained from all participants.

The patients completed the self-assessment questionnaires before chemotherapy (T1), after 3 (T2) and 7 days (T3), and before the second chemotherapy cycle (T4), after 3 (T5) and 7 days (T6), at 3 (T7) and 6 months (T8) (Fig. 1). The enrolment questionnaires were completed before initiation of the first chemotherapy cycle, and questionnaires for the next five measurements were given to the patients. For the last two measurements, the questionnaires were sent to the patients' home address along with an addressed, stamped return envelope. The study nurse telephoned the patients at T2–T6 to remind them to complete the questionnaires.

Patients

Patients were eligible for inclusion if they were ≥ 18 years of age, scheduled to start a new chemotherapy regimen for CRC, and were able to read and write Norwegian. Patients with brain metastases or diseases affecting their cognitive ability were excluded.

Data collection

Demographic and clinical characteristics

The patients completed a questionnaire on demography including age, sex, marital/cohabitation status, care of children, occupation, sick leave, and level of education. Height and weight were measured and body mass index (BMI) calculated. Information of disease, stage, and treatment was obtained from the medical records, and the treatment intent was registered as either curative or palliative. Information about survival was obtained from the medical records.

Multiple symptoms To measure multiple symptoms, the Memorial Symptom Assessment Scale (MSAS) was used.

Fig. 1 Timeline of data collection over 6 months' chemotherapy
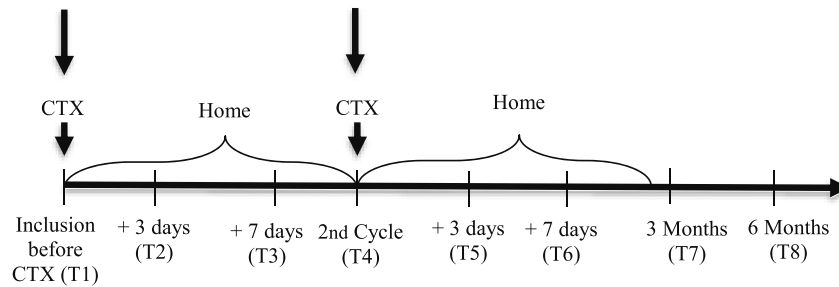
Abbreviations: CTX= chemotherapy; T1 = at enrolment; T2 and T3 = 3 days and 7 days after initiation of the first chemotherapy cycle; T4 = before chemotherapy administration at the second cycle; T5 and T6 = 3 days and 7 days after initiation of the second chemotherapy cycle; T7 = 3 months after enrolment; T8 = 6 months after enrolment

MSAS contains of 32 physical and psychological cancer or treatment symptoms and three optional symptoms [27]. For each symptom, patients were asked to indicate whether they had the symptom during the past week (i.e., occurrence), and to rate its frequency, severity, and distress. Symptom severity (1 = slight, 2 = moderate, 3 = severe, 4 = very severe) were rated using four-point scales. Only occurrence and severity were used in the present study. The reliability and validity of the MSAS are satisfactory [27], and the MSAS has been used previously in CRC patients [2, 4] and other Norwegian cancer patients [26].

The symptom selection was based on the following: worrying and lack of energy were the two most occurring symptoms previously reported in the current patient group [3]; numbness/tingling and nausea are known side effects of chemotherapy, and pain is a common and distressing symptom and often underreported [17, 23]. Symptom severity was only presented for the five abovementioned symptoms.

Comorbidity

The Self-Administered Comorbidity Questionnaire (SCQ-19) comprises 16 common and three optional comorbidities [28]. The total number of comorbidities registered (0–19) was used in the analyses. The SCQ-19 has well-established validity and reliability in patients with cancer [28] and has been used previously to assess comorbidity in Norwegian cancer patients [26].

Performance status

The performance status was self-assessed using the Karnofsky Performance Status (KPS) scale with scores ranging from 40 (i.e., disabled, requires special care and assistance) to 100 (i.e., normal no complaints, no evidence of disease). The KPS scale is used extensively and has well-established validity and reliability in cancer patients [29].

Data analysis

Descriptive statistics are used to present the demographic and clinical characteristics. Continuous variables are described with median and range, and mean and standard deviation (SD) (when normally distributed), and categorical data as proportions and percentages.

To analyze possible differences between treatment groups after adjusting for possible confounders, and using worrying, lack of energy, numbness/tingling, nausea, and pain as outcomes, linear mixed models (LMMs) for repeated measures were fitted. The outcome variable for each of the selected symptoms on MSAS was constructed as follows: If a patient reported not having a symptom, the symptom severity was coded as zero. If the patients rated severity > 0 despite reporting "no" on symptom occurrence, they were coded as having the symptom. When a patient reported having a symptom and a level of severity, this level was used as a category in the new combined occurrence/severity variable. Thus, the new symptom variable score ranged from 0 (no symptom) to 4 (the highest possible level of severity).

An unstructured covariance matrix was used to model dependencies among measurements for the same individual at different time points to accommodate the uneven spacing between measurements when fitting LMM. Individual differences at enrolment were accounted for by a random intercept parameter. To test whether possible confounders affected the results, the LMMs were adjusted for covariates measured at enrolment (sex, age, educational level (primary/secondary school or high school/university), treatment intent (curative or palliative), primary tumor site (colon or rectum cancer), type of chemotherapy (three groups), metastatic sites (0 or ≥ 1), SCQ score (0 or ≥ 1 comorbidities, and KPS)), and status as fixed effects. An interaction term between time (measurement time point) and type of chemotherapy (group 1 = 5FU, group 2 = irinotecan/5FU, and group 3 = oxaliplatin/5FU (reference)) was added to evaluate whether the symptom * time trajectories developed differently among the groups. The covariates were selected based on previous research

and clinical considerations and tested together in the same model for each symptom.

The LMM provides estimates using all available data; thus, no imputation of missing data was considered necessary. The results are presented as p values for the overall effects of the variables when taking the time from the inclusion scores and all seven additional time points into consideration. The results are also presented as point estimates of the regression parameter beta with 95% confidence interval (CI). Our analyses were considered exploratory; thus, no correction for multiple testing was made. For all tests, a two-sided p value $< .05$ was considered statistically significant. Analyses were performed using IBM SPSS Statistics version 23 (Armonk, NY: IBM Corp).

Results

Patient and disease characteristics

A total of 134 patients were approached; 125 provided informed consent and agreed to participate, 120 completed the enrolment questionnaires and were included in the analyses, and 88 completed all eight assessments. Their demographic and clinical characteristics are presented in Table 1. The median age was 65 years, 39% were women, and 44% were retired. The median number of comorbidities (SCQ) was 2.0 (range 0–8), most commonly hypertension (31%). Median BMI was 25 kg/m^2 (range 16–38).

Curative chemotherapy was scheduled for 68 (57%) patients (adjuvant or neoadjuvant) and palliative chemotherapy for 52 (43%) (Table 1). The primary tumor was in the colon for 72% of the patients and in the rectum for 28%, and liver was the predominant metastatic site. Patients received 5FU monotherapy (17%), irinotecan/5FU combination (23%) or oxaliplatin/5FU combination (60%) regimens. Three patients received bevacizumab or cetuximab in combination with irinotecan.

At the last assessment (T8), 47 patients (39%) were alive with no evidence of disease, 41 (34%) with stable disease, and 21 (18%) with progression of disease. Five (4%) patients had died. Six patients withdrew consent before the last assessment (T8).

Symptom occurrence during chemotherapy

The occurrence rates at all assessment times for worrying, lack of energy, numbness/tingling, pain, and nausea are presented in Table 2. Worrying was the most occurring symptom at enrolment, and lack of energy at 6 months. Lack of energy, numbness/tingling, and nausea showed a peak in occurrence in the days and week after each chemotherapy administration and lower prevalence before start of the next chemotherapy. Worrying and pain declined in occurrence during the 6-month treatment. The occurrence rates for all 32 MSAS symptoms at all eight assessments are shown in Appendix Table 4.

Symptom severity during chemotherapy

When adjusted for selected covariates, the patients reported the greatest severity of *worrying* at enrolment and decreased with time (Table 3; Fig. 2). *Lack of energy* increased in severity 3–7 days after each chemotherapy cycle (Table 3, Fig. 2). *Numbness/tingling* increased in severity 3–7 days after each cycle; however, this symptom also increased markedly with time for oxaliplatin-based chemotherapy (Table 3; Fig. 2). *Nausea* was markedly worst on day 3 of each cycle among the chemotherapy groups (Table 3; Fig. 2). There were no significant changes in severity scores for *pain* with time (Table 3; Fig. 2).

Worrying

In the adjusted analyses, the severity score for *worrying* did not differ significantly between the chemotherapy groups, treatments groups, or according to educational level (Table 3). Women scored higher on *worrying* than men ($B = 0.35$, 95% CI [0.02–0.68], $p = .04$). Age was significantly associated with *worrying*, with the highest score among the youngest ($B = -0.02$, 95% CI [−0.04 to– 0.01], $p = .04$). The patients scored 0.2 points higher on *worrying* for each 10-point decrease in KPS score ($B = 0.24$, 95% CI [0.12–0.34], $p < .01$).

Lack of energy

In the adjusted analyses, *lack of energy* did not differ between the chemotherapy groups (Table 3). Women scored higher on *lack of energy* than men ($B = 0.30$, 95% CI [0.02–0.58], $p = .04$). Age was significantly associated with *lack of energy*, with the highest score among the youngest ($B = -0.02$, 95% CI [−0.03 to − 0.01], $p = .03$). Palliative patients scored significantly higher on *lack of energy* ($B = 0.33$, 95% CI [0.01–0.66], $p = .05$) compared with curative patients. The patients scored 0.04 points higher on *lack of energy* for each 10-point decrease in KPS score ($B = .43$, 95% CI [0.03–0.05], $p < .01$).

Numbness/tingling

In the adjusted analyses, patients receiving oxaliplatin scored significantly higher on *numbness/tingling* compared with those receiving 5FU ($B = 0.55$, 95% CI [0.19–0.90], $p < .01$) or irinotecan ($B = 0.76$, 95% CI [0.43–1.10], $p < .01$) (Table 3; Fig. 2). Men scored higher on *numbness/tingling* compared with women ($B = 0.22$, 95% CI [−0.01–0.44], $p = .05$). *Numbness/tingling* was scored significantly higher in patients with low educational level ($B = 0.26$, 95% CI [0.03–0.49], $p = .03$).

Table 1 Patient and clinical characteristics at enrolment in colorectal cancer patients ($n = 120$) scheduled to receive chemotherapy

	Number	Percent	Median (range)	Mean (SD)
Age, years			64.7 (33–80)	62.8 (10.2)
Sex				
Male	73	60.8		
Female	47	39.2		
Cohabitation				
Living alone	38	31.9		
Living with someone	81	68.1		
Educational level				
Primary/secondary	68	58.0		
College/university	50	42.0		
Occupation				
Part-/full-time work	9	8.3		
On sick leave	51	47.2		
Retired	48	44.4		
Treatment intent				
Curative	68	56.7		
Palliative	52	43.3		
Primary tumor site				
Colon	86	72.3		
Rectum	33	27.7		
Previous treatment				
Surgery	93	77.5		
Chemotherapy	34	28.3		
Radiotherapy	18	15.0		
Metastasis at enrolment	69	57.5		
Metastatic sites[a]				
Liver	54	45.0		
Lung	25	20.8		
Lymph nodes	25	20.8		
Peritoneum	10	8.3		
Other	10	8.3		
Type of chemotherapy				
5FU[b] monotherapy	20	16.7		
Irinotecan/ 5FU	28	23.3		
Oxaliplatin/5FU	72	60.0		
Karnofsky Performance Status[b]			90 (60–100)	

Some frequencies do not account up to full sample size of $n = 120$ due to missing numbers

5FU fluorouracil, *SD* standard deviation

[a] Metastasis could be present at more than one site

[b] Karnofsky Performance Status range 60 (requires occasional assistance, but able to care for most of his needs)–100 (normal no complaints)

Nausea

In the adjusted analyses, the severity of *nausea* did not differ significantly between the chemotherapy groups. There was a peak in severity scores on day 3 after each chemotherapy cycle (Fig. 2). Women scored significantly higher on *nausea* compared with men ($B = 0.27$, 95% CI [0.05–0.49], $p = .02$). The patients scored significantly 0.2 points higher on *nausea* for each 10-point decrease in KPS score ($B = 0.02$, 95% CI [0.01–0.03], $p = .01$).

Pain

In the adjusted analyses, pain did not differ significantly between the chemotherapy groups with time (Table 3).

Table 2 Occurrence rates for the five selected symptoms at each assessment point

Assessment time Study population (n)	T1 120	T2 116	T3 112	T4 110	T5 108	T6 103	T7 98	T8 88
Symptoms	%	%	%	%	%	%	%	%
Worrying	65.0	55.8	52.5	47.5	49.2	48.3	35.8	35.8
Lack of energy	59.2	71.7	65.8	60.8	65.0	63.3	64.2	53.3
Numbness/tingling	22.5	40.8	35.0	30.8	45.8	46.7	43.3	48.3
Nausea	28.3	61.7	52.5	35.8	51.7	54.2	43.3	29.2
Pain	50.8	49.2	45.0	37.5	35.8	35.0	34.2	33.3

T1 = at enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle before chemotherapy; T5 = 3 days after 2nd chemotherapy; T6 = 7 days after 2nd chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

Palliative patients scored significantly higher on *pain* ($B = 0.45$, 95% CI [0.11–0.79], $p = .01$) compared with curative patients. The patients scored 0.3 points significantly higher on *pain* for each 10-point decrease in KPS score ($B = 0.03$, 95% CI [0.23–0.45], $p < .01$).

Clinical characteristics with no significant effect on symptom trajectories

Cohabitation, marital status, care of children, tumor site (colon or rectum), number of metastatic sites, and the presence of comorbidities (SCQ) had no significant effect ($p > .05$) on the symptom trajectory for any of the analyzed symptoms *worrying*, *lack of energy*, *numbness/tingling*, *nausea*, or *pain* (data not shown).

Discussion

This study reports the occurrence and severity of self-reported physical and psychological co-occurring symptoms at defined time points during chemotherapy for CRC. The patients reported the highest symptom severity scores for *lack of energy*, *numbness/tingling* (oxaliplatin group), and *nausea* in the days following chemotherapy. Palliative patients reported higher *pain* scores than the curative patients with time, whereas the severity of *worrying* was reduced with time in all patient groups. Lower performance status was associated with increased symptom burden.

Symptoms during chemotherapy

Lack of energy, *numbness/tingling*, and *nausea* showed increased symptom severity in the days and week after each

Table 3 The effect of the covariates on five selected symptoms ($n = 120$) measured at enrolment

Source/covariates	Dependent variables									
	Worrying		Lack of energy		Numbness/tingling		Nausea		Pain	
	F	p value	F	p value	F	p value	F	p value	F	p value
Time	2.32	.03	3.83	< .01	7.22	< .01	3.74	< .01	1.30	.26
Chemotherapy group [a]	0.06	.94	1.54	.22	12.60	< .01	0.71	.49	1.71	.19
Treatment intent [b]	1.43	.24	4.06	< .05*	0.29	.59	3.01	.09	6.84	.01
Age	4.36	.04	4.60	.03	1.18	.28	0.98	.33	0.11	.74
Sex [c]	4.53	.04	4.55	.04	3.93	.05	5.99	.02	0.27	.61
Performance status (KPS)	14.97	< .01	67.79	< .01	1.71	.19	17.84	< .01	37.49	< .01
Education group [d]	0.01	.95	0.33	.57	5.14	.03	0.61	.44	0.37	.55
Time × chemotherapy group	0.65	.81	1.61	.09	3.90	< .01	1.18	.31	1.17	.31

italics = $p < .05$

F F-test

*p value = .04

[a] Chemotherapy group = fluorouracil (5FU) monotherapy, irinotecan/5FU, oxaliplatin/5FU (reference)

[b] Treatment intent = curative or palliative (reference)

[c] Men as reference; education group

[d] Primary/secondary (reference) and college/university

Worrying

Lack of energy

Numbness tingling

Nausea

Pain

Chemotherapy regimen
— 5FU
····· Irinotecan/5FU
– – – Oxaliplatin/5FU
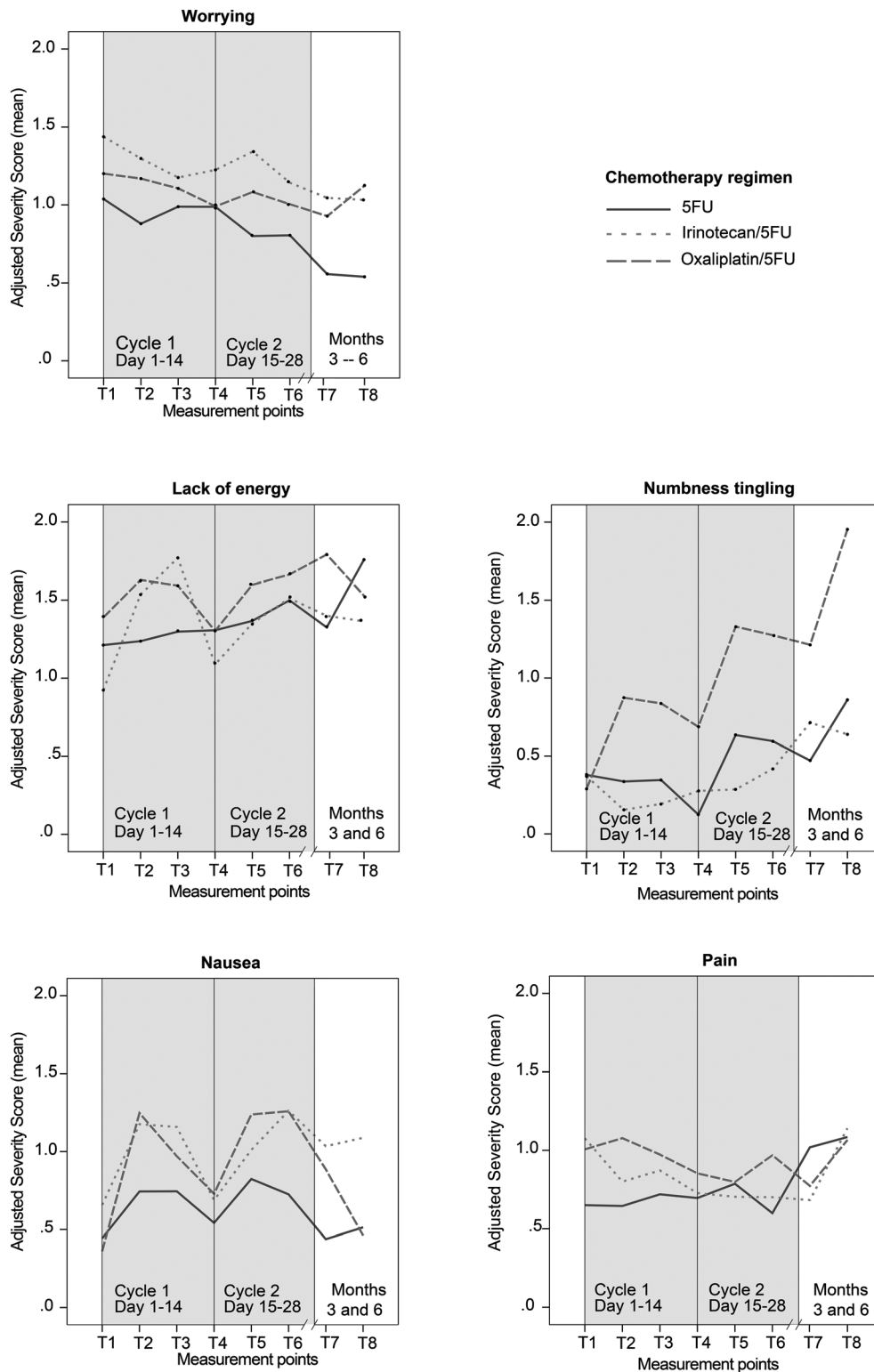
Abbreviations: T1 = at enrollment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle, chemotherapy given after assessment; T5 = 3 days after 2nd chemotherapy; T6 = 7 days after 2nd chemotherapy; T7 = 3 months after enrollment; T8 = 6 months after enrollment

Fig. 2 Graphs presented for each symptom: Worrying, lack of energy, numbness/tingling, nausea, and pain (adjusted for time, chemotherapy groups, treatment intent, age, sex, KPS, educational groups)

chemotherapy administration, followed by a decrease in severity toward the start of the next cycle (Fig. 2).

A progressive worsening of *lack of energy* with time is supported in previous studies with cancer patients [7] as well as for CRC patients [22]. *Lack of energy*, a proxy for fatigue on the MSAS [4], is one of the most frequent [2, 3, 14, 17, 20, 22] and severe reported symptoms by CRC patients [2, 3, 14]. *Fatigue* occurs during all treatment phases and is often more prominent as the disease worsens [20] with negative impact on QoL [30]. Reducing symptoms that interact with *fatigue* [14, 20, 22, 31] might help to alleviate *fatigue*. Despite limited evidence supporting the use of pharmacological agents to treat *fatigue*, physical activity has been shown to have a positive effect [20].

Numbness/tingling worsened significantly with time in patients receiving oxaliplatin in the present study. Cumulative neuropathy is a well-known side effect of oxaliplatin [14–16] may cause *pain* [23], chronic neuropathy, and impaired QoL [15]. Awareness of neuropathy is important in order to make the necessary dose reductions. The increased severity levels of *nausea* 3 and 7 days after chemotherapy administration were unexpected and raises the question whether adequate antiemetic regimens were prescribed, in particular for late-onset nausea. Recent guidelines for the prevention of chemotherapy-induced nausea [32] recommend a regimen with serotonin receptor antagonists and corticosteroids for 2–3 days, which was the institutional practice. In a European multicenter study, 45% of the cancer patients were inadequately treated for *nausea* [33]. In another study including metastatic CRC patients, > 10% reported moderate to severe *nausea* [14]. *Nausea* is one of the most distressing chemotherapy side effects [32], and *nausea* occurrence rates > 50% was found at multiple time point during the treatment in the present study (Table 2). Systematic symptom assessment at multiple time points may aid clinicians to offer improved supportive care at the right time to these patients.

Anxiety is suggested to be a proxy for *worrying* [34]. *Worrying* became less severe as the time from enrolment progressed. This is consistent with previous research in CRC patients with the highest anxiety scores found in the early treatment phase [2, 3, 25], with gradual decrease over time [25]. An adaption to the situation or social and psychological support might reduce the anxiety levels [25].

No significant differences were found for *pain* with time. One might speculate that regular chemotherapy administration facilitates adequate analgesic treatment. In addition, the efficacy of chemotherapy in metastatic disease can result in less *pain* from metastatic lesions because of tumor shrinkage [27]. However, the pain occurrence rates were high at enrolment (51%) [35]. The fluctuations in symptom severity highlight the importance of regular self-reported symptom assessment [7, 18, 36] with correct timing and duration of assessments to capture the true symptom burden in outpatients with CRC [6, 8]. Symptoms often occur simultaneously [3, 21, 34] and are likely to catalyze each other resulting in a vicious circle of symptoms [5]. Symptom assessment may even be beneficial in terms of increased survival [36].

Differences in symptoms between chemotherapy groups

Patients receiving 5FU monotherapy reported less severe symptom scores than patients receiving combination chemotherapy regimens. As expected, we found a significant increase in the severity of *numbness/tingling* in patients receiving oxaliplatin. Oxaliplatin are shown to cause peripheral neuropathy shortly after chemotherapy and increases with cumulative doses [10, 14].

Demographic and clinical characteristics associated with symptom severity

Severity scores for *lack of energy* and *pain* was higher in palliative compared with curative patients. More severe disease, higher disease burden, and the presence of metastases [23] among palliative patients might be one explanation. Being younger and female was associated with more severe *worrying*, *lack of energy*, and *nausea*. In addition, lower performance status was associated with higher severity scores in most of the analyzed symptoms and combined with multiple symptoms shown to be a predictor for hospitalization [8].

Limitations and strength

The study has some limitations. There was no "true" baseline because some patients had received previous chemotherapy. Comorbidity was patient-reported. Advanced stratification analyses were not performed due to the limited number of patients, although the number of patients was considered adequate for the exploratory study design. The patient sample was restricted to CRC outpatients, and these results might not be generalizable to other cancer types or treatments.

The strengths of the present study include the use of reliable, validated, and multidimensional PROMs completed at multiple defined time points during the treatment, which enabled a comprehensive symptom severity assessment.

Conclusion

In this study, we explored symptoms at several time points during chemotherapy cycles. We found highest symptom severity in the days following chemotherapy

administration, in particular lack of energy, nausea, and numbness/tingling for patients receiving oxaliplatin. Clinicians can use this knowledge of symptom fluctuations to offer improved symptom management at the right time. Covariates like age, sex, performance status, educational level, and type of chemotherapy were associated with symptom severity. Therefore, we recommend using PROMs in routine oncology practice to capture the changes in symptom burden [12, 13] and to ensure the day-to-day symptom control in outpatients.

Compliance with ethical standards

The Regional Ethical Committee (2009/1451), the Hospital Privacy Ombudsman, and the institutional review board at Oslo University Hospital approved the study.

Conflict of interest The authors declare that they have no conflict of interest.

Appendix A

Table 4 Occurrence rates of 32 symptoms from the memorial symptom assessment scale (MSAS) in the total study population (n = 120) over 6 month treatment trajectory

Assessment time study population (n)	T1 120	T2 116	T3 112	T4 110	T5 108	T6 103	T7 98	T8 88
MSAS symptom								
Worrying	65.0	55.8	52.5	47.5	49.2	48.3	35.8	35.8
Lack of energy	59.2	71.7	65.8	60.8	65.0	63.3	64.2	53.3
Pain	50.8	49.2	45.0	37.5	35.8	35.0	34.2	33.3
Numbness/tingling in hands/feet	22.5	40.8	35.0	30.8	45.8	46.7	43.3	48.3
Nausea	28.3	61.7	52.5	35.8	51.7	54.2	43.3	29.2
Lack of appetite	34.2	49.2	45.8	35.8	40.0	42.5	26.7	25.0
Feeling drowsy	54.2	65.8	58.3	51.7	55.8	56.7	59.2	44.2
Difficulty sleeping	50.0	48.3	47.5	41.7	44.2	40.0	38.3	35.0
Diarrhea	25.0	34.2	37.5	34.2	35.0	36.7	35.0	26.7
Problems with sexual interest	34.2	40.8	35.0	28.3	34.2	31.7	38.3	31.7
Feeling bloated	53.3	55.8	50.0	44.2	49.2	47.5	40.0	39.2
Feeling irritable	20.8	25.8	26.7	21.7	24.2	21.7	18.3	18.3
Sweats	30.8	35.8	26.7	25.0	27.5	20.0	25.8	21.7
Difficulty concentrating	37.5	44.2	45.8	37.5	40.0	41.7	37.5	35.8
Constipation	22.5	38.3	33.3	27.5	35.0	32.5	27.5	24.2
Problems with urination	12.5	17.5	13.3	11.7	12.5	13.3	9.2	10.8
Feeling sad	41.7	49.2	45.0	34.2	40.8	37.5	36.7	25.0
Dry mouth	33.3	41.7	40.8	40.8	38.3	43.3	43.3	35.0
Feeling nervous	42.5	38.3	33.3	30.8	30.0	31.7	20.8	22.5
Cough	23.3	31.7	30.0	30.0	21.7	26.7	22.5	16.7
Itching	19.2	20.8	15.0	19.2	17.5	20.8	11.7	15.0
Shortness of breath	21.7	27.5	27.5	21.7	25.8	26.7	28.3	21.7
Dizziness	20.8	32.5	28.3	23.3	28.3	27.5	27.5	24.2
Weight loss	25.8	30.0	30.0	25.8	26.7	30.0	14.2	18.3
Food tastes different	18.3	32.5	32.5	23.3	35.8	41.7	35.8	29.2
Changes in skin	14.2	16.7	15.8	17.5	21.7	24.2	22.5	22.5
"I do not look like myself"	10.0	15.8	14.2	15.0	21.7	17.5	17.5	14.2
Swelling of arms or legs	8.3	7.5	8.3	5.8	9.2	9.2	9.2	7.5
Mouth sores	4.2	12.5	17.5	16.7	19.2	26.7	15.8	15.8
Vomiting	7.5	12.5	10.0	8.3	19.2	17.5	14.2	6.0
Hair loss	10.0	6.7	8.3	11.7	13.3	16.7	26.7	21.7
Difficulty swallowing	5.0	15.0	12.5	10.0	15.8	14.2	13.3	6.7

T1 = At enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = at second cycle before chemotherapy; T5 = 3 days after 2nd chemotherapy; T6 = 7 days after 2nd chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

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III

High Symptom Burden is Associated With Impaired Quality of Life in Colorectal Cancer Patients During Chemotherapy -A Prospective Longitudinal Study

Kari Röhrl, RN, MPH; Marianne Grønlie Guren, MD, PhD; Guro Lindviksmoen Astrup, RN, PhD; Milada Cvancarova Småstuen, PhD; Tone Rustøen, RN, PhD

Author Affiliations: Faculty of Medicine, Institute of Health and Society, Department of nursing science, University of Oslo, Oslo, Norway (Röhrl, Rustøen); Department of Oncology, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway (Röhrl, Guren, Astrup); K.G. Jebsen Colorectal Cancer Research Centre, Division of Cancer Medicine, Oslo University Hospital, Oslo, Norway (Guren); Research Support Services, Oslo University Hospital, Oslo, Norway (Astrup); National Advisory Unit on Late Effects after Cancer Treatment, Oslo University Hospital, Oslo, Norway (Småstuen); Oslo Metropolitan University, Faculty of Health Sciences, Oslo, Norway (Småstuen); Department of Research and Development, Division of Emergencies and Critical Care, Oslo University Hospital, Oslo, Norway (Rustøen)

Correspondence

Kari Röhrl

Department of Oncology, Division of Cancer Medicine,

Oslo University Hospital,

Kirkeveien 166, 0450 Oslo,

Norway

Phone: + 47 230 26600

Fax: + 47 230 26601

Email: kari.rohrl@medisin.uio.no

Abstract

Context. Multiple symptoms can have a negative impact on quality of life (QoL), but there is little information about the impact of multiple symptoms on QoL of patients with colorectal cancer (CRC) during outpatient chemotherapy.

Objectives. To assess the physical and mental QoL in CRC patients over six months of chemotherapy, to evaluate the association of QoL with the presence of multiple symptoms, and to determine which demographic and clinical characteristics are associated with physical and mental QoL scores.

Methods. Outpatients with CRC (N = 120) completed the Medical Outcomes Study Short Form (SF-12) and Memorial Symptom Assessment Scale (MSAS) at eight time points during six months of chemotherapy. Linear mixed models for repeated measures were used to analyse QoL over time; and its association with demographic and clinical characteristics; and with the presence of multiple symptoms e.g., 'numbness/tingling' and 'problems with sexual interest'.

Results. The CRC patients had worse physical and mental QoL scores than the general population at all-time points. Impaired physical QoL was significantly associated with psychological symptom burden ($P < 0.001$) and numbness/tingling ($P < 0.027$). Impaired mental QoL was associated with physical symptom burden ($P < 0.001$), with being female ($P < 0.009$), younger age ($P < 0.024$), and having problems with sexual interest ($P < 0.009$).

Conclusions. Impaired QoL was associated with symptoms in CRC outpatients. This information about the symptoms and characteristics associated with worse QoL during chemotherapy may help clinicians identify and inform at-risk patients.

Key Words

Colorectal cancer; quality of life; chemotherapy; MSAS; symptoms

Running title

Quality of life in colorectal cancer patients

Introduction

Colorectal cancer (CRC) is the third most common cancer in the Western world (Arnold et al., 2017). Its incidence is increasing and is expected to increase further because of population ageing (Arnold et al., 2017). Improvements in surgical techniques and the development of more effective chemotherapeutic regimens have had positive impacts on survival, both in terms of increased overall survival rates and prolonged survival time for metastatic CRC (Benitez Majano et al., 2019; Van Cutsem et al., 2016). However, both the disease and its treatments have potential impacts on patients' quality of life (QoL) (Domati et al., 2015; Kaasa et al., 2018; Schmoll et al., 2012). Surgery is the most important curative treatment, combined with additional radiotherapy for patients with rectal cancer; and with chemotherapy for patients with colon cancer and/or resectable metastatic disease (Schmoll et al., 2012; Van Cutsem et al., 2016). For patients with non-curable metastatic CRC, chemotherapy is the primary treatment (Van Cutsem et al., 2016). The treatment goals of chemotherapy of CRC may therefore be cure, reduction of the risk of recurrence, or prolongation of survival, alleviation of symptoms and maintenance or improvement of QoL (Kaasa et al., 2018). Therefore, assessment of QoL and symptoms is important for the evaluation of treatment efficacy and its impact (Basch et al., 2016; Cabilan & Hines, 2017; Kaasa et al., 2018).

Previous research has identified that the factors associated with reduced QoL in CRC patients; are being female (Gray et al., 2011; Reyes et al., 2017), having stage IV disease (Reyes et al., 2017), increased systemic inflammatory markers, and mutated tumours (Thomsen et al., 2017). Findings regarding the impact of having a stoma on CRC patients are inconsistent (Bruheim, Guren, Skovlund, et al., 2010; Gray et al., 2011; Nasvall et al., 2017), varying from its having a negative impact on QoL (Gray et al., 2011; Nasvall et al., 2017), to

not having any significant impact (Bruheim, Guren, Skovlund, et al., 2010). Other symptoms such as neuropathy have been shown to have a negative impact on QoL for years following chemotherapy (Tofthagen et al, 2013). Systematic assessment (Basch et al., 2016; Rohrl, Guren, Smastuen, & Rustoen, 2019), using self-reported questionnaires is important to identify symptoms that are severe or distressing for patients (Pettersson et al 2014; Rohrl et al., 2019; Tantoy et al, 2016) and also to improve symptom management (Papachristou et al., 2018). However, symptoms may go undetected if assessments are not performed several days after chemotherapy administration (Giesinger et al., 2014). Assessment of symptoms only at the start of chemotherapy cycles probably underestimates the true symptom burden (Giesinger et al., 2014) because side effects from treatment are often worse in the days immediately after chemotherapy (Foltran et al., 2014; Rohrl et al., 2019), and/or fluctuate over time (Rohrl et al., 2019). The optimal assessment frequency is unknown (Tantoy et al., 2018), although important changes in QoL (Giesinger et al., 2014; Mayrbaurl et al., 2016) and symptoms (Rohrl et al., 2019) may be missed if there is only one assessment or there is too long between assessments. Longitudinal studies using repeated symptom measures in CRC patients undergoing chemotherapy, are scare (Domati et al., 2015; Hung et al, 2013; Mayrbaurl et al., 2016; Thomsen et al., 2017). The studies that we identified assessed the patients either before the start of treatment (Domati et al., 2015; Hung et al., 2013; Thomsen et al., 2017), or at the beginning of each cycle (Mayrbaurl et al., 2016). In patients receiving adjuvant chemotherapy, worse QoL scores were reported one (Hung et al., 2013) and three months, after initiation of cancer treatment (Domati et al., 2015; Hung et al., 2013), whereof as an improvement in QoL was demonstrated six months after completion of chemotherapy (Domati et al., 2015; Hung et al., 2013). CRC patients undergoing palliative treatment (stage IV) experienced a deterioriation in QoL over time (Hung et al., 2013; Mayrbaurl et al., 2016), as did patients with mutated tumours (Thomsen et al., 2017). These previous studies used a

range of instruments to assess QoL, including Short Form-36 (SF-36) (Domati et al., 2015; Ware, Kosinski, & Keller, 1996), European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C30) (Aaronson et al., 1993; Thomsen et al., 2017), and Functional Assessment of Cancer Colorectal module (FACT-C) (Hung et al., 2013; Ward et al., 1999). Direct comparisons between studies are difficult because of the differences in assessment time points, the heterogeneous population and the variability in QoL instruments. To our knowledge, no studies have assessed multiple symptoms and QoL in CRC patients with repetitive measures during the same chemotherapy cycle.

Because of the relatively limited knowledge the study aims were twofold: first, to assess changes in physical and mental QoL in CRC patients at defined time points during two chemotherapy cycles and after three and six months; and second, to investigate which demographic and clinical characteristics, and selected psychological and physical symptoms, are associated with physical and mental QoL scores during chemotherapy.

Methods

Study Population and Design

This prospective study was part of a larger study (Clinicaltrials.gov, NCT00769301) of symptoms and QoL in cancer outpatients with different cancer diagnoses (n = 534) (Astrup et al., 2017). Only patients diagnosed with colon or rectal cancer (n=120) were eligible for inclusion, if they were scheduled for either their first chemotherapy or a new chemotherapy regimen, were ≥18 years of age and could read and write Norwegian. Participants were recruited from the outpatient clinic at the Department of Oncology, Oslo University Hospital, Norway. Exclusion criteria were having brain metastases or a disease that affected their cognitive abilities. The patients were assessed at eight time points during chemotherapy; T1–

T3 (cycle 1), T4–T6 (cycle 2), T7 (3 months), and T8 (6 months) (Fig.1). These time points were selected based on previous research, clinical experience, and the duration of the chemotherapy cycles, which were administered every second week (Schmoll et al., 2012). Patients received detailed information about the study from a study nurse before the start of chemotherapy. The patients completed the first package of questionnaires prior to the first chemotherapy cycle and received the questionnaires for the following five measurements while they were in the outpatient clinic. The questionnaires for the last two measurements were sent to each patient's home address, along with a pre-addressed, stamped return envelope. The study nurse made telephone reminder calls before study time points T2–T6. The patients completed a questionnaire about their demographic characteristics (e.g. cohabitation status, care of children, employment status, and level of education). Age, sex, disease, and treatment information were obtained from the patients' medical records.

Ethics

The Regional Ethical Committee (2009/1451), the Hospital Privacy ombudsmann, and the Institutional Review Board at Oslo University Hospital approved the study. The study was performed in accordance with the Declaration of Helsinki. All patients provided written informed consent.

Short Form-12

QoL was measured with the Medical Outcomes Study Short Form-12 (SF-12) version 1 (Ware et al., 1996), a self-administered QoL instrument. This quesionnaire consists of 12 items, which are summarized to a physical component summary (PCS) score and a mental component summary (MCS) score (Gandek et al., 1998). The PCS and MCS were scored using norm-based methods from the 1998 U.S. general population with scores transformed to a mean of PCS 50 and standard deviation (SD) of 10. Scores >50 indicate better QoL than the

U.S. general population and scores <50 indicate worse QoL than the general population. The scores from the Norwegian population, have a mean PCS 50.3 (SD 8.8) and a mean MCS 50.6 (SD 9.9), and therefore are similar to those for the U.S. population (Gandek et al., 1998). The SF-12 has been used in CRC populations (Reyes et al., 2017) and has well-established validity and reliability (Gandek et al., 1998).

Memorial Symptom Assessment Scale

The Memorial Symptom Assessment Scale (MSAS) is a self-administered questionnaire covering 32 physical and psychological cancer-related symptoms (Portenoy et al., 1994), with multiple dimensions. Symptom occurrence was measured based on the patient's experience of the symptom during the past week (yes/no), while symptom frequency (1 = rarely to 4 = almost constant), severity (1 = slight to 4 = very severe) and distress (0 = not at all to 4 = very much) were measured using Likert scales. If the patient ticked 'no' for occurrence, but selected >0 on the other symptom dimensions, they were coded as having the symptom.

The MSAS physical (MSAS-PHYS) and MSAS psychological (MSAS-PSYCH) subscales were used for the present study (Portenoy et al., 1994). The MSAS-PHYS subscale is the average of all dimensions for 12 symptoms: lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness. The MSAS-PSYCH subscale is the average of all dimensions for six symptoms: feeling sad, worrying, feeling irritable, feeling nervous, difficulty sleeping, and difficulty concentrating. The MSAS symptoms 'numbness/tingling' and 'problems with sexual interest or activity' (abbreviated as MSAS sexual problems herein) are not included in the original MSAS subscales (Portenoy et al., 1994). Based on their high occurrence; and severity and the distress scores previously reported in this patient cohort (Rohrl et al., 2016;

Rohrl et al., 2019), the scores for these symptoms at enrolment were included as covariates. MSAS has well-established reliability and validity (Portenoy et al., 1994) and has been used previously in CRC patients (Hung et al., 2013; Pettersson et al., 2014; Tantoy et al., 2017).

Karnofsky Performance Status

The patients' physical functioning was assessed using the Karnofsky Performance Status (KPS) scale (Schag, Heinrich, & Ganz, 1984). Because treatment was administered in an outpatient setting, KPS scores ranged from 40 (disabled, requires special care and assistance) to 100 (normal, no complaints, no evidence of disease). The KPS scale has been used in CRC populations (Tantoy et al., 2017) and has well-established validity and reliability (Schag et al., 1984).

Self-Administered Comorbidity Questionnaire

The Self-Administered Comorbidity Questionnaire (SCQ-19) was used to assess self-reported medical conditions. It consists of 16 common and three optional comorbidities (Sangha et al,. 2003). The total number of comorbidities (occurrence) recorded at enrolment (range 0–19) was used in the current analyses. The SCQ-19 was used to categorize the patients into three groups: no comorbidity, 1–2 comorbidities, or ≥3 comorbidities. The SCQ has established validity and reliability (Sangha et al., 2003), and has been used in previous studies to assess comorbidities in cancer patients (Oksholm et al., 2015; Tantoy et al., 2017).

Statistical analyses

Descriptive statistics were used to present the sample's demographic and clinical characteristics. Continuous data are presented as mean and standard deviation (SD) when normally distributed, skewed variables are described using median and range, and categorical data are presented as percentages. Both PCS and MCS scores were treated as continuous

dependent variables. Linear mixed models (LMM) were fitted with unstructured covariance matrices to account for dependencies between measurements for the same individual at all eight measurements. LMM were used to assess changes in PCS and MCS scores over time and to assess possible associations with selected covariates. Covariates measured at enrolment included: sex, age, education, cohabitation status, treatment intent, type of chemotherapy, presence of stoma, previous surgery, radiotherapy or chemotherapy, comorbidity and performance status, and occurrence of numbness/tingling or sexual problems assessed by MSAS. Covariates varying over time included MSAS-PHYS and MSAS-PSYCH symptom subscales. All covariates were selected based on both a thorough literature search and our clinical experience. The covariates were initially examined in univariate analyses; only those that were statistically significant ($P < 0.05$) were entered into multivariable models. Time was entered as a categorical variable with baseline measurement as a reference. To reduce the risk of collinearity, two separate LMM models were fitted. The first model (physical QoL) used PCS score as the dependent variable and assessed associations with sex, age, SCQ-19, and MSAS-PSYCH score, MSAS sexual problems and numbness/tingling. KPS and MSAS-PHYS were omitted prior to the multivariate analyses because of their strong correlations with the PCS score; ($r = 0.67$). The second model (mental) used MCS as the dependent variable and assessed associations with sex, age, previous surgery, KPS, MSAS-PHYS score, and MSAS sexual problems. MSAS-PSYCH was omitted prior to the multivariate analyses because of its strong correlation with the MCS score ($r = 0.70$). The instruments used were scored according to the scoring manual for each instrument, including the handling of missing data. The LMM uses all available data in the dataset; in addition to the estimate for the included covarites to estimate the covariance structure and model the dependencies. All tests were two-sided and P values < 0.05 were considered significant. All analyses were performed using IBM SPSS Version 24.0 (IBM Corp., Armonk, NY).

Results

The patients' flow chart for the recruitment of patients and their compliance is presented in Fig. 2. There were no significant differences in any demographic or clinical characteristics between those who completed and those who did not complete the final questionnaires at six months. At the final assessment, 39% of the participants had no evidence of disease.

Demographic and Clinical Characteristics and Symptoms at Enrolment

The demographic and clinical characteristics of the participants are shown in Table 1. Their median age was 65 years (range 33–80 years), and they were mainly male (61%) and Caucasian (99%). The majority had their primary tumour in the colon (72%), and were scheduled for primary treatment (73%) with curative intent (57%). Overall, 32% of the patients reported ≥3 comorbidities at enrolment, with hypertension being the most common (31%). Patients received either 5-fluorouracil (5-FU) monotherapy, irinotecan in combination with 5-FU, or oxaliplatin in combination with 5-FU. Three patients additionally received bevacizumab or cetuximab in combination with irinotecan. No significant differences were detected between patients commencing chemotherapy, and those starting a new regimen because of recurrence or progression. At enrolment, the patients reported a mean MSAS-PHYS score of 0.69 (SD = 0.6) and a mean MSAS-PSYCH score of 0.84 (SD = 0.8). A complete overview of the 32 symptoms reported on MSAS by this cohort at enrolment (Rohrl et al., 2016) and over time has been previously reported.(Rohrl et al., 2019)

Physical QoL During Chemotherapy

The unadjusted mean PCS scores over time are depicted in Fig. 3. These scores were worse than those of the general population (i.e. below 50) at all time points. Time was

significantly associated with unadjusted PCS (P = 0.005), with a significant increase from enrolment (T1) to T4 (P = 0.028). No significant changes were detected at any of the other assessment time points. The adjusted demographic and clinical variables and associations between symptoms and PCS scores over time are presented in Table 2. There was a significant association between PCS scores and MSAS-PSYCH scores (–3.12, P < 0.001), with better physical QoL in those with fewer psychological symptoms. The PCS scores were also significantly associated with numbness/tingling scores, with better physical QoL in those without numbness/tingling. When results were also adjusted for selected covariates (sex, age, comorbidity, MSAS-PSYCH score, MSAS sexual problems and MSAS numbness/tingling), a significant effect of time on PCS score was observed (P = 0.012), with an increase of 2 units in PCS score prior to the second chemotherapy cycle (T4) compared with the score at enrolment (B = 1.74, 95% confidence interval (CI) [0.13–3.35], P = 0.03). No significant changes were identified at any of the other assessment time points.

Mental QoL During Chemotherapy

As shown in Fig. 3, the unadjusted mean MCS scores at all time points were worse than those of the general population. The unadjusted MCS scores did not change significantly between enrolment and any of the time points (P = 0.41). The demographic and clinical variables and symptoms associated with the MCS scores are presented in Table 3. There was a statistically significant association between sex and MCS, with men reporting better MCS scores than women. Also, there was a significant association between age and MCS scores, with older patients reporting better psychological scores. A significant negative association was found between physical symptoms (MSAS-PHYS) and MCS scores, with patients with more physical symptoms having lower MCS scores (-5.82, P <0.001). Finally, a significant negative association was identified between MSAS sexual problems and MCS; patients with

sexual problems had lower psychological scores. When the results were adjusted for the selected covariates (sex, age, previous surgery, KPS, MSAS-PHYS score and MSAS sexual problems), a significant effect of time on MCS was identified (P=0.015). An increase of 3.6 units in MCS compared with that at enrolment was found for time points T1 to T5 ($B = 3.60$, 95% CI [1.09–6.12], P=0.005) and an increase of approximately 4 units for time points T1 to T7 ($B = 4.01$, 95% CI [0.71–7.32], P = 0.018).

Discussion

This prospective study provides additional knowledge about the trajectory of physical and mental QoL in CRC outpatients undergoing chemotherapy. The CRC patients had worse physical and mental QoL scores than the general population at all time points. Impaired physical and mental QoL were significantly associated with a higher symptom burden.

Physical QoL During Chemotherapy

In the present study, the participants' mean PCS score of 44 at enrolment was lower than the population norm. Over 77% of participants had undergone surgery prior to in the present study, so postoperative symptoms, e.g., pain (Gustafsson et al., 2019) may have reduced their physical QoL at enrolment. It was somewhat surprising that the physical QoL was not further reduced during chemotherapy. This finding may be related to our use of the generic assessment tool SF-12, which may be less sensitive to changes than a cancer-specific tool (Aaronson et al., 1993; Mayrbaurl et al., 2016; Thomsen et al., 2017). The improvement observed in PCS between enrolment and the day of the second dose of chemotherapy (T4) is probably explained by the timing of this measurement on the day furthest from chemotherapy, so patients may have recovered from the acute side effects of chemotherapy (Giesinger et al., 2014). Indeed, time had a small but significant effect on physical QoL after controlling for the

covariates. Previous studies have also reported changes in QoL over time in CRC patients (Domati et al., 2015; Hung et al., 2013; Mayrbaurl et al., 2016; Thomsen et al., 2017). In patients with metastatic CRC, disease progression with accompanying additional symptom burden is a common cause of deterioration in QoL over time (Mayrbaurl et al., 2016; Reyes et al., 2017). One limitation of the present study was the inclusion of both patients starting first-line chemotherapy and those starting a new chemotherapy regimen related to disease progression or recurrence; these two groups may have experienced QoL differently. However, we did not find any significant differences in either physical or mental QoL between patients starting primary chemotherapy and those changing their chemotherapy regimen, or between patients undergoing curative or palliative treatment. Impaired physical QoL in this study was associated with psychological symptoms. The previously reported high psychological symptom burden at enrolment (worrying 65% and sleep disturbance 50%) (Rohrl et al., 2016), might explain this impact on the physical components of QoL. Furthermore, numbness/tingling (experienced with oxaliplatin chemotherapy), had an impact on physical QoL, as has also been previously reported in CRC survivors (Mols et al., 2013; Soveri et al., 2019; Tofthagen et al., 2013). However, studies assessing the association between neuropathy and QoL during chemotherapy are scarce, and further research is needed (Soveri et al., 2019).

Mental QoL During Chemotherapy

In the present study, the participants' mean MCS score of 46 at enrolment was lower than the population norms. Receiving a cancer diagnosis or being in the early phase of treatment might provoke high levels of worrying (Pettersson et al., 2014; Rohrl et al., 2016) which negatively affects mental QoL. In the present study, we found improvement in the adjusted mental QoL at time points T5 and T7 compared with the levels at enrolment. The difference was relatively small, and may not be of clinical relevance. However, it could be

that the patients found that the treatment procedures had become more predictable. Some studies show an improvement in emotional functioning or mental QoL during chemotherapy (Hung et al., 2013; Mayrbaurl et al., 2016), while others show a worsening of mental health over time in patients receiving palliative chemotherapy (Domati et al., 2015; Hung et al., 2013).

In the present study there was a negative association between increased physical symptoms and mental QoL; this has also been previously reported (Gray et al., 2011). Awareness of the patients' symptoms by clinicians' thorough chemotherapy is important for the detection and anticipation of patients' changing needs (Basch et al., 2016), and to prevent a reduction of QoL (Basch et al., 2016; Gray et al., 2011).

In the present study, men reported better mental QoL than women. However, it is inconclusive whether there is a possible difference in mental QoL between the sexes. Our findings support the results of several previous studies (Gray et al., 2011; Reyes et al., 2017), although Domati et al., (Domati et al., 2015) did not find any sex-related differences. In addition, the mean difference of 3.95 points in MCS score seen in our study may be of little clinical relevance. Thus, it is difficult to draw conclusions from these findings.

We observed that mental QoL was better in older patients than in younger, which corroborates the results of a previous study of CRC patients (Reyes et al., 2017). Younger patients are described as being more vulnerable to change because of their responsibilities for children/family and financial difficulties (Farkkila et al., 2013; Quinten et al., 2015). Family distress has been shown to be associated with a reduction in mental QoL (Sun et al., 2012). Career demands and loss of role function might also contribute to reducing mental QoL in younger patients. An interesting finding of the present study was the association between mental QoL and sexual problems. Sexual problems have previously been reported as a severe and distressing symptom in this patient cohort during treatment (Rohrl et al., 2016; Rohrl et

al., 2019), and as a highly prevalent symptom among CRC patients (Ekholm et al., 2013; Farkkila et al., 2013; Pettersson et al., 2014; Sun et al., 2012), yet this topic is rarely addressed in clinical studies (Traa et al., 2012). Problems with intimacy, high levels of worrying, pain, or fatigue (Rohrl et al., 2016), or sequelae after surgery (Bruheim, Guren, Dahl, et al., 2010) might explain some of these findings.

Strengths and Limitations

The strengths of the present study include the longitudinal design that assessed only CRC patients at defined time points during their chemotherapy cycles, using several validated self-reported questionnaires. The use of instruments assessing physical and mental symptoms, including sexual problems and numbness/tingling, provided information about the impact of symptoms on QoL, and insight into patients' physical and mental QoL over time. The use of a generic rather than a disease-specific instrument may have reduced our ability to detect changes in QoL over time, although SF-12 is recommended as a generic QoL assessment tool in CRC patients (Wong et al., 2015). There was an overlap in the recall time (i.e.,from the present to last week) of the questionnaires because of the frequent measurements, which could have 'blurred' the longitudinal changes in QoL. Further, there was no 'real' baseline, because some patients (28%) had undergone chemotherapy prior to study enrolment; however, no significant differences were found between the two patient groups. Chemotherapy toxicities can be cumulative, and the variations in treatment trajectory and chemotherapy regimens might affect our findings. We did not perform any correction for multiple testing because we regarded our study as exploratory; therefore, our results must be confirmed in future studies. There may have been conceptual overlaps between the measures because we used several questionnaires to address our research questions. However, the main aim of our study was to

learn more about the relationship between physical and mental symptoms and QoL, and it was necessary to use different questionnaires to accommodate this aim.

Conclusion

CRC patients' are affected by chemotherapy, which leads to impaired physical and mental QoL. QoL is associated with both physical and psychological symptom burden. Clinicians could use these results to identify patients to allow them to offer the best quality cancer care at the right time (Basch et al., 2016; Giesinger et al., 2014), and targeting their treatments to the associated symptoms relevant to this patient group. Systematic symptom assessment reduces the risk of underestimation of the symptom burden and its impact on QoL, and increases opportunities to detect fluctuations in QoL over the treatment course (Domati et al., 2015; Hung et al., 2013; Mayrbaurl et al., 2016; Walker et al., 2012).

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Legends for Tables and Figures

Table 1 Colorectal Cancer Patients' Demographic and Clinical Characteristics at Study Enrolment (N = 120)

Table 2 Variables Associated with Short Form-12 Physical Component Summary Score over Time using Linear Mixed Models of Fixed Effects (N = 120)

Table 3 Variables Associated with Short Form-12 Mental Component Summary Score over Time using Linear Mixed Models of Fixed Effects (N = 120)

Figure 1 Timeline of data collection during two chemotherapy cycles and at 3 and 6 months after enrolment in colorectal cancer patients

Figure 2 Patient inclusion and compliance

Figure 3 Short Form-12 physical component summary scores and Short Form-12 mental component summary scores at enrolment and over six months of chemotherapy in colorectal cancer patients (boxes show unadjusted mean values for PCS and MCS at each time point)

Table 1. Demographic and Clinical Characteristics of Colorectal Cancer Patients at Study Enrolment (n = 120)

	Median	Range
Age (years)	64.7	33–80
Number of comorbidities (0–19)	2.0	0–8
Performance status (KPS)	90	60–100

Characteristics	n	%
Sex		
Male	73	61
Female	47	39
Cohabitation		
Living alone	38	32
Living with someone	81	68
Education		
Primary/secondary	68	58
College/university	50	42
Occupation		
Part/full-time work	9	8
On sick leave (part/full-time)	51	43
Disability benefit	12	10
Retired	48	40
Site of primary tumour		
Colon	86	72
Rectum	33	28
Treatment intent		
Curative (neoadjuvant)	68 (19)	57 (16)
Palliative	52	43
Treatment status		
Primary	88	73
Recurrence/progression	32	27
Metastasis present at enrolment [a]	69	57
Metastatic sites		
Liver only	24	20
Lung only	3	3
Lymph nodes only	3	3
Peritoneum only	2	2
Multiple sites	37	31
Type of chemotherapy		
5FU monotherapy	20	17
Irinotecan/5FU	28	23
Oxaliplatin/5FU	72	60
Patients with stoma	19	16

Abbreviations: 5FU, 5-fluorouracil; KPS, Karnofsky Performance Status

Footnotes: a Metastasis could be present at more than one site; some frequencies do not add up to the full sample size of n = 120 because of missing values.

Table 2. Variables Associated with Short Form-12 Physical Component Summary Score over Time using Linear Mixed Models with Fixed Effects (n = 120)

Variables	Estimate	95% CI	P-value
Sex (men/women)	-1.22	-4.70 to 2.26	0.487
Age (years)	0.10	-0.08 to 0.28	0.274
Comorbidity (0 reference)			
1-2 comorbidities	-0.81	-5.10 to 3.47	0.706
≥3 comorbidities	-4.23	-9.04 to 0.57	0.084
MSAS-PSYCH score	-3.12	-4.23 to -2.00	**< 0.001**
MSAS sexual problems (yes/no)	-1.01	-2.44 to 0.43	0.123
MSAS numbness/tingling (yes/no)	-1.34	2.53 to 0.16	**0.027**

Abbreviations: CI, confidence interval; Comorbidity, Self-Administered Comorbidity Questionnaire-19; MSAS, Memorial Symptom Assessment Scale; MSAS numbness/tingling, MSAS question regarding numbness/tingling; MSAS sexual problems, MSAS question regarding problems with sexual interest or activity.

Footnotes: Reference categories: Comorbidity, no comorbidities; MSAS numbness/tingling, yes occurrence; MSAS sexual problems, yes occurrence; sex, men; MSAS-PSYCH, MSAS psychological subscale, the average of the dimensions (occurrence, frequency, severity and distress) of six mental symptoms: feeling sad, worrying, feeling irritable, feeling nervous, difficulty sleeping, and difficulty concentrating.

Table 3 Variables Associated with Short Form-12 Mental Component Summary Score over Time using Linear Mixed Models with Fixed Effects (n = 120)

Variables	Estimate	95% CI	P-value
Sex (men/women)	3.95	1.01 to 6.89	**0.009**
Age (years)	0.16	0.02 to 0.31	**0.024**
Previous surgery (yes/no)	3.36	0.11 to -6.82	0.058
Karnofsky Performance Status	0.06	-0.00 to 0.12	0.063
MSAS-PHYS score	-5.82	-8.04 to -3.59	**< 0.001**
MSAS sexual problems (yes/no)	-1.85	0.46 to 3.25	**0.009**

Abbreviations: CI, confidence interval; MSAS-PHYS score, Memorial Symptom Assessment Scale physical score; MSAS sexual problems, Memorial Symptom Assessment Scale question regarding problems with sexual interest or activity.

Footnotes: Reference categories: MSAS sexual problems, yes occurrence; previous surgery, yes; sex, men; MSAS-PHYS, MSAS physical symptom subscale, the average of the dimensions (occurrence, frequency, severity, and distress) of 12 physical symptoms: lack of appetite, lack of energy, pain, feeling drowsy, constipation, dry mouth, nausea, vomiting, change in taste, weight loss, feeling bloated, and dizziness.

Fig. 1. Timeline of Data Collection from Colorectal Cancer Patients during two Chemotherapy Cycles and at 3 and 6 Months after Enrolment.

Abbreviations: T1 = at enrolment; T2 and T3 = 3 days and 7 days after initiation of the first chemotherapy cycle; T4 = before chemotherapy administration at the second cycle; T5 and T6 = 3 days and 7 days after initiation of the second chemotherapy cycle; T7 = 3 months after enrolment; T8 = 6 months after enrolment

Fig. 2. Patient Inclusion and Compliance.
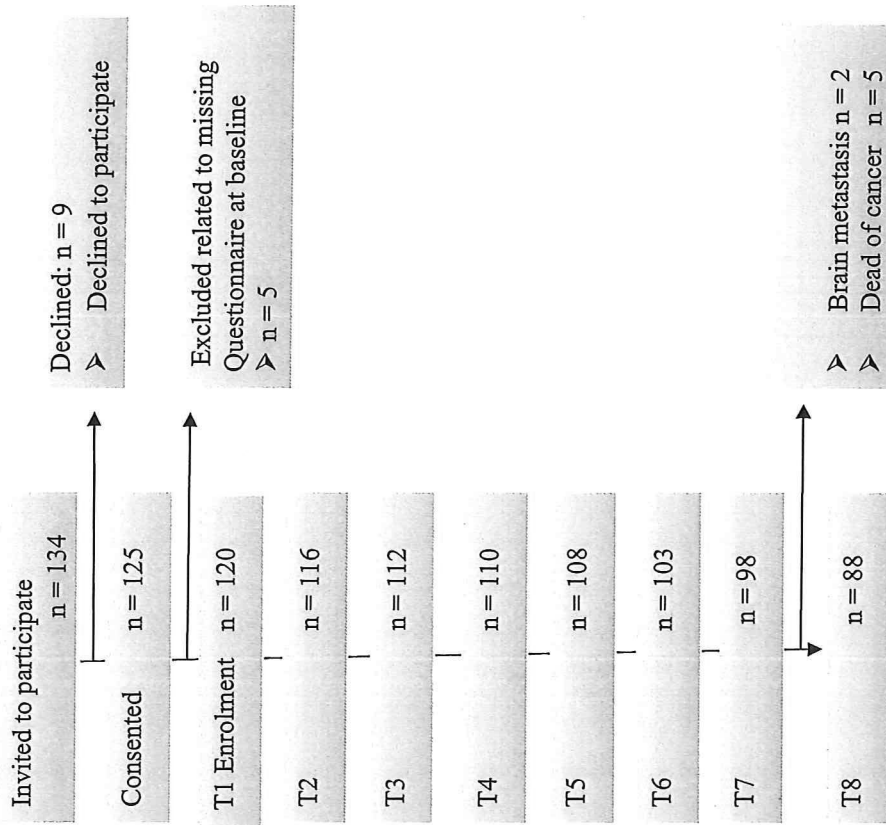
Invited to participate
n = 134

Consented   n = 125

Declined: n = 9
⋏ Declined to participate

T1 Enrolment   n = 120

Excluded related to missing
Questionnaire at baseline
⋏ n = 5

T2   n = 116

T3   n = 112

T4   n = 110

T5   n = 108

T6   n = 103

T7   n = 98

Brain metastasis n = 2
Dead of cancer n = 5
⋏
⋏

T8   n = 88

Abbreviations: T1 = At enrolment before chemotherapy; T2 = 3 days after chemotherapy; T3 = 7 days after chemotherapy; T4 = At second cycle, assessed before chemotherapy; T5 = 3 days after second chemotherapy; T6 = 7 days after second chemotherapy; T7 = 3 months after enrolment; T8 = 6 months after enrolment

Kreftklinikken
RADIUMHOSPITALET

2008 Cluster Studien

"Symptomer hos kreftpasienter i behandling"

Spørreskjemaer til pasienter

R RIKSHOSPITALET

DATO FOR UTFYLLING:

⬜⬜.⬜⬜.⬜⬜⬜⬜
dag   måned   år

BAKGRUNNSOPPLYSNINGER

Vennligst fyll inn eller sett kryss ved det som passer

1. **Kjønn**

   ☐ Mann

   ☐ Kvinne

2. **Hvilket år er du født?**

   ⬜⬜.⬜⬜.⬜⬜⬜⬜
   dag   måned   år

3. **Hva er din sivilstatus?**

   ☐ Ugift

   ☐ Gift / samboer

   ☐ Skilt

   ☐ Enke / enkemann

4. **Hvordan bor du?**

   ☐ Bor alene

   ☐ Bor sammen med noen

5. **Hvor mange barn har du daglig omsorg for?**

   ⬜⬜ antall barn

SNU ARKET!

6. Hvilken utdanning er den <u>høyeste</u> du har <u>fullført</u>?
(sett bare <u>ett kryss</u>)

☐ Grunnskole 7-10 år (framhaldsskole)

☐ Ett- eller toårig videregående skole, yrkesskole, real- eller middelskole

☐ Artium, økonomisk gymnas, 3-årig videregående skole

☐ Universitet og/eller høgskole opptil 4 år

☐ Universitet og/eller høyskole mer enn 4 år

☐ Hvis annet, spesifiser, inkl. hvor mange år

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┌────────────────────────────────┐
│                                │
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7. Er du i arbeid utenfor huset for tiden?
(sett bare <u>ett kryss</u>)

☐ Ja, heltidsarbeid

☐ Ja, deltidsarbeid

☐ Sykemeldt (helt eller delvis)

☐ Uføretrygdet

☐ Alderspensjonert

☐ Arbeidsledig

☐ Hvis annet, spesifiser

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┌────────────────────────────────┐
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TILLEGGSSYKDOMMER (SCQ-18)

Det følgende er en liste over vanlige medisinske problemer.
Sett ett kryss for hvert problem om hvorvidt du har problemet <u>nå</u> (ja eller nei).
Hvis du HAR problemet, så svar på spørsmålene om behandling og aktiviteter
til høyre. Hvis du IKKE HAR problemet, gå videre til neste problem.

Problem	Har du problemet?		HVIS JA: Får du behandling for det?		HVIS JA: Begrenser det dine aktiviteter?	
1. Hjertesykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
2. Høyt blodtrykk	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
3. Lungesykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
4. Diabetes	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
5. Magesår / magesykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
6. Tarmsykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
7. Nyresykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
8. Leversykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
9. Anemi eller annen blodsykdom	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
10. Hodepine	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
11. Depresjon	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
12. Slitasjegikt / artrose	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
13. Rygg / nakkesmerter	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
14. Leddgikt / revmatoid artritt	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
15. Sykdom i bindevev eller muskulatur	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei
16. Hudlidelser	☐ Ja	☐ Nei	☐ Ja	☐ Nei	☐ Ja	☐ Nei

17. Andre medisinske problemer (angi)

	Får du behandling?		Begrenser aktiviteter?	
[_____]	☐ Ja	☐ Nei	☐ Ja	☐ Nei
[_____]	☐ Ja	☐ Nei	☐ Ja	☐ Nei
[_____]	☐ Ja	☐ Nei	☐ Ja	☐ Nei

SNU ARKET!

FUNKSJONSTILSTAND (KARNOFSKY)

Sett <u>ett kryss</u> i den ruten som passer best.

100 ☐ Normal, ingen plager eller subjektive tegn på sykdom

90 ☐ Klarer normal aktivitet, sykdommen gir lite symptomer

80 ☐ Klarer med nød normal aktivitet. Sykdommen gir en del symptomer

70 ☐ Klarer meg selv, ute av stand til normal aktivitet eller aktivt arbeide

60 ☐ Trenger noe assistanse, men klarer stort sett å tilfredsstille egne behov

50 ☐ Trenger betydelig hjelp og stadig medisinsk omsorg

40 ☐ Ufør, trenger spesiell hjelp og omsorg

SYMPTOMLISTE (MSAS)

Veiledning: Vi har listet opp 32 symptomer nedenfor. Les hvert av dem nøye. Hvis du har hatt symptomet i løpet av siste uken, la oss få vite hvor <u>ofte</u> du hadde det, hvor <u>kraftig</u> det var det meste av tiden, og hvor mye det <u>plaget</u> eller <u>bekymret</u> deg, ved å sette ett kryss i den ruten du synes passer best. Hvis du IKKE HAR HATT symptomet, sett ett kryss i den ruten merket HAR IKKE HATT symptomet.

I løpet av den <u>siste uken</u>: Har du hatt noen av de følgende symptomene?	Har ikke hatt symptomet	**Hvis JA:** Hvor ofte hadde du symptomet?				**Hvis JA:** Hvor kraftig var symptomet, det meste av tiden?				**Hvis JA:** Hvor mye plaget eller bekymret symptomet deg?				
		Sjelden	Av og til	Ofte	Nesten hele tiden	Svakt	Moderat	Kraftig	Svært kraftig	Ikke i det hele tatt	Litt	En del	Ganske mye	Svært mye
Vanskelig å konsentrere seg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Smerter	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Har lite energi	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hoste	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Føler meg nervøs	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Tørr i munnen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kvalme	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Søvnig, mye trøtt	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Nummen / prikker i hender / føtter	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Søvnvansker	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Luft i magen / oppblåst	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Problemer med vannlating	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kaster opp	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Kortpustet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Diaré	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Føler meg trist	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Svette	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Bekymrer meg	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Problemer med seksuallyst / aktivitet	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

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SYMPTOMLISTE (MSAS) - del 2

I løpet av den <u>siste uken</u>:

Har du hatt noen av de følgende symptomene?

	Har <u>ikke</u> hatt symptomet	**Hvis JA:** Hvor ofte hadde du symptomet?				**Hvis JA:** Hvor kraftig var symptomet, det meste av tiden?				**Hvis JA:** Hvor mye plaget eller bekymret symptomet deg?				
		Sjelden	Av og til	Ofte	Nesten hele tiden	Svakt	Moderat	Kraftig	Svært kraftig	Ikke i det hele tatt	Litt	En del	Ganske mye	Svært mye
Kløe	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Manglende matlyst	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Svimmel / ør	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vanskelig å svelge	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Føler meg irritabel	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sår i munnen	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Maten smaker annerledes	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Vekttap	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Mistet håret	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Treg mage / forstoppelse	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Hoven i armer og ben	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
"Jeg ser ikke ut som meg selv lengre"	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Forandringer i huden	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Hvis du har hatt noen andre symptomer i løpet av den <u>siste uken</u>, vennligst skriv de opp nedenfor, og angi hvor mye det <u>plaget</u> eller <u>bekymret</u> deg.

		Ikke i det hele tatt	Litt	En del	Ganske mye	Svært mye
Annet:		☐	☐	☐	☐	☐
Annet:		☐	☐	☐	☐	☐
Annet:		☐	☐	☐	☐	☐

SMERTER (BPI)

1. Gjennom livet har de fleste av oss hatt smerter (som lett hodepine, forstuelser eller tannpine).

Har du <u>i dag</u> smerter av et annet slag enn slike dagligdagse smerter?

☐ Ja ☐ Nei   **Hvis NEI, gå til side 10**

2. Vil du skravere de områdene på kroppen hvor du har smerter. Marker med <u>et kryss</u> der du har <u>mest vondt</u>.

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D. Wilkie and K. Puntillo

kke ll t r tene   lles t a st ie r ppen

mest vondt

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3. **Vennligst sett ett kryss i den ruten som best beskriver de sterkeste smertene du har hatt i løpet av de siste 24 timer.**

Ingen smerter	0	1	2	3	4	5	6	7	8	9	10	Verst tenkelige smerter
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

4. **Vennligst sett ett kryss i den ruten som best beskriver de svakeste smertene du har hatt i løpet av de siste 24 timer.**

Ingen smerter	0	1	2	3	4	5	6	7	8	9	10	Verst tenkelige smerter
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

5. **Vennligst sett ett kryss i den ruten som best angir hvor sterke smerter du har i gjennomsnitt.**

Ingen smerter	0	1	2	3	4	5	6	7	8	9	10	Verst tenkelige smerter
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

6. **Vennligst sett ett kryss i den ruten som best angir hvor sterke smerter du har akkurat nå.**

Ingen smerter	0	1	2	3	4	5	6	7	8	9	10	Verst tenkelige smerter
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

7. **Hvilken behandling eller medisiner får du for å lindre smertene dine?**

8. **I hvor stor grad har behandling eller medisiner lindret smertene dine de siste 24 timene? Vennligst sett ett kryss i den ruten med prosenttallet som viser hvor stor smertelindring du har fått.**

Ingen lindring	0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%	Fullstendig lindring
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

Sett ett kryss i den ruten som for de <u>siste 24 timene</u> best beskriver hvor mye smertene har virket inn på:

9. Daglig aktivitet

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

10. Humør

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

11. Evne til å gå

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

12. Vanlig arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

13. Forhold til andre mennesker

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

14. Søvn

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

15. Livsglede

Ikke påvirket	0	1	2	3	4	5	6	7	8	9	10	Fullstendig påvirket
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

SNU ARKET!

SPØRRESKJEMA OM HELSE (SF-12)

INTRODUKSJON: Dette spørreskjemaet handler om hvordan du ser på din egen helse. Disse opplysningene vil hjelpe oss til å få vite hvordan du har det og hvordan du er i stand til å utføre dine daglige gjøremål.

Hvert spørsmål skal besvares ved å sette <u>ett kryss</u> (X) i den ruten som passer best for deg. Hvis du er usikker på hva du vil svare, vennligst svar så godt du kan.

1. **Stort sett vil du si at din helse er:**

   ☐ Utmerket   ☐ Meget god   ☐ God   ☐ Nokså god   ☐ Dårlig

De neste spørsmålene handler om aktiviteter som du kanskje utfører i løpet av en vanlig uke. Er din helse slik at den <u>begrenser deg</u> i utførelsen av disse aktivitetene <u>nå</u>? Hvis ja, hvor mye?

	Ja, begrenser meg mye	Ja, begrenser meg litt	Nei, begrenser meg ikke i det hele tatt
2. **Moderate aktiviteter som å flytte et bord, støvsuge, gå en tur eller drive med hagearbeid**	☐	☐	☐
3. **Gå opp trappen flere etasjer**	☐	☐	☐

I løpet av <u>den siste uken</u>, har du hatt noen av de følgende problemer i ditt arbeid eller i andre av dine daglige gjøremål <u>på grunn av din fysiske helse</u>?

	Ja	Nei
4. **Du har <u>utrettet mindre</u> enn du hadde ønsket**	☐	☐
5. **Du har vært hindret i å utføre visse typer arbeid eller gjøremål**	☐	☐

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I løpet av de <u>siste 4 ukene</u>, har du hatt noen av de følgende problemer i ditt arbeid eller andre av dine daglige gjøremål på grunn av <u>følelsesmessige problemer</u> (som for eksempel å være deprimert eller engstelig)?

		Ja	Nei
6.	**Du har <u>utrettet mindre</u> enn du hadde ønsket**	☐	☐
7.	**Du har utført arbeidet eller andre gjøremål mindre <u>grundig</u> enn vanlig**	☐	☐

8. **I løpet av de <u>siste 4 ukene</u>, hvor mye har smerter påvirket ditt vanlige arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)?**

☐ Ikke i det hele tatt   ☐ Litt   ☐ En del   ☐ Mye   ☐ Svært mye

De neste spørsmålene handler om hvordan du har følt deg og hvordan du har hatt det de <u>siste 4 ukene</u>.
For hvert spørsmål, vennligst velg det svaralternativet som best beskriver hvordan du har hatt det.
Hvor ofte i løpet av de <u>siste 4 ukene</u> har du:

	Hele tiden	Nesten hele tiden	Mye av tiden	En del av tiden	Litt av tiden	Ikke i det hele tatt
9. Følt deg rolig og harmonisk	☐	☐	☐	☐	☐	☐
10. Hatt mye overskudd	☐	☐	☐	☐	☐	☐
11. Følt deg nedenfor og trist	☐	☐	☐	☐	☐	☐

12. I løpet av de <u>siste 4 ukene</u>, hvor mye av tiden har din fysiske helse eller følelsesmessige problemer påvirket din sosiale omgang (som det å besøke venner, slektinger osv.)?

☐ Hele tiden   ☐ Nesten hele tiden   ☐ En del av tiden   ☐ Litt av tiden   ☐ Ikke i det hele tatt

SNU ARKET!

SØVNPROBLEMER (GSDS)

Tenk tilbake på den <u>siste uken</u>. Hvor mange dager har du: *(sett ett kryss i den aktuelle ruten)*

		Aldri							**Hver dag**
1.	Hatt problemer med å sovne	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
2.	Våknet i løpet av søvnperioden	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
3.	Våknet for tidlig og fikk ikke til å sovne igjen	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
4.	Følt deg uthvilt når du våkner på slutten av en søvnperiode	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
5.	Sovet dårlig	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
6.	Følt deg søvnig i løpet av dagen	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
7.	Kjempet for å holde deg våken gjennom dagen	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
8.	Følt deg irritabel i løpet av dagen	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
9.	Følt deg trøtt eller utmattet i løpet av dagen	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
10.	Følt deg tilfreds med søvnkvaliteten	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
11.	Følt deg våken og energisk gjennom dagen	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
12.	Fått for mye søvn	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
13.	Fått for lite søvn	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
14.	Tatt en blund til planlagt tid	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
15.	Sovnet uten at det var planlagt	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
16.	Drukket alkohol for å få til å sovne	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
17.	Brukt tobakk for å få til å sovne	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
18.	Brukt andre stimuli for å sovne (f.eks: avslapping, musikk, lesing)	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
19.	Brukt naturmedisinske midler for å sovne	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
20.	Brukt reseptbelagt sovemedisin for å få til å sovne	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐
21.	Brukt Paracet eller annet smertestillende for å sove	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐

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DEPRESJON (CES-D)

Vennligst sett ett kryss i den ruten som markerer hvor ofte du har følt det slik i løpet av den <u>siste uken</u>.

	Aldri eller nesten aldri (Mindre enn 1 dag i uken)	Litt av tiden (1-2 dager i uken)	En del av tiden (3-4 dager i uken)	Hele eller nesten hele tiden (5-7 dager i uken)
1. Jeg var plaget av ting som vanligvis ikke plager meg	☐	☐	☐	☐
2. Jeg hadde dårlig appetitt	☐	☐	☐	☐
3. Jeg var nedstemt og kunne ikke riste det av meg, til tross for støtte fra familie og venner	☐	☐	☐	☐
4. Jeg følte meg like mye verdt som andre	☐	☐	☐	☐
5. Jeg hadde problemer med å konsentrere meg om det jeg holdt på med	☐	☐	☐	☐
6. Jeg følte meg deprimert	☐	☐	☐	☐
7. Jeg følte at alt var et ork	☐	☐	☐	☐
8. Jeg så lyst på framtiden	☐	☐	☐	☐
9. Jeg tenkte at livet mitt hadde vært mislykket	☐	☐	☐	☐
10. Jeg følte meg engstelig	☐	☐	☐	☐
11. Jeg sov urolig	☐	☐	☐	☐
12. Jeg følte meg lykkelig	☐	☐	☐	☐
13. Jeg var mer taus enn vanlig	☐	☐	☐	☐
14. Jeg følte meg ensom	☐	☐	☐	☐
15. Folk var uvennlige	☐	☐	☐	☐
16. Jeg satte pris på livet	☐	☐	☐	☐
17. Jeg gråt	☐	☐	☐	☐
18. Jeg følte meg trist	☐	☐	☐	☐
19. Jeg følte at folk mislikte meg	☐	☐	☐	☐
20. Jeg var initiativløs	☐	☐	☐	☐

SNU ARKET!

Reg. nr.:

TRETTHET (LFS)

Vi ønsker å vite mer om energinivået ditt.
Nedenfor er det 18 utsagn vi ber deg svare på.

INSTRUKSJONER: For hvert utsagn nedenfor -
Sett ett kryss i den ruten som best indikerer hvordan du føler deg <u>akkurat nå</u>.

1.

Ikke sliten i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært sliten
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

2.

Ikke trøtt i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært trøtt
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

3.

Ikke døsig i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært døsig
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

4.

Ikke utmattet i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært utmattet
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

5.

Ikke utslitt i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært utslitt
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

6.

Ikke energisk i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært energisk
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

7.

Ikke aktiv i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært aktiv
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

8.

Ikke sprek i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært sprek
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

9.

Ikke effektiv i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært effektiv
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

10.

Ikke livlig i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Svært livlig

11.

Ikke utkjørt i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Svært utkjørt

12.

Ikke utslått i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Svært utslått

13.

Å holde øynene åpne er ikke anstrengende i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Å holde øynene åpne er veldig anstrengende

14.

Å bevege kroppen er ikke anstrengende i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Å bevege kroppen er veldig anstrengende

15.

Å konsentrere seg er ikke anstrengende i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Å konsentrere seg er veldig anstrengende

16.

Å holde i gang en samtale er ikke anstrengende i det hele tatt

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Å holde i gang en samtale er veldig anstrengende

17.

Jeg har absolutt ikke noe behov for å lukke øynene

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Jeg har et veldig sterkt behov for å lukke øynene

18.

Jeg har absolutt ikke noe behov for å legge meg nedpå

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Jeg har et veldig sterkt behov for å legge meg nedpå

SNU ARKET!

Reg. nr.:

LIVSKVALITETS SPØRRESKJEMA - KREFT (MQOLS-CA)

Nedenfor følger noen spørsmål om din sykdom og din livskvalitet. Vær vennlig å sette ett kryss i den ruten du synes passer best for å beskrive din situasjon.

1. Hvordan er din nåværende helsetilstand?

Ekstremt dårlig helse	0	1	2	3	4	5	6	7	8	9	10	Svært god helse
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

2. Hvor lett eller vanskelig er det for deg å tilpasse deg din sykdom og behandling?

Tilpasningen er ikke lett i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Tilpasningen er veldig lett
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

3. Hvor stor glede har du av livet?

Ingen glede	0	1	2	3	4	5	6	7	8	9	10	Mye glede
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

4. Føler du økonomisk trygghet?

Ingen økonomisk trygghet i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Veldig stor økonomisk trygghet
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

5. Hvis du har smerter, hvor plagsomt er det?

Ikke plagsomt i det hele tatt, eller ingen smerter	0	1	2	3	4	5	6	7	8	9	10	Svært plagsomt
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

6. Hvor nyttig føler du deg?

Ikke nyttig i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Veldig nyttig
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

7. Hvor lykkelig føler du deg?

Føler meg ikke lykkelig i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært lykkelig
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

8. Hvor tilfredsstillende er livet ditt?

Ikke tilfredsstillende	0	1	2	3	4	5	6	7	8	9	10	Svært tilfredsstillende
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

9. Får du nok kjærlighet fra familie og venner?

Ikke nok eller for mye kjærlighet	0	1	2	3	4	5	6	7	8	9	10	Akkurat passe med kjærlighet
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

10. Påvirker din sykdom eller behandling dine personlige relasjoner?

Påvirker ikke mine personlige relasjoner i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Meget stor påvirkning på mine personlige relasjoner
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

11. Er du bekymret (redd eller engstelig) for utfallet av sykdommen din?

Aldri bekymret	0	1	2	3	4	5	6	7	8	9	10	Bekymret hele tiden
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

12. I hvor stor grad er du i stand til å gjøre ting du liker å gjøre, som f.eks, å se på TV, lese, gjøre hagearbeid, høre på musikk, gå turer, spille tennis, spille kort, osv.?

Absolutt ikke i stand til å gjøre ting jeg liker å gjøre	0	1	2	3	4	5	6	7	8	9	10	I full stand til å gjøre ting jeg liker å gjøre
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

13. Hvordan er din nåværende konsentrasjonsevne?

Veldig dårlig konsentrasjons-evne	0	1	2	3	4	5	6	7	8	9	10	Utmerket konsentrasjons-evne
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

14. Hvor mye krefter har du?

Ingen krefter i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Mye krefter
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

15. Blir du fort sliten?

Jeg blir ikke fort sliten	0	1	2	3	4	5	6	7	8	9	10	Jeg blir svært fort sliten
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

16. Får du dekket ditt behov for søvn?

Jeg får ikke nok søvn	0	1	2	3	4	5	6	7	8	9	10	Jeg får dekket mitt behov for søvn
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

SNU ARKET!

17. Hvor god er din livskvalitet?

Svært dårlig livskvalitet	0	1	2	3	4	5	6	7	8	9	10	Svært god livskvalitet
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

18. Klarer du å ivareta dine personlige behov (kle på deg, gre håret, gå på toalettet, spise, dusje, bade)?

Jeg kan ikke gjøre noenting selv	0	1	2	3	4	5	6	7	8	9	10	Jeg er fullstendig selvhjulpen
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

19. Hvor mye smerter har du?

Ikke smerter i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Svært mye smerter
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

20. Hvordan er appetitten din?

Ingen appetitt	0	1	2	3	4	5	6	7	8	9	10	Utmerket appetitt
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

21. Hvordan er tarmfunksjonen din?

Det har aldri fungert så dårlig før (enten for mye diaré, eller forstoppelse)	0	1	2	3	4	5	6	7	8	9	10	Veldig bra tarmfunksjon (regelmessig, ingen diaré eller forstoppelse)
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

22. Spiser du nok i forhold til ditt behov?

Spiser ikke riktig mengde (for mye eller for lite)	0	1	2	3	4	5	6	7	8	9	10	Spiser passe mye
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

23. Er du bekymret for vekten din?

Ikke bekymret for vekten i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Veldig bekymret
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

24. Er du plaget av kvalme?

Aldri kvalm	0	1	2	3	4	5	6	7	8	9	10	Konstant kvalm
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

25. Kaster du opp?

Kaster aldri opp	0	1	2	3	4	5	6	7	8	9	10	Kaster opp hele tiden
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

26. Smaker maten annerledes?

Maten smaker som vanlig	0	1	2	3	4	5	6	7	8	9	10	Maten smaker veldig annerledes
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

27. Klarer du å komme deg rundt i den grad du ønsker (gå rundt i rommet, eller hjemmet ditt, komme deg ut, handle, kjøre bil eller ta offentlig transport, osv.)?

Fullstendig bundet til sengen	0	1	2	3	4	5	6	7	8	9	10	Kommer meg rundt på egenhånd
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

28. Hvor fornøyd er du med utseendet ditt?

Meget misfornøyd med mitt utseende	0	1	2	3	4	5	6	7	8	9	10	Meget fornøyd med mitt utseende
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

29. Er du bekymret for noe du ikke har fullført (privat eller på jobb)?

Ikke bekymret i det hele tatt	0	1	2	3	4	5	6	7	8	9	10	Veldig bekymret
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

30. Føler du at du ivaretar ditt ansvar overfor andre (familie, nærmiljøet, kirke, el.)?

Ivaretar ikke dette ansvaret	0	1	2	3	4	5	6	7	8	9	10	Ivaretar dette ansvaret godt
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

31. Har livet mening for deg?

Livet har ingen mening	0	1	2	3	4	5	6	7	8	9	10	Livet er svært meningsfylt
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

32. Får du tilstrekkelig emosjonell støtte fra familie og venner?

Ikke nok eller for mye emosjonell støtte	0	1	2	3	4	5	6	7	8	9	10	Riktig mengde emosjonell støtte
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

33. Føler du at du bidrar til å gjøre andre glad (familie og venner)?

Jeg bidrar ikke til å gjøre andre glad	0	1	2	3	4	5	6	7	8	9	10	Jeg bidrar til å gjøre andre veldig glad
	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	

SNU ARKET!

RIKSHOSPITALET

Vennligst legg ferdig utfylt spørreskjema i svarkonvolutten. Porto er betalt.

Tusen takk for hjelpen!

Senter for pasientmedvirkning og sykepleieforskning

Besøksadresse: Forskningsveien 2b, Oslo

Postadresse: Rikshospitalet HF, 0027 Oslo

Sentralbord: 23 07 00 00

Direktelinje: 23 07 54 64

Epost: kristin.hofso@rr- research.no

                 tone.rustoen@rr- research.no