Doctoral theses at NTNU, 2024:34

Ingunn Hatlevoll

Chemotherapy for colorectal cancer – Physical exercise and quality of life

Doctoral thesis

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

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Trondheim, February 2024

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Fysisk aktivitet og livskvalitet for pasienter som mottar kjemoterapi for kolorektalkreft

Kolorektal kreft (CRC) er den nest vanligste årsaken til kreftrelaterte dødsfall både nasjonalt og internasjonalt. Stillesittende livsstil er assosiert med økt risiko for å utvikle CRC og med redusert sjanse for overlevelse etter diagnose. Vi har sett en jevn økning i overlevelse de siste tiårene, og et økende antall mennesker lever med seneffekter av behandling.

Kombinasjon av ulike cellegifter er sentralt i behandlingen av CRC. Slik behandling medfører flere bivirkninger både på kort og lang sikt, som fatigue (utmattelse), perifer nevropati (prikkinger, nummenhet og ev. smerter i hender og føtter) og redusert fysisk funksjon. Når helbredelse ikke er mulig, er hovedmålet med behandlingen å la pasienter leve lengst mulig og best mulig. CRC rammer først og fremst de eldre. Det er en bekymring om eldre pasienter vil tåle cellegiftbehandling like godt som de yngre.

Det er økende dokumentasjon på at fysisk trening både under og etter kreftbehandling har gunstige effekter på symptomer som oppstår som følge av sykdom og behandling, men flertallet av studiene er gjennomført blant pasienter med bryst- og prostatakreft. Mulige fordeler med trening under adjuvant (tilleggs) behandling med cellegift for CRC er lite studert, og forskning viser at det har vært vanskelig å rekruttere pasienter med CRC til slike studier.

Denne avhandlingen er basert på to ulike pasientgrupper; CRC pasienter under adjuvant cellegift og CRC pasienter under palliativ (livsforlengende) cellegift. Målsettingen er å få økt innsikt i gjennomførbarheten av en treningsintervensjon under adjuvant cellegift, hvordan pasientene opplever å delta i fysisk trening under cellegift, og hvordan cellegift påvirker livskvalitet i palliativ fase.

Vi har gjort en studie som undersøker gjennomførbarhet av et individuelt tilpasset og veiledet treningsprogram under adjuvant cellegift for CRC. Vi har vist at denne intervensjonen er gjennomførbar og trygg, men vi har også vist at det er behov for å tilrettelegge for veiledet trening nærmere pasientenes hjem. Videre har vi gjort en kvalitativ intervjustudie blant deltakerne som viser at pasientene opplever flere både fysiske og mentale fordeler ved å delta i treningsprogrammet, og de opplever at det er viktig at treningen er veiledet.

Til slutt har vi gjennomført en observasjonsstudie av en uselektert kohort av pasienter med metastatisk (pasienter med spredning) CRC i Midt-Norge. Vi har analysert endringer i livskvalitet det første året etter oppstart av palliativ cellegift. Resultatene viser at en betydelig andel av pasientene opplevde store forverringer i fatigue og fysisk funksjon de første månedene av behandlingen, men de eldre (>70 år) pasientene opplevde ikke mer forverring av livskvalitet enn de yngre.

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Disputas finner sted i auditorim KA 11 på Kunnskapssenteret
1. februar 2024 kl. 12.15

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Norsk sammendrag

Kolorektal kreft (CRC) er den tredje vanligste kreftformen på verdensbasis, den nest vanligste kreftformen i Norge og den nest vanligste årsaken til kreftrelaterte dødsfall både nasjonalt og internasjonalt. I Norge ble det påvist 4745 nye tilfeller i 2022, og 1591 personer døde av sykdommen året før. Stillesittende livsstil er assosiert med økt risiko for å utvikle CRC og med redusert sjanse for overlevelse etter diagnose. En jevn økning i overlevelse er blitt observert de siste tiårene, og et økende antall mennesker både lever med en nåværende eller tidligere CRC diagnose og med seneffekter av behandling.

Kombinasjon av ulike cellegifter er sentralt i behandlingen av CRC, både i den kurative og den palliative (livsforlengende) setting. Slik behandling medfører flere bivirkninger både på kort og lang sikt, som fatigue (utmattelse), perifer nevropati (prikkinger, nummenhet og ev. smerter i hender og føtter) og redusert fysisk funksjon, med påfølgende negativ virkning på helserelatert livskvalitet (HRQoL). Vurdering av hvilken behandling pasientene skal ha bør ikke bare fokusere på overlevelse og respons, men også på pasientenes symptomer, funksjon og generelle velvære. Når helbredelse ikke er mulig, er hovedmålet med behandlingen å la pasienter leve lengst mulig og best mulig. De senere år er det observert en bekymringsfull økning av CRC blant yngre, selv om CRC først og fremst rammer de eldre, med median alder ved diagnose på omtrent 73 år. Det er en bekymring om eldre pasienter vil tåle cellegiftbehandling like godt som de yngre.

Det er økende dokumentasjon på at fysisk trening både under og etter kreftbehandling har gunstige effekter på symptomer som oppstår som følge av sykdom og behandling, men flertallet av studiene er gjennomført blant pasienter med bryst- og prostatakreft i tidlig stadium. Potensielle fordeler med trening under adjuvant (tilleggs) behandling med cellegift for CRC er lite studert, og forskning viser at det har vært vanskelig å rekruttere pasienter med CRC til slike studier.

Denne avhandlingen er basert på to ulike pasientpopulasjoner; CRC pasienter under adjuvant cellegift og CRC pasienter under palliativ cellegift. Målsettingen er å få økt innsikt i gjennomførbarheten av en treningsintervensjon under adjuvant cellegift, hvordan pasientene opplever å delta i fysisk trening under cellegift, og hvordan cellegift påvirker HRQoL i palliativ fase.

Som forberedelse til en fremtidig randomisert kontrollert studie (RCT), er det utført en studie på gjennomførbarhet av et individuelt tilpasset og veiledet treningsprogram som kombinerer utholdenhet-, styrke- og balansetrening under adjuvant cellegift for CRC. Vi har vist at denne intervensjonen er gjennomførbar og trygg med både høy villighet til å delta og etterlevelse til treningsprogrammet, men vi har også vist at det er behov for å tilrettelegge for veiledet trening nærmere pasientenes hjem. Videre er det gjennomført en kvalitativ intervjustudie blant deltakere i treningsintervensjonen som viser at pasientene opplever flere både fysiske og mentale fordeler ved å delta i programmet, og de opplever at det er viktig at treningen er veiledet.

Siste delstudie er en observasjonsstudie av en uselektert kohort av pasienter med metastatisk (pasienter med spredning) CRC i Midt-Norge. Vi har analysert endringer i utvalgte HRQoL-utfall det første året etter oppstart av palliativ cellegift. Resultatene viser at en betydelig andel av pasientene opplevde store forverringer i fatigue og fysisk funksjon de første månedene av behandlingen, eldre (>70 år) pasienter opplevde ikke mer forverring av HRQoL enn de yngre, og at den positive effekten på HRQoL av en pause fra cellegift ser ut til å være større i en «real-life» populasjon enn blant pasienter inkludert i en RCT.

English summary

Colorectal cancer (CRC) is the third most common cancer worldwide, the second most common cancer in Norway, and the second leading cause of cancer deaths both globally and nationally. In Norway, 4745 new cases were diagnosed in 2022, and 1591 persons died from the disease the year before. Sedentary lifestyle is associated with increased risk of developing CRC and with reduced chance of survival after the diagnosis. A steady increase in survival has been observed over the past decades, and an increasing number of people are living with a present or former diagnosis of CRC and with long-term side effects from treatment.

Different chemotherapy combinations play a central part in treatment of CRC, both in the curative and the palliative settings. Chemotherapy has several both short- and long-term side effects, such as fatigue, peripheral neuropathy and reduced physical function, negatively affecting health-related quality of life (HRQoL). Choice of treatment should not only focus on survival and tumour response, but also on patients´ symptoms, functioning and overall well-being. When cure is not an option, the main treatment goals are to allow patients to live longer and to live better. During recent years, an increased incidence of CRC among younger people has been observed, although CRC primarily affects the elderly, with a median age at diagnosis of approximately 73 years. There are concerns whether older patients will tolerate chemotherapy as well as the younger patients.

There are increasing evidence that physical exercise (PE) both during and after cancer treatment have beneficial effects on several cancer-related health outcomes, but the majority of studies performed are in early stage breast cancer and in prostate cancer. Potential benefits of a PE intervention during adjuvant chemotherapy for CRC are less studied, and recruiting patients with CRC to PE interventions has been found challenging by several investigators.

This thesis is based on studies from two different patient populations; CRC patients during adjuvant chemotherapy and CRC patients during palliative chemotherapy. The aim is to gain increased insight in the feasibility of a PE intervention during adjuvant chemotherapy for CRC, how patients experience physical exercise during chemotherapy, and how chemotherapy affects HRQoL in the palliative phase.

As a preparation for a future randomized controlled trial (RCT), we have conducted a feasibility study of an individually adjusted and supervised PE program combining aerobic,

strength and balance training during adjuvant chemotherapy for CRC. We have demonstrated that this intervention is feasible and safe with both a high willingness to participate and adherence to the program, but with a need to accommodate PE interventions closer to patients´ homes. Further, we have performed a qualitative interview study among participants in the PE intervention, demonstrating that patients experience several benefits, both physically and mentally, participating in the program and the importance of PE being supervised.

Finally, we have conducted an observational study of an unselected cohort of metastatic CRC patients in Middle-Norway, analysing changes in selected HRQoL outcomes the first year of palliative chemotherapy, demonstrating that large deteriorations in fatigue and physical functioning are experienced by a significant proportion of the patients the first months of treatment, that older (>70 years) patients did not experience more deterioration in HRQoL than the younger, and that the positive impact of a chemo-break on HRQoL seems to be larger in a real-life population than in patients included in RCTs.

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The work of this thesis has been carried out at the Cancer Clinic, St. Olav´s hospital and at the Department of Clinical and Molecular Medicine at the Norwegian University of Science and Technology (NTNU). The PhD has been funded by the Dam Foundation, and the observational mCRC study was funded by the Joint Research Committee between St. Olav´s hospital and the Faculty of Medicine and Health Sciences, NTNU.

First, I would like to thank all the patients participating in the present studies, offering time and effort to the benefit of future patients. Clinical health-research is nothing without all the people who volunteer to improve medical treatment and care.

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Third, I will thank the physiotherapists on 'Pusterommet' for providing the participants with supervised exercise, Siri Alstad Svestad for doing and transcribing a major part of the interviews, and the Cancer Clinic for providing research support.

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Last, but not least, I want to thank my family. My wonderful children, Kristianne, Vilde, Maria and Kaja, thank you for believing in me and cheering me on, and also showing me good times outside this project. Kure, my love in life, thank you for your everlasting patience. I know this has taken its toll on you, and I promise to be more present in the future.

List of papers

Paper I

Physical exercise during adjuvant chemotherapy for colorectal cancer—a non-randomized feasibility study

Hatlevoll I, Oldervoll LM, Wibe A, Stene GB, Stafne SN, Hofsli E.

Support Care Cancer. 2021 Jun;29(6):2993-3008. doi: 10.1007/s00520-020-05789-z. Epub 2020 Oct 8.

Paper II

Colorectal cancer patients' experiences with supervised exercise during adjuvant chemotherapy-A qualitative study

Hatlevoll I, Skolbekken JA, Oldervoll LM, Wibe A, Hofsli E.

Scand J Med Sci Sports. 2021 Dec;31(12):2300-2309. doi: 10.1111/sms.14048. Epub 2021 Sep 18.

Paper III

Do older patients with colorectal cancer experience more deterioration in health-related quality of life during the first year of palliative chemotherapy? – A prospective real-world observational study.

Hatlevoll I, Kristensen AK, Solheim TS, Elvebakken H, Salvesen Ø, Oldervoll LM, Wibe A, Hofsli E.

Submitted

Abbreviations

BMI	Body Mass Index
BSC	Best supportive care
Capox	Combination of oral capecitabine and intravenously oxaliplatin
CIPN	Chemotherapy induced peripheral neuropathy
QLQ-C30	Quality of Life Questionnaire Core 30
CRC	Colorectal cancer
CRF	Cancer-related fatigue
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
Flv	5-FU combined with calcium folinate
Folfox	Combination of intravenously 5-FU, calcium folinate and oxaliplatin
FQ	Fatigue Questionnaire
HRQoL	Health-related quality of life
HUNT	North Trondelag Health Study
iv.	Intravenously
mCRC	Metastatic colorectal cancer
MF	Mental fatigue
MID	Minimally important difference
Min	Minutes
MMR	Mismatch repair
MSAS	Memorial Symptom Assessment Scale

MSI	Microsatellite instability
MSS	Microsatellite stable
NCCN	National Comprehensive Cancer Network
PA	Physical activity
PE	Physical exercise
PEACE	Physical Exercise Across the Cancer Experience
PF	Physical fatigue
PRO	Patient reported outcome
PROM	Patient reported outcome measure
PROMS	Patient reported outcome measures
PS	Performance status
QoL	Quality of life
RCT	Randomized controlled trial
RPE	Rate of perceived exertion
RS	Raw score
S	Score
SAE	Serious adverse event
SD	Standard deviation
SF-12	Medical Outcomes Study Short Form-12
TA	Thematic Analysis
TF	Total fatigue
TNM	Tumour node metastasis
VEGFR	Vascular endothelial growth factor receptor
5-FU	5-Fluorouracil

Definitions and clarification of concepts

Physical activity is any bodily movement produced by contraction of skeletal muscle that results in energy expenditure above resting energy expenditure (1). Physical activity interventions may be less structured than exercise interventions and often focus on promoting the integration of activities into daily life (e.g. gardening, walking or active travel) (2)

Physical exercise is a subset of physical activity that is planned, structured and repetitive, done to improve or maintain one, or more of the components of physical fitness (1).

Physical fitness is a set of attributes that are either health- or skill-related. The health-related components of physical fitness are cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility (1).

Endurance training is synonymous to aerobic exercise including activities aimed at improving and maintaining the fitness of the cardiovascular system (3).

Strength training is synonymous to resistance training. It consists of anaerobic activity including exercise aimed at inducing muscular contraction to increase the strength, anaerobic endurance, and size of skeletal muscles (3).

Balance and sensorimotor training is associative training in which observation of one action is systematically paired with performance of another action. It includes vestibular, visual and oculomotor activities, cervical neuromotor control and strength training, and postural/balance exercises (3).

Feasibility and pilot studies are conducted in preparation for a future definitive randomised controlled trial (RCT). A feasibility study asks whether the future RCT can be done, should be done, and if so, how. Pilot studies are a subset of feasibility studies that ask the same questions, in addition to conducting the future RCT, or part of it, on a smaller scale (4, 5)

1. Background

1.1. Colorectal cancer (CRC)

1.1.1. Epidemiology, treatment and prognosis

Worldwide, CRC is the second leading cause of cancer deaths and ranks third in terms of new cases (both sexes together), representing about one in 10 new cancer cases and deaths (Fig. 1) (6). CRC can be considered a marker of socioeconomic development, as incidence rates are approximately 4-fold higher in developed countries compared with developing countries, and incidence rates tend to rise parallel with increasing human development index in countries undergoing major transition (e.g. Eastern Europe, South Eastern and South Central Asia, and South America) (6). Among females, Norway has the highest incidence rates for colon cancer (6). Except for hereditary factors, known risk factors for CRC are increased intake of animal-source foods, sedentary lifestyle with decreased physical activity (PA) and overweight. Additional risk factors include heavy alcohol consumption, cigarette smoking, and consumption of red or processed meat (7, 8).

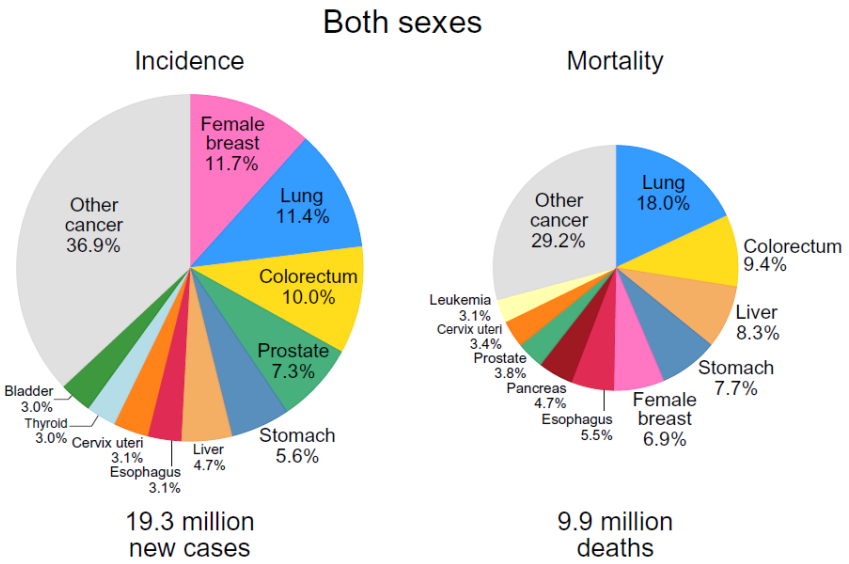

Fig. 1. Distribution of cases and deaths for the Top 10 Most Common Cancers in 2020 for both sexes. From GLOBOCAN 2020 (6).

In Norway, CRC is the second most common cancer for both men and women with 4745 new cases in 2022 (9). Colon cancer constitutes 70% of the cases and is evenly distributed between the sexes, while rectal cancer is more common in men. Median age at diagnosis is 74 and 70 years for colon and rectal cancer respectively, but an increasing number of CRC affecting younger people (< 50 years) has been observed in the resent years (9-11). During the last decades, modern treatment principles for CRC have become more complex with improved surgical techniques, radiotherapy, and systemic therapies, and thus, more people are surviving their cancer (Fig 2), but also living with long-term side effects after treatment. Today, more than 40 000 people are living with a present or former CRC diagnosis in Norway, while the same number ten years ago was below 29 000 (9).

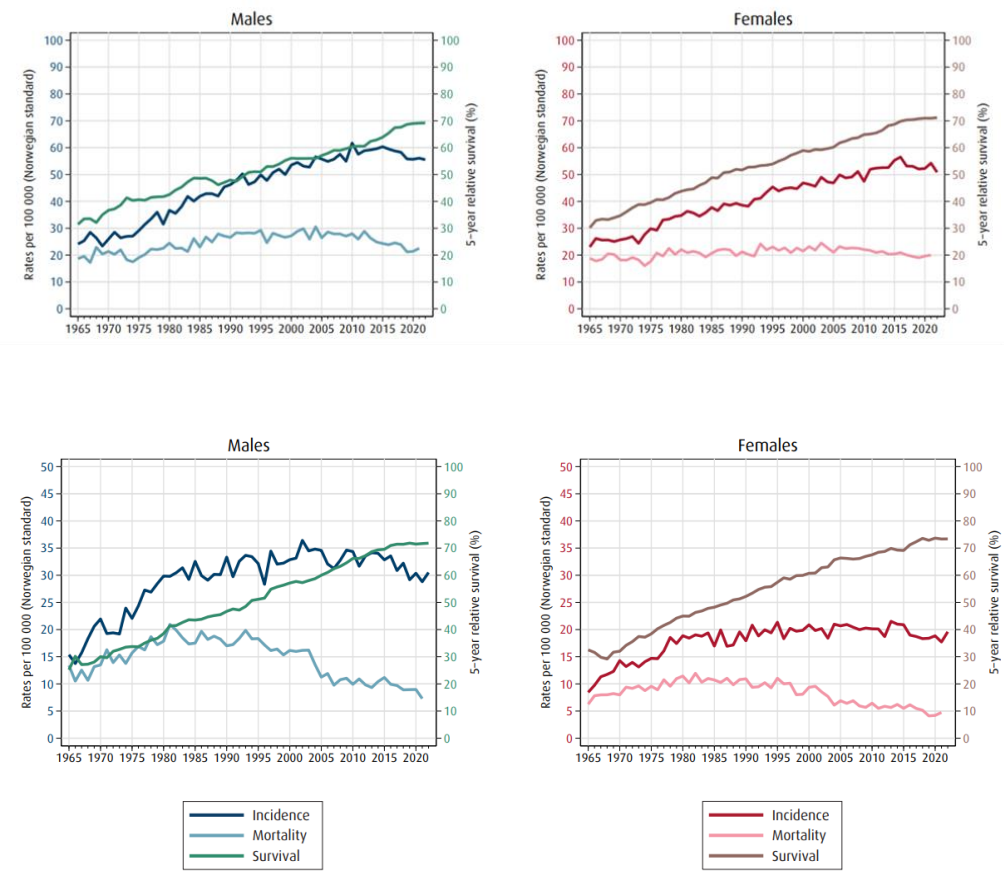

Fig. 2. Trends in incidence and mortality rates and 5-year relative survival proportions in colon (top) and rectum, recto-sigmoid (bottom) cancer. From Cancer in Norway 2022 (9).

1.1.2. Pathological classification

The main histological type of CRC is adenocarcinoma. Other histological entities also originating in the colon or rectum, such as lymphomas, neuroendocrine tumours and sarcomas, are not part of this thesis. Colorectal adenocarcinomas are classified according to degree of differentiation, low-grade vs. high-grade, and presence of mucin- or signet ring cell differentiation, the three latter indicating worse prognosis. Other histopathological findings of prognostic magnitude are tumour budding, extramural vascular infiltration and perineural infiltration (12).

Molecular pathological analyses of tumour tissue have had increasing value with new, targeted therapies emerging. Analyses routinely performed today, potentially having therapeutic consequences, are mutations in the RAS- and BRAF genes and expression of mismatch repair (MMR) proteins and/or presence of microsatellite instability (MSI) (12).

1.1.3. Diagnosis, staging and prognosis

Symptoms from CRC partly depends on tumour location and growth patterns. Less than half of the patients experience obstructive symptoms (change in bowel habits or abdominal pain). A common symptom is bleeding, either as bloody stools or more occult, presenting with anemia. Fresh bleeding and bowel obstruction are more common in left-sided tumours, and anemia is common in the right-sided. Asthenia and weight loss are less common symptoms. Approximately 10-15% of the patients have an acute debut with ileus, major bleeding or bowel perforation necessitating acute surgery (12, 13).

In addition to medical history, general clinical examination and blood tests with the tumour marker CEA, investigations for CRC should include endoscopy with biopsy, CT-scan of the chest, abdomen and pelvis, and for rectal cancer, MRI of the rectum/pelvis. Endoscopic ultrasound of small rectal tumours is recommended, and MRI of the liver is performed to clarify unresolved liver lesions.

These examinations aid staging of the disease. The tumour, node, metastasis (TNM) staging system is used to characterize the extent of the disease, and to determine the overall stage grouping (I-IV), which in turn is linked to treatment recommendations (14). In stage I-II, the

tumour is confined to the intestinal wall, with or without involvement of adjacent structures. In stage III, the tumour has spread to regional lymph nodes, and in stage IV, distant metastases are present. Approximately 24% are diagnosed with localized disease, 53% with regional-, and 23% with metastatic disease. Additionally, another 14-19% will develop metastasis in their disease trajectories (9, 13).

Over the past decades, CRC survival in Norway has steadily improved in all stages. Five-year relative survival for the whole group is now approximately 70% for colon- and 72% for rectal cancer, with women having slightly better prognosis. Corresponding survival rates are 97, 84 and 22% for stage I+II, III and IV CRC, respectively. Stage III colon cancer has better survival than stage III rectal cancer, and for stage IV, it is vice versa (9).

1.1.4. Treatment of resectable CRC

Standard treatment for CRC is surgery alone in the earliest stages. In stage III and high risk stage II, surgery followed by adjuvant chemotherapy is employed for colon cancer and some cases of rectal cancer. Locally advanced rectal cancer is treated with different combinations of chemo- and radiotherapy neoadjuvant, followed by surgery. After curative surgery for synchronous metastatic disease, adjuvant chemotherapy is, after an individual assessment, also offered. Surgery for CRC will in some cases entail a stoma, either as a temporary or a permanent solution (12).

The intention of adjuvant chemotherapy is to eliminate microscopic disease and thus reduce the risk of relapse. Six months 5-fluorouracil (5-FU) based treatment combined with calcium folinate adjuvant, has well documented improvement in five-year disease free survival in colon cancer, and has been in routinely use since the nineties (15-18). In the mid-2000, it was demonstrated that adding oxaliplatin further improved survival, especially among those under 70 years (19-22). In 2018, a large study concluded that three months combinational treatment safely could replace six months of treatment among those with low risk stage III colon cancer (23).

Norwegian guidelines recommend adjuvant chemotherapy for 3-6 months according to risk assessments, and should be started 4-6 weeks postoperatively. It consists of intravenously (iv.) combinations of 5-FU, calcium folinate and oxaliplatin (Folfox) or oral capecitabine

combined with iv. oxaliplatin (Capox). For those above 70 years, monotherapy with 5-FU/calcium folinate (Flv) or capecitabine for six months is recommended (12).

1.1.5. Treatment of non-resectable, metastatic CRC (mCRC)

During the last four decades, medical treatment options for mCRC have improved from offering best supportive care (BSC) only, to fluorouracil monotherapy, to combination chemotherapy, and to adding monoclonal antibodies or other targeted therapies. In the same period, improvement in survival has been registered from an expected median survival of six months with BSC, to 12 months with monotherapy, 15-18 months with combination therapy, and now median survival up to 30 months with the addition of targeted therapies is reported in recent trials (24-27).

When incurable disease, main treatment goals are prolongation of life, symptom relief, and maintenance of quality of life (QoL) (28). Palliative chemotherapy is given alone or in combination with other chemotherapy and/or targeted therapies. The most commonly used compounds are 5-FU, oxaliplatin, irinotecan, vascular endothelial growth factor receptor- (VEGFR) and epidermal growth factor receptor (EGFR) blockers. Recently, BRAF- and immune checkpoint inhibitors have proven useful for selected groups (29-31). Randomized controlled trials (RCTs) are the basis of treatment recommendations, and the strategy in these trials often is treatment to progression or unacceptable toxicity (32-34). In clinical practice, the strategy usually is to introduce a chemo-break in a stop-and-go manner, or maintenance therapy with a milder regimen to let patients recover from side effects of treatment (35). Norwegian guidelines recommend considering a chemo-break four to six months after start of first line palliative chemotherapy. Re-challenge with the same regimen at progression, and switch to second or third line therapies after progression on a particular therapy are common strategies (12).

1.2. Side effects from treatment

Chemotherapy induces cell death in dividing cells through different mechanisms of action, both in cancer cells and in normal cells. Normal tissue has greater potential for repair than cancer tissue, and this is exploited when giving cytotoxic treatment (36). Chemotherapy is

associated with numerous side effects, which include immediate signs of acute toxicity and late signs of chronic toxicity. Organs and tissues with a high cell-turnover will typically be more susceptible to damage from chemotherapy, such as the bone marrow, mucous membranes and the skin. General side effects from chemotherapy are nausea and vomiting, anemia, thrombocytopenia and neutropenia, increased risk of infections, alopecia, diarrhoea, mucositis and skin rash. In addition, there are more specific side effects associated with a particular compound, and any organ of the body might be affected (37). Additionally, PA levels, physical fitness, and functional capacity have shown to deteriorate during and following CRC treatment, negatively impacting patients' QoL (38, 39).

1.2.1. Chemotherapy-induced peripheral neuropathy (CIPN)

CIPN is a common problem occurring in a substantial proportion of cancer survivors receiving neurotoxic chemotherapy, with incidence and severity varying depending on the specific agent, dosage, and treatment schedule used (40-42). Oxaliplatin is a neurotoxic compound causing symptoms of CIPN in more than 90% of the patients (43). The exact mechanism of oxaliplatin-based neurotoxicity is not fully clarified, but is believed to involve mitochondrial dysfunction and oxidative stress, altered ion channel activity, impaired intracellular signalling and inflammatory mediators (44). It can be divided into an acute and a chronic form. The acute neuropathy which is most common, is often cold-induced and presents with distal paresthesias, dysesthesias and mild muscle contractions in hands, feet and perioral. It typically peaks in the first three days following the oxaliplatin infusion and resolves within one week (45). The chronic neuropathy is mainly sensory and can appear after ending oxaliplatin treatment, causing ongoing functional impairment in terms of proprioception, balance and increased risk of falls (46). CIPN has a major negative effect on patients' QoL (47-49), it can last for several years, and for approximately 15% it will be irreversible (50). A systematic review of long-term CIPN following adjuvant oxaliplatin for CRC reported a pooled prevalence of CIPN 6, 12, 24 and 36 months after chemotherapy of 58, 45, 32 and 24%, respectively (45).

An observational study of 2450 stage III colon cancer patients enrolled in an RCT of three vs. six months of adjuvant Folfox concluded that lower PA, higher Body Mass Index (BMI), diabetes, and longer planned treatment duration, but not celecoxib use or vitamin B6 intake,

may be associated with significantly increased CIPN severity (51). Currently, there is no established treatment to prevent or counteract oxaliplatin-induced peripheral sensory neuropathy, other than reducing the dose or discontinuing the drug (52).

Discrepancies between clinician-reported grade of CIPN and patient reported symptoms and functional impairment due to CIPN have been described (53, 54). Bennet et al. examined a patient population reporting persistent neuropathy one year after oxaliplatin treatment. While only 10% of the patients after clinician assessment were graded with severe neuropathy, 60% of the patients reported having significant physical limitations due to neuropathic symptoms. The majority (85%) of the patients had objective signs of sensory neuropathy by nerve conduction measurements (53). Thus, it is reasonable to assume that CIPN is underreported in studies, and using patient reported outcome measures (PROMS) seems crucial when studying these symptoms.

1.2.2. Fatigue

Fatigue is a common symptom experienced by cancer patients through all stages of the disease trajectory. It is perceived to be the most distressing symptom associated with cancer and its treatment, and it has a greater negative impact on functioning and health-related quality of life (HRQoL) than other symptoms such as pain, nausea and vomiting or depression (55-57). The National Comprehensive Cancer Network (NCCN) defines cancer-related fatigue (CRF) as ‘a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with functioning’ (58).

During active treatment, the rate of CRF varies between 62 and 85% (57). Among CRC survivors, fatigue is present in approximately half of the patients with localized tumours (59). The fatigue usually peaks immediately after adjuvant chemotherapy, being experienced by 70% of patients, but remains a significant problem until 10-year post-diagnosis, persisting in 39% of long-term CRC survivors (57, 59). In patients with metastatic disease, the prevalence of CRF is more than 75% (58).

The aetiology underlying CRF is not well-understood, it appears complex and multi-factorial, involving the interaction of cognitive, emotional, psychosocial, and somatic factors, with

highly variable clinical expression. Proposed mechanisms include pro-inflammatory cytokines, hypothalamic-pituitary-adrenal axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting, and genetic dysregulation (56, 58).

Also here, significant discrepancies in grading of CRF severity have been observed between physician- and survivor reports, with physician ratings much lower than that of the survivor (60), and it seems reasonable to use self-report questionnaires for assessment of CRF.

1.3. Physical exercise and cancer

Until the late 1980s, the common notion was that cancer patients should rest during their treatment period and avoid physical exercise (PE). Two pioneer oncology nurses, Drs Winningham and MacVicar, were the first to demonstrate in a randomized trial beneficial effects of a 10-week interval based, aerobic exercise program on functional capacity, body composition, and patient reported nausea, in 45 women receiving conventional adjuvant chemotherapy for operable breast cancer (61-63). Since then, the research field of PE in oncology has grown exponentially.

Courneya and Friedenreich proposed in 2001 a framework for organizing research on PE and cancer control. The now established framework, Physical Exercise Across the Cancer Experience (PEACE), divides the cancer experience into six time periods: two pre-diagnosis (pre-screening and screening/diagnosis) and four post diagnosis (pre-treatment, treatment, post treatment, and resumption or palliation) (64).

Epidemiological studies have given strong evidence linking PA with reduced risk of developing several types of cancer, including colon cancer (65). Additionally, observational studies have demonstrated that high level of PA pre-diagnosis was associated with 18 and 23% lower cancer-specific mortality risks in breast- and CRC, respectively. Observational studies have also found associations between reduced cancer-specific- and all-cause mortality and higher levels of PA post-diagnosis in breast cancer, CRC and prostate cancer (65, 66).

PE as a pre-treatment intervention, is not as extensively investigated as PE during or after cancer treatment, but it is an evolving field of research and has shown promising results in various cancer types (67-71). Most studies performed are in lung cancer patients pre-surgery,

and improved pre-operative pulmonary function and reduced postoperative complication rates and length of hospital stay have been demonstrated in this group (72-74).

There are published numerous RCTs, reviews and meta-analyses that evaluate effects of PE both during and after cancer treatment, providing strong evidence that moderate intensity aerobic training alone or in combination with resistance training (both during and after treatment) have beneficial effects on several cancer-related health outcomes such as anxiety, depressive symptoms, fatigue, HRQoL and physical function, but there is still insufficient evidence to interpret the potential benefits of PE on CIPN, cardiotoxicity, cognitive function, and treatment tolerance, among others (75-78). The PE programs studied, typically lasted 12 weeks, containing 2-3 sessions per week with 30-60 minutes (min) duration. Supervised PE appears to be more effective than unsupervised in improving HRQoL, exercise-adherence, and other physical and psychological outcomes (75, 79). The majority of studies performed are in early stage breast cancer and in prostate cancer, and the results will not necessarily apply for all other cancer diagnoses or stages.

In the palliative stage, PE interventions are less studied, but also this field of research is evolving. It seems to be feasible and beneficial in improving cancer-related symptoms, QoL, physical performance, fatigue, and physical function (80-83). Further research is needed before generalizable conclusions can be made (83).

1.3.1. Physical exercise and CIPN

A large Dutch prospective registry study investigated associations between PA, CIPN and HRQoL among CRC survivors diagnosed between 2000 and 2009 (84). Not meeting the Dutch recommendation of 150 min of moderate to vigorous PA a week was associated with more CIPN among patients treated with chemotherapy, two to 11 years after diagnosis.

The first RCT exploring potential benefits of PE on CIPN was published by Streckmann et al. in 2014 (85). Sixty one lymphoma patients, scheduled for chemotherapy, were randomized to either a control group or a 36-week intervention with supervised sensorimotor-, endurance- and strength training twice a week. Primary end point was QoL, and secondary end points were movement coordination, endurance, strength and therapy-induced side effects. Significant improvements in QoL, peripheral neuropathy-related deep sensitivity, balance

control and aerobic performance level were revealed in the intervention group, compared to the control group (85).

After 2014, several RCTs have explored different PE interventions addressing CIPN in various patient groups (86-102). Most studies performed are with mixed diagnoses receiving different neurotoxic treatments, some are with pure breast cancer populations, and breast cancer is often in majority in the mixed studies. The interventions also differ, most often with some kind of sensorimotor- or balance training being investigated, either alone or in combination with endurance- and/or resistance exercises. Duration of the intervention program varies from 4 – 26 weeks with a median of 12 weeks. Some studies have included patients with established CIPN, while others have included patients before commencing neurotoxic chemotherapy. Great variations are also seen in choice of outcome measures in the different studies, with patient reported sensory symptoms, neuropathic pain and QoL being common, in addition to different balance- and other physical tests. A systematic review identified 75 outcome measures assessing PE and rehabilitation in CIPN across 26 studies (103). The majority of the performed studies are small, with sample sizes less than 50 (86, 89-96, 98, 100, 101).

During the recent years, several systematic reviews and meta-analyses on effects of PE on CIPN have been published (3, 52, 104-114). Some have focused on prevention, some on treatment after established CIPN, others on both, and one on breast cancer only (112). Common conclusions are that different PE interventions, both during and after cancer treatment, show promise in mitigating or alleviating consequences of neurotoxic treatment by improving QoL, physical function (balance control and muscle strength), neuropathic pain and other CIPN symptoms. One review highlights that aerobic exercise might be a key component of PE intervention for CIPN (105), while two others indicate sensorimotor training as the most crucial component (110, 113). Due to the great heterogeneity regarding patient population, cytotoxic treatments, mode of intervention (type, intensity and duration) and outcome measures, results must be interpreted with caution, and definitive recommendations cannot be made. Other limitations emphasized are the small sample sizes and low-moderate quality of the studies performed, and further higher quality research is warranted (3).

1.3.2. Physical exercise during adjuvant chemotherapy for CRC

PE interventions during or after treatment for CRC are less studied than in breast cancer and prostate cancer. The first RCT in this setting was published in 2003 by Courneya et al. (115). One hundred and two patients were randomized 2:1 after surgery for CRC to either a four months home based PE intervention at moderate intensity or a control group. All stages were included, less than 5% were metastatic, and approximately 2/3 were under treatment with chemotherapy. There was no significant difference between the two groups in the primary outcome, QoL, but contamination in the control group was a major problem (> 50%).

In 2014, when planning of the present feasibility study and future RCT commenced, only a handful RCTs handling PE interventions after curative surgery for CRC had been published, and none 'purely' during adjuvant chemotherapy (115-119). The first systematic review and meta-analysis available on PE for CRC patients was published in 2014, identifying five RCTs (120). One was partly during adjuvant chemotherapy by Courneya et al. described above (115), while the rest were after completion of primary treatment, and two had biomarker outcomes only. A meta-analysis performed on three of these RCTs (n=166) found strong evidence for short-term improvements of physical fitness in CRC patients after PE interventions compared with controls, but no effects on HRQoL or fatigue (120). The PE interventions were a mixture of different home-based aerobic exercises at moderate intensity with or without additional resistance exercises and supervised group exercises. The duration of the PE programs was 12-16 weeks, with a frequency of 2-5 times per week, and each session lasting 20-30 min. Main limitations were the small number of eligible RCTs and lack of safety reporting.

After 2014, several systematic reviews and meta-analyses on various PE interventions for patients with CRC have been published (2, 76, 121-128). Most of these have included studies both during and after treatment, and some included studies with mixed diagnoses in addition. The majority of studies are performed after completion of cancer treatment. A systematic review from 2018 by van Rooijen et al., investigated the effects of PE during adjuvant chemotherapy for patients with CRC (122). Seven studies were included in the review. Five of the studies included a mixture of several diagnoses, where CRC patients were in minority and constituting 5-22% of the participants (129-133). One study included a mixture of gastrointestinal cancers in metastatic setting (134), and the last study with CRC patients only,

was not a randomized study, but participants were allocated to intervention or control according to their preference (135). This systematic review concluded that a supervised combined strength-and endurance/interval training appeared to be potentially effective to improve functional capacity and muscle strength (lower extremity). Limitations of the review were that the studies were heterogeneous in terms of population and training modalities, and five studies had a small sample size of less than 50 (122).

A Cochrane systematic review and meta-analysis on PA interventions for disease-related physical and mental health during and following treatment in people with non-advanced CRC was published in 2020 (2). Sixteen RCTs were identified, whereof ten studies included participants who had finished, only two studies included participants who were receiving, and two studies included both those receiving and had finished active treatment. In two studies it was unclear whether participants were receiving or had finished treatment. The PA interventions varied regarding, type, setting and duration, and the most common duration was 12 weeks. The authors concluded that PA interventions may be beneficial for aerobic fitness, CRF and HRQoL up to six months follow-up, but the findings should be interpreted with caution due to the low number of studies included and the very low to moderate quality of the evidence (2).

Also published in 2020 was a meta-analysis by Lund et al., investigating effects of PE interventions during chemotherapy (neoadjuvant, adjuvant or palliative) on self-reported physical function, physical fitness, psychological well-being assessed by PROMS, PA, body composition, cancer- or treatment-related symptoms, and safety (124). Six of the eight RCTs included were during adjuvant chemotherapy (136-141), one was during neoadjuvant chemo-radiotherapy (142), and one was during palliative chemotherapy (90). Low levels of evidence for a small beneficial effect of PE on self-reported physical function and global QoL, and a moderate effect of PE on fatigue was found. No evidence for an effect of PE on the other outcomes was found. All studies included, showed that PE was feasible and safe, and no adverse events related to PE were reported (124). Also here, the main limitations were the heterogeneity of the included RCTs in terms of both the participants, the training modalities and the small sample sizes.

In 2022 Machado et al. published a meta-analysis on six RCTs investigating the effectiveness of PE on CRF during or after adjuvant chemotherapy for CRC. Six trials involving 330 CRC

patients were included, two during and four after adjuvant chemotherapy. An overall small-to-moderate effect of PE on CRF was found, and subgroup analysis revealed moderate effects of PE interventions performed during chemotherapy and small, non-significant effects, when PE was performed after cancer treatment. When a combination of aerobic plus resistance exercise was used, steady improvements were achieved in interventions lasting 12 to 24 weeks (126).

Another systematic review and meta-analysis from 2023 evaluated the content and effectiveness of PA interventions on CRF among CRC survivors. Eight RCTs involving 542 patients, three during and five after completion of adjuvant chemotherapy were included, demonstrating that PA interventions significantly reduced CRF. Subgroup analyses indicated that fatigue was significantly improved when the length of interventions was at least 6 months and the weekly duration of PA was less than 150 min/week, while PA interventions lasting less than six months with a volume of ≥150 min/week did not reduce fatigue (127).

When exploring the literature on PA and PE in CRC patients, there is great heterogeneity in the different studies performed. There are large variations in the patient populations included, both regarding type of cancer (mixtures of several diagnoses), stage of disease, and where the patients are in their disease trajectories. Type of PA interventions also show great variations, from regular telephone calls encouraging participants to be more physically active, to unsupervised and home-based PE programs, and to more individualized and supervised PE interventions including both aerobic- and resistance exercises. The intensity, frequency and duration of the PE interventions also show great variability, as well as the outcome measures. No studies have investigated potential effects of a PE intervention during adjuvant chemotherapy for CRC on CIPN. Table 1 gives a summary of RCTs and randomised pilot/feasibility studies published on different PE interventions among CRC patients ***during*** adjuvant chemotherapy. Regarding studies involving other diagnoses than CRC, only those reporting data for CRC separately are included.

Table 1. RCTs and pilot RCTs on exercise during adjuvant chemotherapy for CRC.

Year Author Country	Design (SSE)	Patients, n	Intervention, Exercise type, Frequency, Duration	Primary outcome	Results
2014 Backman Sweden (136)	Pilot RCT (NA)	**Tot. 17** IG = 8 CG = 9	IG, SV 1-h group walk/wk. + USV walking 10,000 steps/d. 10 wks.	Feasibility	43% acceptance rate 93% adherence Mean 7660 steps/d
2015 Møller Denmark (137)	Pilot RCT (NA)	**Tot. 12** IG A = 4 IG B = 3 CG = 5	IG A, SV RE/AE, 9 h/wk., then 6 h/wk.; IG B, USV walking 10,000 steps/d, x5/wk. 12 wks.	Feasibility	33% acceptance rate 50% adherence (IG A)
2016 Van Vulpen Netherlands (138)	RCT (Yes, 150)	**Tot. 33** IG = 17 CG = 16	IG, SV MI RE/AE 1 h, x2/wk. + USV 30 min, x3/wk. + CT 18 wks.	Fatigue (18 & 36 wk.)[1]	Wk. 18: Large ES in PF in favour of IG. Wk. 36: Large ES in GF in favour of IG.
2018 Van Waart Netherlands (139)	Pilot RCT/ RCT[2] (Yes, 360)	**Tot. 23** IG A = 8 IG B = 7 CG = 8	IG A, USV LI 30 min, x5/wk. + BRT; IG B, SV MHI RE/AE 50 min, x2/wk. + USV 30 min, x5/wk. 24 wks.	CRFi Muscle-strength Fatigue Feasibility	Low sample size, no effectiveness established 37% acceptance rate 75% adherence (IG A) 61% adherence (IG B)
2019 Li China (140)	RCT (Yes, 298)	**Tot. 298** IG =149 CG =149	IG, SV LI restorative exercise 90 min x1/wk., then SV HI 60 min RE/AE x3/wk. + IPCP[3]. 13 + 13 wks.	Anxiety Depression QoL	After 6 months: Slight decrease in anxiety (NS), significant reduction in depression and improvement in QoL in favour of IG.
2019 Lu China (141)	RCT (Yes, 90)	**Tot. 90** IG =45 CG =45	IG, USV 20-40 min Baduanjin qigong AE x5/wk. 24 wks.	CRF at 24 weeks	Significant smaller proportion with moderate-to-severe CRF in IG vs. CG (23.2 vs. 59.1%)

AE = aerobic exercise; BRT = behavioural reinforcement techniques; CRFi = cardiorespiratory fitness; CG= control group; CRC = colorectal cancer; CRF = cancer-related fatigue; CT = cognitive therapy; ES = effect size; GF = general fatigue; HI = high intensity; IG = interventional group; IPCP = incremental patient care program; LI = low intensity; MI = moderate intensity; MHI = moderate-to high intensity; NA = not applicable; NS = not significant; PF = physical fatigue; QoL = quality of life; RCT = randomized controlled trial; RE = resistance exercise; SSE = sample size estimate; SV = supervised; USV = unsupervised; wk. = week;

[1]*Interpret results with caution, due to low sample size*
[2]*Study part of a larger RCT including breast cancer*
[3]*Including patient health education, physical exercise, telephone counselling, regular examinations and care activities*

1.3.3. Recruiting CRC patients to physical exercise interventions

Recruiting CRC patients to PE interventions has been found challenging by several investigators (124, 131, 139, 143). This is also reflected in the relatively low proportions of CRC patients who have been recruited into PE trials with mixed diagnoses (130, 136, 138, 139). The Phys-Can RCT, newly performed in Sweden, compared the effects of high vs. low-to-moderate intensity PE program with or without additional behaviour change support on CRF in patients undergoing adjuvant cancer treatment (144). Of the 577 patients included, only 23 had CRC, while 457 had breast cancer, and 97 had prostate cancer.

1.3.4. RCT or feasibility study?

To assess the benefits and potential harm of new interventions in health care, RCTs are considered as the gold standard. Pilot and feasibility work is conducted to evaluate the operational feasibility and acceptability of the intervention itself. It would be futile to run a large-scale trial of interventions if these interventions are unlikely to ever see the light of day and be implemented in clinical practice. Even so, if trial procedures prove to be unfeasible, the results about clinical effectiveness will not be valid in implementing them in clinical practice. Conducting pilot and feasibility studies to sort out methodological issues in advance of a large-scale trial is critical if that larger trial is to become part of an evidence-base to inform new practice. To optimise the design and conduct of any subsequent largescale trial, findings from feasibility and pilot work about trial parameters will be useful (145).

When planning for the present feasibility study, we had no experience studying a PE intervention during adjuvant chemotherapy for CRC patients. Our future goal was to conduct an RCT to investigate whether a PE intervention during adjuvant chemotherapy could reduce the development of CRF and CIPN in this patient group. Before performing a full-scale RCT, issues of recruitment and retention needed to be properly addressed. To estimate the sample size in a future RCT, exploration of changes in patient-reported fatigue and CIPN also needed to be done.

1.3.5. CRC patients' perspectives on physical exercise

Patients´ views on and experiences from performing PE after a CRC diagnosis have also been explored in qualitative studies (146-154).

Romero-Elías et al. explored barriers to engage in PA during adjuvant chemotherapy for CRC among patients, relatives and physicians (146). Perceived barriers were related to difficulties associated with the stoma, limitations due to carrying an intravenous chemotherapy device, fatigue, reduced physical fitness, families' overprotection, the health professionals' lack of knowledge and time to prescribe PA, and the lack of PA services in health centres. Another study explored patients´ views on PA after surgery for rectal cancer with placement of a stoma. Reported barriers to PA were side-effects from chemotherapy, and stoma-related barriers could be wounds from surgery, fear of hernia, insecurity about the right amount or types of activities, fear of leakage, and feeling uncomfortable around others when having a stoma. (147). Limited time, not receiving or misunderstanding information, physical ailments, and emotional impact of the diagnosis have also been described as barriers to engage in preoperative PE among older CRC patients (148).

Renman et al. explored how the diagnosis of colon cancer might affect physically active individuals in their attitudes to PA, reporting these varied from a will to increase PA and fight the cancer, to the diagnosis putting a stop to PA (149). A second study demonstrated that PA promotion was largely absent throughout the chemotherapy pathway for patients with CRC, and when discussed, PA levels were only used to determine fitness for future oncological treatment. PA promotion was more routinely delivered post-treatment (150).

Locally advanced rectal cancer patients´ perceptions of QoL during participation in a pre-surgery structured PE program was explored by Burke et al., describing that participation facilitated positive changes in QoL over time by 'fostering a greater sense of vitality, cultivating a positive attitude, enhancing social connections, and fostering a strong sense of purpose in life for these patients' (151). A change in attitude was also described among physically inactive breast- and colon cancer patients participating in a pilot RCT with a PE intervention during adjuvant chemotherapy: An attitude towards PE changed from being non-exercisers to exercisers, and this was attributed to the oncologist recommendations, and counselling and support from healthcare professionals (152).

Experiences from a PE rehabilitation program immediately after completion of adjuvant chemotherapy for CRC has also been described (153). This was a 12 week individualized and supervised 20-40 min of moderate- to high-intensity aerobic exercise three times per week. It was concluded that patients experienced benefits from PE offered immediately after treatment, and preferably with individual attention from exercise staff. A preference for supervision from health professionals was also found by Hubbard et al. in a pilot RCT with a 10-12 week cardiac rehabilitation program for CRC patients after treatment completion, also describing participation provided confidence and motivation to exercise (154).

To summarize, several barriers to engage in PA after being diagnosed with CRC have been identified, both physical and emotional factors within the patients, but also external factors such as lack of supporting and promoting PA by healthcare providers and lacking access to training facilities. Patients that have engaged in PA both before, during and after treatment experienced several positive benefits, and the importance of supervised PE and recommendations and support from healthcare professionals have been emphasized.

As described above, there are limited studies exploring CRC patients´ experiences with PE *during* adjuvant chemotherapy. More information on this topic is warranted, as increased knowledge in this field might aid healthcare providers in engaging more CRC patients in PA, to better adjust interventions and thus being accessible to more patients.

1.4. Health-related quality of life (HRQoL)

1.4.1. Definitions of HRQoL

As the medical field evolved in the last century, allowing different treatments to prolong life or to improve QoL without extension of life, QoL became more important in health care (155), and QoL was discussed in the medical literature already in the 1960s (156).

The three terms health status, QoL and HRQoL are interchangeably being used in the literature, there are several definitions of the terms, and most definitions of HRQoL do not sufficiently differentiate from the two others (157, 158).

QoL is a complex construct, having different meanings for different people. The World

Health Organization (WHO) defines QoL as ‘an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns’ (159). Other examples of definitions of QoL are: ‘a conscious cognitive judgment of satisfaction with one’s life’ (160), and ‘an overall general well-being that comprises objective descriptors and subjective evaluations of physical, material, social, and emotional well-being together with the extent of personal development and purposeful activity, all weighted by a personal set of values’ (161). The two first focusing on subjective judgements, while the last also included objective factors.

In 1946 WHO defined health as ‘a state of complete physical, mental and social well-being, and not merely the absence of disease and infirmity’ (162). Another definition of health was proposed by Patrick et al. in 1973 as ‘an individual’s level of function, where optimum function is judged in comparison to society’s standards of physical and mental well-being’ (163).

HRQoL relates to the health aspects of QoL. Also here, there are several proposed definitions (164-167), without one universally accepted. The European Organization for Research and Treatment of Cancer (EORTC) QoL Clinical Trials Conference stated in 2019 that ‘Health-related QoL is a multidimensional concept referring to the patient’s subjective perception of the effect of their disease and treatment on physical, psychological and social aspects of daily life’ (168). It is widely accepted that HRQoL is a subjective phenomenon and should be assessed by the patients.

1.4.2. How HRQoL is affected by cancer

Both the disease itself and its treatments will often affect a person´s HRQoL. Proximal effects occur directly as a consequence of the cancer and/or treatment for the disease, such as cancer symptoms (e.g. pain, fatigue, abdominal discomfort) and side-effects from treatment (e.g. nausea, vomiting, CIPN) (169). These effects may in turn affect a person’s ability to function and their overall sense of well-being, causing distal effects. Cancer and its treatments can impact psychological well-being both directly or indirectly, via experience of symptoms, side-effects and loss of functional ability (Figure 3) (170). Additionally, both proximal and distal effects are modified by patient-specific factors (e.g. personality, comorbidity), and external factors (e.g. family support, finances, culture, access to health care). Since distal outcomes to

a greater extent will be influenced by factors external to healthcare, a proximal outcome is more likely to be more sensitive to treatment effects than a distal measure, and this should be taken into account when choosing HRQoL instruments in clinical trials (170).

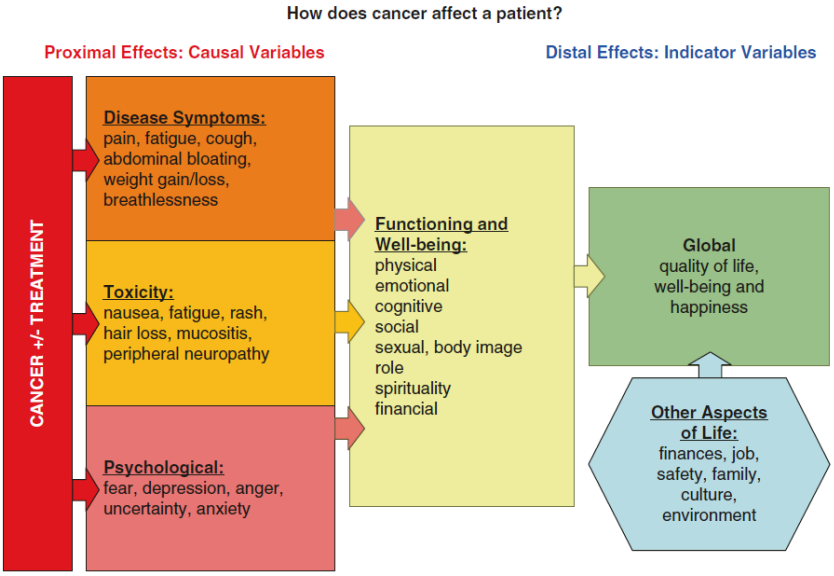

Fig. 3. How cancer affects HRQoL: proximal versus distal effects.

Reprinted from Rutherford C et al. (2018) Health-Related Quality of Life in Cancer. In: Olver I (eds) The MASCC Textbook of Cancer Supportive Care and Survivorship. With permission from Springer Nature.

1.4.3. Patient reported outcome measures (PROMS)

In 2006, the US Food and Drug Administration (FDA) defined the term 'patient-reported outcome' (PRO) as 'a measurement of any aspect of a patient's health status that comes directly from the patient, without the interpretation of the patient's responses by a physician or anyone else' (171). PROs can be symptoms (e.g. pain, anxiety, nausea, fatigue), aspects of functioning (e.g. role, physical, emotional, social) or multidimensional constructs such as HRQoL. A patient reported outcome measure (PROM) is the tool used to measure the PRO, usually a standardized questionnaire (172). Hence, a HRQoL questionnaire is one example of a PROM.

The patients´ perspectives, as being fundamental to ensure high quality health services, have gained increased recognition over the last decades (173). Both the US FDA and the European Medicines Agency (EMA) encourage incorporating PROs in clinical trials (174, 175). Although PROMS were originally developed for use in research, their applications have broadened to several other settings, such as supporting clinical decision making and comparing outcomes among health-care providers, stimulating quality improvement, and evaluating practices and policies (176-178).

There are two main categories of PROMS: condition-specific and generic. Generic PROMS measure health concepts that are relevant to a wide range of patient groups, while condition-specific PROMS capture elements of health relevant to a particular patient group or condition (172). EQ-5D is an example of a generic PROM, it includes five questions asking about the patient's health that day, mobility, self-care, usual activities, pain/discomfort and anxiety/depression (179). An example of a condition-specific PROM, is the widely used EORTC QLQ-C30, developed by the EORTC to assess the QoL of patients with cancer. This is the core instrument, containing 30 questions examining global QoL, functions and symptoms relevant to a broad range of cancer patients, irrespective of a specific cancer diagnosis (180). In addition, the EORTC has developed several modules targeting symptoms and outcomes of different cancer diagnoses (e.g. EORTC QLQ-CIPN20) (181). The QLQ-C30 has been translated and validated in over 110 languages, and it has been used in more than 3 000 studies worldwide (168). Numerous PROMS have been developed, and in the literature more than 300 generic and condition-specific PROMS have been identified (172).

The questionnaire together with the algorithm used to transform responses into scale scores for analysis and reporting is often referred to as the HRQoL instrument. Developing a HRQoL or other PRO instruments is a lengthy process involving careful item selection, informed by the literature review and expert and patient opinion, and testing of the instruments' validity and reliability with populations of interest (175, 182). PROMS should satisfy certain properties as validity, reliability, sensitivity, and responsiveness (170, 183-185). *Validity* refers to what extent the instrument measures what it is supposed to measure, and the *reliability* of a measurement is its ability to yield reproducible and consistent results. In the context of HRQoL, *sensitivity* is the ability to discriminate different states of HRQoL, while *responsiveness* is the ability to detect change in HRQoL.

1.4.4. HRQoL during palliative chemotherapy for mCRC

With advancements in the oncology field with more treatment options to extend survival, the need to assess HRQoL in addition to merely survival has been acknowledged. During the 1980s there was an exponential growth of methods to measure HRQoL, and inclusion of HRQoL as an endpoint in cancer clinical trials (170). In 1985, the US FDA called for HRQoL data as one of the 'key efficacy parameters' in clinical trials for new anticancer therapies (186). The American Society of Clinical Oncology (ASCO) treatment guidelines reinforced in 1996, that HRQoL was one of three key endpoints for cancer clinical trials in addition to response and survival (187). As described above, this has been repeated by major health authorities worldwide (174, 175).

HRQoL can be affected by cancer and its treatments in different ways through the disease trajectory from diagnosis through curative, adjuvant, palliative and end-of-life care. The intent of treatment will vary between curative and palliative, as well as the symptoms and side-effects (188). Patients will also differ in which HRQoL outcomes they are willing to trade off for specific treatment benefits (symptom palliation or increased chances of survival) (170).

When cure is not an option, main treatment goals of advanced CRC are prolongation of life, symptom relief, and maintenance of QoL. Knowledge of treatment effects from different chemotherapy regimens is mainly derived from RCTs which usually constitute highly selected patients who may not be representative for the whole patient population. Participants in RCTs are often younger, with a median age typically 10 years below the general patient population, and with a better performance status (PS) (189, 190). Still, treatment guidelines are based on such trials. Since elderly patients are underrepresented in RCTs, there have been concerns whether these patients will tolerate palliative chemotherapy as good as their younger counterparts.

In RCTs investigating new chemotherapy regimens, the strategy often is treatment to progression or unacceptable toxicity (32-34). In contrast, the clinical practice in Northern Europe is to introduce a chemo-break in a stop-and-go manner or maintenance therapy with a milder regimen to let patients recover from side effects of treatment (35). Several trials have explored whether maintenance or intermittent treatment is preferable regarding efficacy and tolerability, but no final consensus has been established (191-195). In a meta-analysis from 2020, Sonbol et al. concluded that there is no clear overall survival (OS) benefit with either

strategy, but a maintenance strategy is preferred (196). More information from real-life populations regarding effects and side-effects from different treatment regimens is needed for patients to make well-informed choices on receiving chemotherapy, withholding treatment, or introducing a chemo-break.

1.4.5. Investigating HRQoL in real-life mCRC populations.

Several observational studies have investigated HRQoL among CRC patients receiving chemotherapy (197-207), but to our knowledge none comparing changes in HRQoL between younger (<70 years) and older from a real-world unselected cohort of mCRC patients the first year of palliative chemotherapy.

An Austrian prospective single-centre observational study assessed HRQoL across the various lines of palliative chemotherapy among 100 consecutive mCRC patients starting a new line of treatment (199). The HRQoL instrument used was the EORTC QLQ-C30. Patients were followed up to three years with regular assessments. A steady worsening of physical functioning, fatigue, pain, dyspnoea and appetite from first-line chemotherapy to the later treatment phases was found, while global QoL, emotional function and role function improved somewhat after the end of first-line chemotherapy, only to deteriorate again during second and later lines of chemotherapy. Lower symptom burden and better QoL among patients achieving a treatment response, compared to those with progressive disease, were also observed.

A prospective longitudinal observational study performed in Oslo compared symptom burden and QoL of 120 CRC patients receiving curative (n=68) versus palliative (n=52) chemotherapy before start and during the first six months of chemotherapy (200-202). Symptoms were assessed with the Memorial Symptom Assessment Scale (MSAS), and QoL with the Medical Outcomes Study Short Form-12 (SF-12). Assessments were repeated at multiple time points: Baseline, days 4 and 8 of the two first cycles of chemotherapy, right before start of the second cycle, and after three and six months. Before start of treatment, an average of ten co-occurring symptoms were present among patients in both groups, the most prevalent (present in 50-65%) being worrying, lack of energy, feeling drowsy or bloated, pain and difficulty sleeping. No significant differences were found between the two patient groups (201). During treatment, 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 higher pain scores over time, as well as for lack of energy. Severity of worrying decreased over time in both groups, whereas younger age was significantly associated with higher scores on worrying and lack of energy (202). Finally, this study demonstrated that CRC patients had worse physical and mental QoL scores than the general population at all the time points, impaired physical QoL was significantly associated with psychological symptom burden and symptoms of CIPN, and impaired mental QoL was associated with physical symptom burden, being female, having younger age, and having problems with sexual interest (200).

A large German cohort study regularly assessed HRQoL for up to five years in 2314 patients with metastatic breast-, pancreatic-, lung- or CRC (207). The primary aim was to examine the association of disease progression with various HRQoL domains. The CRC group constituted 702 patients, and HRQoL was assessed with the QLQ-C30. The first disease progression was associated with a significant worsening of 37 of 45 HRQoL scales, whereas for 17 of the scales, the worsening was clinically meaningful. Irrespective of cancer type, the most affected domains were appetite loss, physical functioning and fatigue. An even larger decrease in HRQoL was associated with the second progression.

2. Aim of the thesis

The overall aim of this thesis was to gain increased insights in the feasibility of a PE intervention during adjuvant chemotherapy for CRC, how patients experience PE during chemotherapy, and how chemotherapy affects HRQoL among patients with CRC.

More specifically, the following research questions were asked:

Paper I:

1. What is the feasibility of a PE intervention during adjuvant chemotherapy for CRC?

Paper II:

1. What are the expectations to and experiences with participating in an individually tailored and supervised PE program during adjuvant chemotherapy for CRC?

Paper III:

1. With key focus on global QoL, physical- and role functioning, fatigue, pain, nausea and vomiting - How is HRQoL changing in older (> 70 years) compared with younger CRC patients the first year of palliative chemotherapy in a real-life population?
2. What is the impact of a chemo-break on HRQoL?

3. Material and methods

3.1. Methodological framework

Methods used in the present thesis are derived from two different scientific traditions; the quantitative and the qualitative paradigms. In the field of medicine and oncology, quantitative research methods have long traditions, with the RCT being held as the gold standard for measuring the effectiveness of a new treatment or intervention (208). Qualitative research has its roots in social science, but has in recent decades gained increased recognition in health science, realising that knowledge is more than what can be objectively weighed and measured; medical and healthcare knowledge encompasses people´s experiences with disease, health and encounters with the health care system, among others, as well (209).

Different philosophical worldviews, or epistemologies and ontologies, frame the different research methods. Coming from a tradition of quantitative research, discussing which philosophical and theoretical assumptions are informing one´s analysis, is not so common. This is more common (and expected) in the qualitative paradigms, as there are different assumptions that can underpin an analysis, of which some could be at odds with a specific method(ology) (210, 211). Quantitative research is typically based on a realist ontology and post-positivist epistemology: A world knowable through systematic observation and experimentation. (212). An ontological position of realism assumes the existence of objective reality. Positivism was the dominant epistemological framework underpinning scientific research for centuries, assuming an objective reality and the possibility of generating objective knowledge about this through the appropriate application of scientific methods. Post-positivism retains positivism´s belief in the existence of an objective reality and objective knowledge remains the ideal, but observation is acknowledged to be imperfect and influenced by the researcher´s values and culture (212).

Qualitative research methods encompass a wide range and diversity of theoretical frameworks and research approaches. It is not one single approach, but they share some common features, such as focusing on meaning – from understanding situated meaning to interrogating meaning-making practises (212). They are research strategies for description, analysis and interpretation of character traits and characteristics or qualities of the phenomena to be studied (209). The epistemology underpinning ‘true’ qualitative research is non-positivist (e.g.

contextualism, constructionism) (212). Contextualism views knowledge, and the humans who created it, as contextually situated, partial and perspectival, while constructionism is founded on the premise that research practices produce rather than reveal evidence, and is based on the assumption that that reality is subjective and changing, and dependent on its context (212).

Although the present thesis applies methods derived from different scientific traditions, our work is situated within the post-positivist worldview. Given the research question addressing the feasibility of a PE intervention in paper I, utilizing qualitative methods exploring participants´ experiences from such an intervention seemed appropriate. Thematic Analysis (TA) is a qualitative method which we have employed in paper II. It is a method for analysing themes within data (213), with the data in the present work being transcripts from semi-structured interviews of CRC patients participating in a supervised PE program during adjuvant chemotherapy.

3.2. Study design and patient population

The analyses of this thesis are based on data from two different patient populations:
CRC patients engaging in a supervised PE program during adjuvant chemotherapy and CRC patients during palliative chemotherapy.

Paper I is the primary publication of the FAKT feasibility study. This was a single-centre, non-randomized interventional study with a pre-post design evaluating the feasibility of a PE intervention and data collection among patients during adjuvant treatment for CRC (Additionally, one participant was recruited from Ålesund hospital in order to prepare this hospital for the upcoming RCT).

Paper II is a qualitative study exploring (in a longitudinal manner) the experiences of CRC patients participating in a supervised PE program during adjuvant chemotherapy.

Paper III is based on HRQoL data from subjects in the mCRC study the first year of palliative chemotherapy. The mCRC study was a prospective, longitudinal observational study of real-world patients with metastatic or inoperable CRC in the health region of Middle-Norway.

The FAKT feasibility study included CRC patients commencing adjuvant chemotherapy, and the main inclusion criteria were:

- Radical resection for stage II–IV CRC within the last 3 months and scheduled for adjuvant chemotherapy.
- Age 18–80 years.
- Performance status 0–2 according to the Eastern Cooperative Oncology Group.
- Ability to conduct the intervention based on the treating physician's assessment and ability to understand Norwegian language.
- No serious comorbidity contraindicating PE and no treatment for other invasive cancers during the five past years.

The mCRC study included patients with metastatic or inoperable CRC, and the main inclusion criteria were:

- Newly diagnosis of metastatic or non-resectable CRC.
- Age ≥ 18 years.
- Written informed consent.

FAKT feasibility study, 2016-2018, n=19

As a preparation for a future RCT, aiming to investigate whether a PE intervention during adjuvant chemotherapy for CRC could reduce the development of CRF and CIPN, the FAKT feasibility study was performed at St. Olav´s and Ålesund hospitals. The primary aim was to evaluate the feasibility of a PE intervention and data collection among patients during adjuvant treatment for CRC. The secondary aims were to explore post-intervention changes in CIPN and fatigue.

mCRC study, 2014-2018, n=354

The aim of the mCRC-study was to evaluate treatment and patient care given to unselected 'real life' patients during their disease trajectories.

Eligible patients were consecutively included from the seven hospitals in Mid-Norway. Patient- and tumour characteristics were recorded at baseline. All tumour directed treatment, response of treatment, toxicity and time of death were prospectively recorded. HRQoL was

assessed with EORTC QLQ-C30. Questionnaires were filled in at inclusion and were sent with a pre-stamped return envelope every second month lifelong.

In our work in paper III, we focused on the patient population in the mCRC study who started first line palliative chemotherapy, aiming to investigate changes in HRQoL the first year of treatment. Only patients who had filled in the baseline questionnaire and were scheduled to start first line palliative chemotherapy were included in this work (n=214).

Table 2. Characteristics of patients included in papers I-III.

	Paper I	**Paper II**	**Paper III**
Enrolment period	Dec. 2016 – Nov. 2018[1]	Jan. 2018 – Oct. 2020[2]	Sep. 2014 – Nov. 2018
Number of centres	2	2	7
Location	Mid-Norway	Mid-Norway	Mid-Norway
Numbers included	19	15	214
Age (years)			
Median	63	65	69
Range	33-80	43-80	27-89
Gender (%)			
Male	52,6	53,3	59,8
Female	47,4	46,7	40,2
PS (%)			
0	47,4	66,7	46,3
1	47,4	33,3	41,6
2	5,2	0	12,1
Stage of disease (%)			
III	78,9	86,7	0
IV	21,1	13,3	100
Intent of treatment (%)			
Curative	100	100	0
Palliative	0	0	100

[1]*One participant was recruited from Ålesund hospital preparing for the upcoming RCT.*

[2]*Additional five participants were recruited from the upcoming FAKT RCT (76).*

3.3. Treatments

In the FAKT- feasibility study, the patients received adjuvant combination- or monotherapy for three to six months according to general guidelines, irrespective of study participation. Similarly, patients in the mCRC study received first line palliative chemotherapy in line with general guidelines, clinical practice and at the discretion of the treating physician, irrespective of study participation.

3.3.1. Physical exercise intervention

The PE intervention was individually adjusted and supervised, and it comprised progressive aerobic endurance-, resistance-, and balance exercises. A physiotherapist, certified in giving PE for cancer patients, supervised the PE sessions twice a week at a specialized outpatient training facility for cancer patients located within the hospital area. Additionally, the participants were encouraged to perform one weekly, unsupervised PE session with endurance- and balance exercises. Duration of the PE program was 12-24 weeks, same as duration of the adjuvant chemotherapy.

Each session comprised 10 min warmup, 20 min aerobic endurance-, 15 min resistance-, and 15 min balance exercises. The warmup and endurance exercises were performed on a treadmill. Endurance exercise was standardized as a gradual approach to intervals of four min (Table 3). The Borg's scale (214) was used to instruct the participants regarding intensity and to map the participants' rate of perceived exertion (RPE). The physiotherapist recorded RPE after warmup and following each interval. On a scale from six (no effort) to 20 (maximal effort), the participants reported how strenuous the PE was (RPE). For progression, the intensity of the interval training was increased during the intervention period; from 12–14 ('somewhat hard') on Borg's scale in weeks 1-16 to 14–16 ('hard') from week 17.

The resistance exercises aimed at large muscle groups and followed a period plan that involved individually tailored progression according to standardized training principles (Table 3). During the first two weeks, the focus was adaptation, learning of technique, and intensity management. In weeks 3-8, participants performed the PEs with submaximal intensity (low resistance, up to 12 repetitions in three series) to account for any postoperative limitations (e.g. avoiding high abdominal pressure and pain provocation). In weeks 9-16, PE load was adjusted based on the weight the participant managed to lift a maximum 10 times and

repeated in three series. In the last period (weeks 17-24), intensity was increased by reducing the number of repetitions (6-8) and increasing the number of series (3-4) to work up to maximum strength. In line with individually adapted progression, manual weights, elastic bands, and various exercise equipments were used.

Balance training consisted of a set of exercises, lasting 15-20 minutes, to be performed on various surfaces (floor, cushions, or bosu balls). Individual tailoring was based on the physiotherapist making a selection from a standardised pool of exercises with increasing difficulty from static to dynamic balance, and progress was monitored in the two weekly supervised sessions.

Table 3. Endurance and resistance exercise.

Aerobic endurance exercise		
Period/exercise	Duration	Borg's scale
Week 1 – 2		
Walking on treadmill[1]	5 min	12 - 14
Week 3 – 8		
Intervals of uphill walking	4 – 6 x 2 min	12 - 14
Week 9 – 16		
Intervals of uphill walking	3 – 4 x 3 min	12 - 14
Week 17 – 24		
Intervals of uphill walking	4 x 3 – 4 min	14 - 16
Resistance exercise		
Period/exercise	Period	Repetitions (reps)
Week 1 - 8	Week 1	1 x 12 reps
Knee extension	Week 2	2 x 12 reps
Sitting chest press	Week 3 - 8	3 x 12 reps
Standing rowing		
Seat raise		
Week 9 - 24	Week 9 – 16	3 x 10 reps
Leg press	Week 17 - 24	3 x 8 RM[2] / 4 x 6 RM
Oblique Seated chest press with manuals		
Standing rowing		
Back lying one leg lowering		

[1]*Getting accustomed to the treadmill*
[2]*RM = repetition maximum*

The mCRC study was an observational study, and there was no study intervention.

3.4. Assessments and outcome measures

In paper I, the FAKT feasibility study, participants filled in questionnaires at baseline, after 3, 6, 9, and 12 months, and they performed physical tests at baseline, after 3, and after 6 months. The questionnaires used were the EORTC QLQ-C30, EORTC QLQ-CIPN20, and the Fatigue Questionnaire (FQ) (180, 215, 216). To assess self-reported PA level, a questionnaire for patient-reported PA developed for use in the North Trondelag Health Study (HUNT) was used (217). Physical tests were 'Modified Shuttle walk', 'Sit-to-stand', 'Tandem stance', and 'Unipedal stance' (218-221). Demographic variables, clinical characteristics, treatment given, and sick leave were also assessed.

In the qualitative study in paper II, individual, semi-structured interviews were performed at baseline, after three and six months, following an interview-guide.

In paper III, the EORTC QLQ-C30 was collected at baseline and every second month. Patient- and tumour characteristics and the different treatments given, with response, were prospectively recorded.

3.4.1. Quantitative measures

Feasibility outcomes

(1) Willingness to participate; the rate of consenting participants among those invited for participation.

(2) Inclusion rate; the number of included participants among eligible participants identified.

(3) Dropout rate; the number of participants who withdrew from the study among consenting participants. These were termed 'dropouts', while the rest were termed 'completers'.

(4) Attendance to supervised PE; the rate of performed sessions compared to the number of planned sessions.

(5) Adherence to supervised PE; the content of each session when a participant met was compared to the PE program according to protocol.

(6) Attendance to unsupervised PE; the number of performed unsupervised PE sessions divided by the number of unsupervised PE sessions according to protocol.

(7) Safety; any serious adverse events (SAEs), occurring from the participants started the intervention until 1 month after the end of the intervention were registered , and any adverse event occurring during supervised PE was noted.

(8) Completion rate of questionnaires and physical testing

Reasons for declining study participation, dropping out or not attending PE sessions were recorded, if known.

Chemotherapy induced peripheral neuropathy (CIPN)

The self-reported questionnaire, EORTC QLQ-CIPN 20, is a 20 questions QoL form, developed to reveal patients' experience of symptoms and functional limitations related to CIPN. It has three subscales; a sensory, motor and autonomous (181). Measuring changes in patient-reported CIPN between baseline and three months after inclusion, we used the 9-item sensory subscale, since the sensory peripheral neuropathy is the most pronounced induced by oxaliplatin. Each item is rated on a scale from 1 (‘not at all’) to 4 (‘very much’). The raw score (RS) in CIPN is calculated by the sum of each item’s score (1–4), divided by the number of items. The RS is then transformed into a scale from 0 to 100, as described in the EORTC scoring manual (222), resulting the score (S), where higher S indicates worse CIPN. For each participant, S at baseline was subtracted from S at month 3 after inclusion, to calculate the change in CIPN.

Fatigue

The self-reported Fatigue Questionnaire (FQ) contains 13 questions, is generic and has well documented psychometric properties (216). Each question is rated on a scale from 0 (‘not at all’ or ‘less than usual’) to 3 (‘much worse than usual’). FQ measures physical fatigue (PF) (seven questions, scores 0–21) and mental fatigue (MF) (four questions, scores 0–12). All questions combined give total fatigue (TF) (scores 0-33). Higher score indicates more fatigue**.** For each participant, PF and MF scores at baseline were subtracted from PF and MF scores at month 3 after inclusion, to calculate the changes in PF and MF during the intervention period.

Physical activity (PA)

Assessing self-reported PA level, a questionnaire for patient-reported PA developed for use in the North Trondelag Health Study (HUNT) was utilized (217). This is a three-item questionnaire on leisure-time PA regarding frequency, intensity, and duration (three–five alternatives) giving rise to a PA index, placing the participants in three different levels of activity, from low to high. In paper II, PA level at baseline among participants in the qualitative study is presented.

HRQoL

The EORTC QLQ-C30 version 3.0 was used assessing HRQoL in paper III (180). This is a cancer-specific, self-reported questionnaire aggregating 30 items, constituting five functioning scales, three symptom scales, six single items and one overall QoL scale covering the past week. The two items assessing overall health and QoL are scored on a categorical scale from 1 to 7 giving rise to global QoL, and the rest of the items are scored from 1 (‘not at all’) to 4 (‘very much’). Higher scores on the functioning and global QoL scales indicate better functioning, while higher scores on the symptom scales and single items indicate more symptoms.

HRQoL scores are transformed into a scale from 0 to 100, as described in the EORTC scoring manual (222). Changes or differences in QoL scores of >20, 10-20, and 5-10 points are considered to be of large, moderate, and small clinical magnitude, respectively (223). Comparing means of different QoL scores between groups or over time, a threshold of 5-10 is considered the minimally important difference (MID) (224). No imputation of missing data was performed.

At baseline and after 12 months, all domains from the QLQ-C30 are presented according to age group, comparing younger (<70 years) vs. older (≥70 years). Describing changes in HRQoL, the key six domains are global QoL, physical- and role functioning, fatigue, pain and nausea/vomiting. The domains were chosen based on what clinicians often experience is affected by cancer and its treatments, and thus often reflected in clinical studies in this patient population (225).

Impact on HRQoL of a chemo-break

To evaluate the impact of a chemo-break, the time period between months six and eight was chosen, since clinical guidelines often recommend to consider a chemo-break after six months of treatment (12, 226). To be eligible for this analysis, patients had to have returned questionnaires at both time points, and to be on treatment and not having progressive disease at month six.

3.4.2. Qualitative inquiry

Semi-structured interviews

To explore participants´ expectations to and experiences with individually adjusted and supervised PE during adjuvant chemotherapy for CRC, individual, semi-structured interviews were performed with a prospective longitudinal design, before, during and right after completion of the intervention period.

To best gain knowledge of the topic of the study aim, purposive sampling was used (227), meaning recruiting participants that were about to, or were participating in supervised PE during adjuvant chemotherapy for CRC. Consecutive participants entering PE interventions during adjuvant chemotherapy for CRC were invited in a separate written information- and consent form to participate in the qualitative study between Jan. 2018 and Oct. 2020.

The interviews were held in a private room at the hospital and scheduled in concordance with the patients' other appointments. A semi-structured interview guide was used to ensure guidance to the aim of exploring patients´ expectations to and experiences with engaging in a supervised PE intervention during adjuvant chemotherapy for CRC. The interview guide covered topics based on results from previous studies regarding factors providing motivation and barriers to exercise during cancer treatment. Based on experiences from the first interviews, the interview guide was adjusted. The interviewers strived to use broad open-ended questions, allowing for pauses to facilitate sharing of information, and to use follow up questions to get deeper understandings. The interviews lasted 20-45 minutes, were audio recorded and transcribed verbatim.

Three researchers, none of which were involved in the medical treatment or supervising the PE intervention, conducted the different interviews. One was a physiotherapist (SAS) having long experience with cancer patients, the other an oncologist (IH) (the PhD candidate), and the third a psychologist and an experienced qualitative researcher (JAS), supervising the two others, considered as novices in the field of qualitative research. The first 15 interviews were performed by SAS as part of her master's project and the next four by IH in order to get familiar with the research method. Given the inexperience in qualitative research of the two first, the rest of the interviews were performed by JAS, aiming to provide more richness and depth to the data.

During the study period, 15 participants at St. Olav´s University Hospital (n=14) and Aalesund Hospital (n=1) provided 29 interviews distributed over the three time points (baseline, after 3 and 6 months). Inclusion was stopped based on the research group´s agreement that the collected data contained sufficient information to provide answers to the research question and provide new knowledge to the research field (228, 229).

Table 4 provides baseline characteristics of the participants included in the interview study.

Table 4. Patient characteristics in the interview study

No. of patients	15
Age, years, median [range]	65 [43-80]
Males	8
Females	7
Stoma	
Yes	2
No	13
Type of surgery	
Laparoscopy	7
Open	8
Stage[1]	
III	13
IV	2
Adjuvant treatment planned	
3 months Capox	4
6 months Capox	8
6 months Capecitabine	3
Marital status	
Living alone	7
Married/partner	8
Employment	
Working	7
Partly working/partly disabled	2
Retired	6
Education	
Elementary or high school	6
College/university	9
Self-reported physical activity	
Low levels of activity	7
Medium activity	4
High activity	4

[1]*Stage according to TNM Classification of Malignant Tumours, 8th edition*

3.5. Analysis

3.5.1. Quantitative analysis

No formal sample size calculations were performed due to the feasibility- and observational designs of the FAKT and mCRC studies, respectively. For the FAKT study, it was estimated that 20 participants could be recruited within a year at St. Olav's hospital, and this number was considered to be sufficient in evaluating whether the intervention and test procedures were feasible and in estimating the sample size for the larger RCT. In the mCRC study, consecutive patients were included at the seven hospitals in Mid-Norway within a given time frame.

In paper I, feasibility outcomes are presented using descriptive statistics and simple arithmetic. Continuous variables are reported by median values, range, and standard deviation (SD). Also in paper III, statistical analyses performed are mainly descriptive, mean scores are compared between groups with the two-sample t-test, and for the survival analyses the Kaplan-Meier method is used. The Log Rank test is used comparing survival between groups. Patient baseline characteristics are described with median and range (continuous variables) or with numbers and percentages (categorical variables), and compared between groups with the Pearson's Chi-Square test, which also is used comparing individual changes from baseline to month four and twelve. A two-sided p-value of <0.05 was considered statistically significant. The analyses were performed using IBM SPSS Statistics versions 25 (paper I) and 28 (paper III).

3.5.2. Thematic Analysis

The interviews were analysed using TA as described by Braun and Clarke in 2006 (213). This is a method for identifying, analysing and reporting patterns (themes) within data. Advantages with TA are its flexibility, its independence of theory and epistemology, and hence can be applied across a range of theoretical and epistemological approaches (213). A main reason for choosing TA, was that it was considered easily accessible to beginners in qualitative research. The analytic process is guided by six phases: 1. Familiarizing yourself with your data, 2. Generating initial codes, 3. Searching for themes, 4. Reviewing themes, 5. Defining and naming themes, and 6. Producing the report. In later work, Braun and Clarke have developed

and refined their method, and they have renamed it reflexive TA (210, 212, 230). Also, they have suggested dividing TA into three different clusters, named 'coding reliability', 'codebook' and 'reflexive' variations (210). Our analysis in paper II is based on the method described in the original article from 2006, not the codebook or coding reliability variants.

Given the explorative nature of our work, no theoretical framework was applied to guide our analysis, which was more data-driven and was approached in an inductive way. We took an experiential orientation centring the meanings and experiences articulated by participants, who were given the opportunity to tell about their experiences in their own words (212). Further, our work assumed and ontological position of critical realism and a post-positivist epistemology. Critical realism provides a position that retains a concept of truth and reality, but recognises that human practices always shape how we experience and know this (212).

The analytic process started by reading and re-reading all the transcribed interviews. The whole research team for paper II read the interviews, generated codes and suggested initial themes. Additionally, the PhD candidate (IH) listen through all the audio recorded interviews at least once. The research team had regular meetings, discussing initial findings, reflecting over what was in the data, discussing codes and initial themes. A code represents the most basic element of the raw data that can be assessed in a meaningful way. Examples of codes in our work could be 'loss of energy', 'desire to relax' and 'gratitude'.

All the interviews were coded systematically, and data extracts relevant to each code were collated. Two examples of data extracts corresponding to the code, 'gratitude', were: *"I don't know, just hope all people in the whole world get the opportunity to do this, anytime really, but especially when you're sick and need some extra help...not to push you, but they're there in a way,"* and *"I'm just so happy that I got to participate, very happy that I was selected."*

The codes were then collated into potential themes. Codes that seemed to have something in common, were put together. We organized this by using tables in Microsoft Word. One column for the codes, and three columns for the three time points (baseline, after 3 and 6 months). Data extracts were sorted according to participant number, time point and corresponding code. JAS and IH were mainly involved in this process, which was a recursive one, discussing back and forth, moving codes between different themes. Re-reading the interviews was also done, making sure the themes worked in relation to the data set.

Initially, we generated six themes. Two of these where discarded, both because of word limits provided by the journal, but also because they were considered less relevant for the research question. These themes were ‘disease experiences’ and ‘side-effect experiences’. Having agreed on the four themes, named them, and organized the collated data extracts for each theme, writing an analysis for each theme was done. We aimed to provide a concise, coherent, logical and non-repetitive account of the story the data told. Finally, quotations were supplied the analysis, as examples of the different issues. We chose quotations from a wide variety of the participants, avoiding using data extracts just from a few.

Our analysis was mostly on a semantic level, exploring meaning on the surface/explicit level, but also touching the more latent, exploring meaning at the more underlying or implicit level. The initial design was to explore relevant themes in a pre-post fashion, but the prolonged therapeutic period for a minority of the participants allowed for additional elements of a longitudinal analysis (231). Although JAS and IH were mainly involved in the last phases of the analysis, the whole research team participated in discussions regarding the analysis, read through, and approved the final report.

Braun and Clarke place their refined version of reflexive TA under Big Q qualitative research, with epistemologies underpinning ‘true’ qualitative research being non-positivist (212). Kidder and Fine used the term Big Q for ‘fully qualitative’ research in contrast to the use of qualitative data in a limited way, or with values more aligned to quantitative positivist research, which they designated ‘small q’ qualitative research (232). In the present work, our research should be categorized as small q, in line with other mainstream qualitative research in medicine. We considered the described approach being sufficient for the aim of our project.

3.6. Ethics

The FAKT feasibility study and the accompanying qualitative study were approved by the Regional Committee for Medical and Health Research Ethics of Northern Norway (Record no. 2015/1050/REK nord). After provided with both oral and written information, all participants gave their written consent. A separate written consent was obtained for the interview-study, and information regarding the qualitative study was repeated before starting the interviews.

The mCRC-study was approved by the Norwegian Data Protection Authority (Reference no. 36627 13 /01039-6 / CGN), and the work provided in paper III was approved by the Regional Committee for Medical and Health Research Ethics of Middle Norway (Reference no. 216433). Written informed consent was obtained from all individual participants included in the study after being provided oral and written information.

All participants were informed that they at any time, without providing any reason, and without any consequences for future treatment or care, could withdraw from the study. The studies were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

4. Results of papers

4.1. Paper I

Physical exercise during adjuvant chemotherapy for colorectal cancer—a non-randomized feasibility study

Between December 2016 and November 2018, 52 potential participants were identified at the Cancer Clinic, St. Olav's hospital. In addition, one participant was identified and recruited from Ålesund hospital. Nine patients were found ineligible, and additionally 14 eligible patients were not asked for participation, mainly due to long travel distance to the hospital. With 19 consenting to participate among the 30 eligible patients asked, the willingness to participate was 63 %, and the inclusion rate was 43% (19 among 44 eligible).

Five of the 19 included never started the intervention; two because of serious complications after the first course of chemotherapy, and further adjuvant chemotherapy was stopped, two withdrew consent shortly after inclusion, reporting having 'too much going' and having transportation issues, and the fifth dropout was not contacted, due to misunderstanding. Further two participants dropped out after one and four PE sessions, respectively. One reported pre-existing back pain got worse, and the other did not show up after the first session despite repeated proposals of new appointments. Total dropout rate was 37% (7 of 19).

The median rate of attendance to supervised PE was 85% (range 33-100). The median adherence to supervised endurance, resistance, and balance exercises was 96, 95, and 100%, respectively. The planned increase in intensity of endurance exercise from the first to the second intervention period was not achieved, as the intensity of the endurance exercise was slightly lower in the second period (week 17–24) with a median of 13,5 on Borg's scale, opposed to 14 in the first period (week 1–16). Only four participants achieved the planned intervals of 4 times 3–4 min. (Table 5). Median attendance rate to unsupervised PE was 59% (42-88), but was systematically registered only in the second half of the completers.

During supervised PE, no adverse events were registered. The SAEs registered during the intervention period, none with a temporal relationship with the PE intervention, were most likely related to the adjuvant chemotherapy.

Table 5. Attendance and adherence to supervised exercise

	According to protocol	N	Median	Range	SD
Planned sessions (number)	48	12	44	[22, 46]	7.6
Performed sessions (number)		12	37.5	[12, 46]	11.1
Attendance to supervised exercise (%)		12	85.4	[33.3, 100]	19.9
Adherence to supervised endurance exercise (%)[1]		12	95.8	[81.6, 100]	6.9
Borg's scale week 1 - 16	12 - 14	12	14	[12, 16]	1.1
Borg's scale week 17 - 24	14 - 16	10	13.5	[12, 16]	1.5
Adherence to supervised resistance exercise (%)[1]		12	94.5	[76.5, 100]	6.5
Adherence to supervised balance exercise (%)[1]		12	100	[86.5, 100]	4.3
Did participants achieve 4 times 3-4 minutes intervals?	N				
Yes	4				
No	6				
Not applicable[2]	2				

[1]*Adherence to the exercise programme when a participant met.*
[2]*Adjuvant chemotherapy and the intervention lasted less than 17 weeks.*

The completion rate of questionnaires was close to 100%, and the completion rate of physical testing was 100%. Eighteen of 19 consenting participants completed the baseline questionnaires. At 3, 6, and 12 months, all 12 completers returned the questionnaires, with the QLQ-C30 missing in one participant at 12 months. At 9 months, 11 of 12 were completed, with the CIPN20 and FQ missing in one participant.

The symptoms of CIPN increased from baseline to three months after inclusion with a median increase of 14.8 on a scale from 0-100. Physical fatigue (PF) decreased one point on a scale from 0-21, and mental fatigue (MF) increased one point on a scale from 0-12 (Table 6).

Table 6. Individual changes in patient-reported chemotherapy induced peripheral neuropathy and fatigue.

		CIPN[1]			PF[2]			MF[3]		
	N	Median	Range	SD	Median	Range	SD	Median	Range	SD
T_0[4]	10	0.5	[0, 33.3]	10.3	16.0	[6.0, 24.0]	6.3	4.5	[4.0, 8.0]	1.3
T_1[5]	10	20.4	[0, 44.4]	13.0	15.0	[7.0, 25.0]	5.5	5.5	[4.0, 10.0]	2.1
$T_1 - T_0$	10	14.8	[-3.7, 25.9]	9.6	- 1.0	[-6.0, 13.0]	5.9	1.0	[0, 5.0]	1.6

[1]*European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chemotherapy Induced Peripheral Neuropathy 20 sensory subscale (score 0-100)*
[2]*Physical fatigue from Fatigue Questionnaire (score 0-21)*
[3]*Mental fatigue from Fatigue Questionnaire (score 0-12)*
[4]*Baseline*
[5]*After 3 months*

4.2. Paper II

Colorectal cancer patients' experiences with supervised exercise during adjuvant chemotherapy - A qualitative study

Paper II addresses patients´ expectations to and experiences with participating in an individually tailored and supervised PE program while undergoing adjuvant chemotherapy for CRC. Four main themes developed were ‘structuring life with cancer’, ‘motivation to exercise’, ‘training experiences’, and ‘effects of exercise’.

‘Structuring life with cancer’ refers to patients seeing several potential benefits of being included in the study, as hoping for positive effects of exercise, but also an opportunity to structure their lives as cancer patients through scheduled appointments and commitments. The importance of filling the days when on sick leave, in addition to avoid isolation were recognized, as well as advantages from getting out instead of sitting indoors doing nothing. It gave them something to look forward to, and regular appointments contributed in getting up and out when feeling depressed or tired.

‘Motivation to exercise’ refers to patients´ initial scepticism and insecurity towards participation, but also what provided motivation, such as the threat of losing strength. There was faith in exercise, both being good for your physical and mental health, including a hope that exercise might increase the efficacy of chemotherapy. Both external and internal sources for exercise motivation was demonstrated. Regular appointments with the physiotherapist reinforced motivation, making participants feel obliged to attend, as well as the guidance from a professional gave a sense of security, providing motivation to perform a little extra. Motivation could be threatened if a session for some reason was cancelled, if the exercises were found boring, and when the participants felt fatigued. Providing motivation could be earlier experiences of symptoms decreasing during and after exercise. With time, an ambition to continue exercising without supervision after the study period also emerged, reflecting a change from outer to inner motivation.

‘Training experiences’ describes the variations in previous experience with PE among the participants from almost nothing to regular exercising. A common feature was the appreciation of walking outdoors. Both in and between individuals, variations in physical fitness and how they responded to exercise, were observed. Starting chemotherapy after

recovering from surgery, would give a setback, and physical fitness could vary within each chemotherapy cycle. The main obstacle to attending a training session was intercurrent illness. A factor contributing to the high adherence was individual adjustments made by the staff to accommodate various complaints.

'Effects of exercise' refers both to the hopes of effects prior to entering the program and the experienced effects of PE. Participants hoped that PE would improve their endurance and strength, regaining their pre-cancerous physical status and resuming activities they had been capable of before. These hopes were paired with a belief that staying in good shape would make the treatment more tolerable, and possibly reduce long-term side effects from chemotherapy. Several positive effects of PE were perceived by the participants, such as feelings of increased energy and being in better shape right after a session, reduced symptoms of depression and feeling of joy during and after PE. Although tiredness was a regular experience after a PE session, it most often was in terms of feeling tired in a good way. Towards the end of the study period, the perceived physical fitness diverged, ranging from feeling in better shape than for a long time, to feeling major fatigued. To be able to keep in shape, increasing and keeping their strength, despite receiving chemotherapy, led to feelings of satisfaction. Additionally, symptoms from peripheral sensory neuropathy could often diminish after commencing PE, lasting for several hours.

4.3. Paper III

Do older patients with colorectal cancer experience more deterioration in health-related quality of life during the first year of palliative chemotherapy? – A prospective real-world observational study.

Among 354 patients in the mCRC-study, 214 patients were included in the present study. Major reasons for exclusion were, missing baseline form, curative treatment intent and never started palliative chemotherapy. The completion rate of QLQ-C30 among those alive to answer was 100, 88, 87, 84, 83, 80 and 78% from baseline to month 12, respectively. After one year, 146 of the originally 214 patients were still alive.

At baseline, younger patients had better PS, and a larger proportion had their primary tumour intact compared to the elderly (42% vs. 25%). A larger proportion of the elderly (73% vs. 62%) had not received earlier curative intended chemotherapy. Almost all of the younger, as opposed to 73% of the older patients were scheduled for combination chemotherapy. The addition of a monoclonal antibody was more often given to the younger (80% vs. 59%). Baseline scores among younger patients were significant worse for global QoL, pain and financial difficulties, but better for physical functioning, compared to older patients (Table 7). Except for pain, the differences between mean scores in the two age groups were of a small clinical magnitude, but above the threshold for MID. Mean score for pain was 11 points higher in the younger group.

Younger patients reported better physical functioning but more pain at all time points through the first year (Fig. 4). Both groups experienced a decline in physical functioning, increased fatigue, and less pain from baseline to four months after introduction of chemotherapy. The two groups underwent similar changes in the six selected HRQoL domains through the first year of palliative chemotherapy. Compared to baseline, mean scores for these domains were on the same level one year after initiation of chemotherapy, except for the younger experiencing improvement in pain. After 12 months, using a threshold of 5-10 for the MID, an improvement in role- and social functioning (younger), emotional functioning, insomnia and appetite loss (both groups), and a deterioration in cognitive functioning (younger) and dyspnoea (older) were reported. Except for financial difficulties, there was no significant difference between the groups after one year (Table 7).

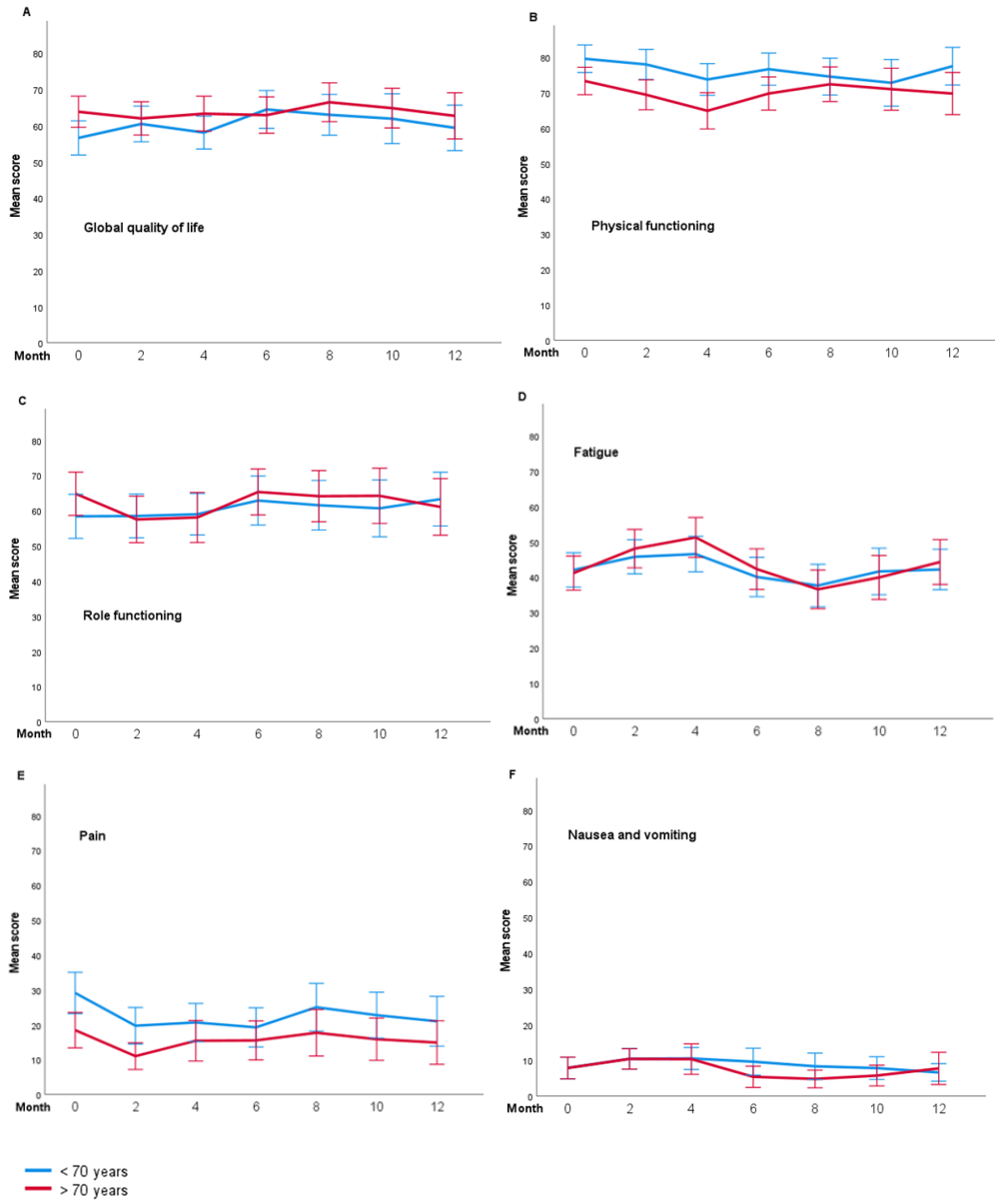

Fig. 4. Mean scores of A) global quality of life, B) physical functioning, C) role functioning, D) fatigue, E) pain and F) nausea and vomiting, according to age group, from baseline through 12 months after start first line palliative chemotherapy. The error bars represent 95% confidence intervals. A higher score on the functioning scales indicates better function, while a higher score on the symptom scales reflects more symptoms.

Table 7. HRQoL at baseline and after 12 months comparing younger and older patients.

	< 70 years	≥ 70 years	p **	< 70 years	≥ 70 years	p **
Time	**Baseline**			**After 12 months**		
	n = 110	n = 104		n = 58	n = 56	
Age (years)	62 (median)	75 (median)		60 (median)	76 (median)	
HRQoL	Mean (95% CI)	Mean (95% CI)		Mean (95% CI)	Mean (95% CI)	
Functioning scales*						
Global QoL	57 (52-61)	64 (60-68)	**0.026**	59 (53-65)	63 (56-69)	0.460
Physical functioning	79 (76-83)	73 (69-77)	**0.024**	77 (72-83)	70 (64-76)	0.055
Role functioning	58 (51-64)	65 (58-71)	0.15	63 (56-71)	61 (53-69)	0.691
Emotional functioning	76 (73-80)	80 (76-84)	0.15	82 (76-87)	85 (80-90)	0.327
Cognitive functioning	84 (80-88)	85 (81-89)	0.679	78 (72-85)	81 (76-87)	0.695
Social functioning	61 (56-67)	69 (63-74)	0.051	66 (59-73)	69 (62-76)	0.540
Symptom scales and single items*						
Fatigue	42 (37-47)	41 (36-46)	0.797	42 (36-48)	44 (38-51)	0.622
Nausea and vomiting	8 (5-11)	8 (5-11)	0.990	7 (4-9)	8 (3-12)	0.657
Pain	29 (23-35)	18 (13-23)	**0.008**	21 (14-28)	15 (9-21)	0.201
Dyspnoea	23 (18-28)	20 (15-25)	0.343	22 (14-31)	29 (21-37)	0.187
Insomnia	33 (28-39)	26 (20-31)	0.078	26 (19-34)	20 (12-28)	0.251
Appetite loss	29 (23-36)	26 (19-33)	0.470	21 (14-29)	19 (11-28)	0.852
Constipation	21 (15-26)	23 (17-29)	0.666	20 (13-27)	21 (13-28)	0.768
Diarrhoea	26 (20-31)	22 (18-28)	0.473	24 (19-30)	24 (17-31)	0.910
Financial difficulties	8 (5-12)	3 (0.4-5)	**0.015**	12 (6-18)	4 (1-8)	**0.019**

CI, confidence interval; QoL, quality of life; HRQoL, health-related quality of life.
**Higher scores on the functioning scales indicate better function, while higher scores on the symptom scales and single items indicate more symptoms.*
***Mean scores in age groups < and ≥ 70 years compared with the two-sample t-test.*

The worst mean scores for both fatigue and physical functioning were found four months after start of treatment. In this period, almost 40% of the patients in both groups experienced large deteriorations in fatigue, 25-30% experienced large deteriorations in physical- and role functioning, while on the other hand large improvements were seen in global QoL (16%), role functioning (19%) and pain (18%) (Fig. 5). There was no significant difference between the two age groups regarding individual changes from baseline to month four except for nausea and vomiting, where a larger proportion of the younger experienced a moderate deterioration.

After 12 months, 24% and 38% (not significant) of the younger and elderly, respectively, reported large deteriorations in fatigue. Otherwise, the majority of the patients belonged to the group with a small change in the selected domains one year after start of palliative chemotherapy.

Between month six and eight, 57 patients were evaluable for the impact of a chemo-break, of whom 33 and 24 patients respectively, had initiation of chemo-break or ongoing treatment from month 6. A larger proportion of females, those receiving irinotecan- and VEGFR antibody based therapy, and having RAS and BRAF wild type tumour, had initiation of a chemo-break. There was no significant difference in age between the groups. The group on continuous treatment had significant worsening of global QoL, physical- and role functioning, fatigue, nausea and vomiting from month six to eight, compared to those on a chemo-break, who demonstrated improvements in the same domains in this period (Table 8). The differences in scores between the groups ranged from 11-20 in these domains. There were no significant differences regarding change in pain in the same period or in median OS between the two groups.

Median OS in the whole population was 17.5 months [95% CI 14.4-20.5], with no significant difference between younger and older patients, being 17.4 [95% CI 12.6-22.2] vs. 18.1 months [95% CI 13.7-22.5], respectively (p=0.464).

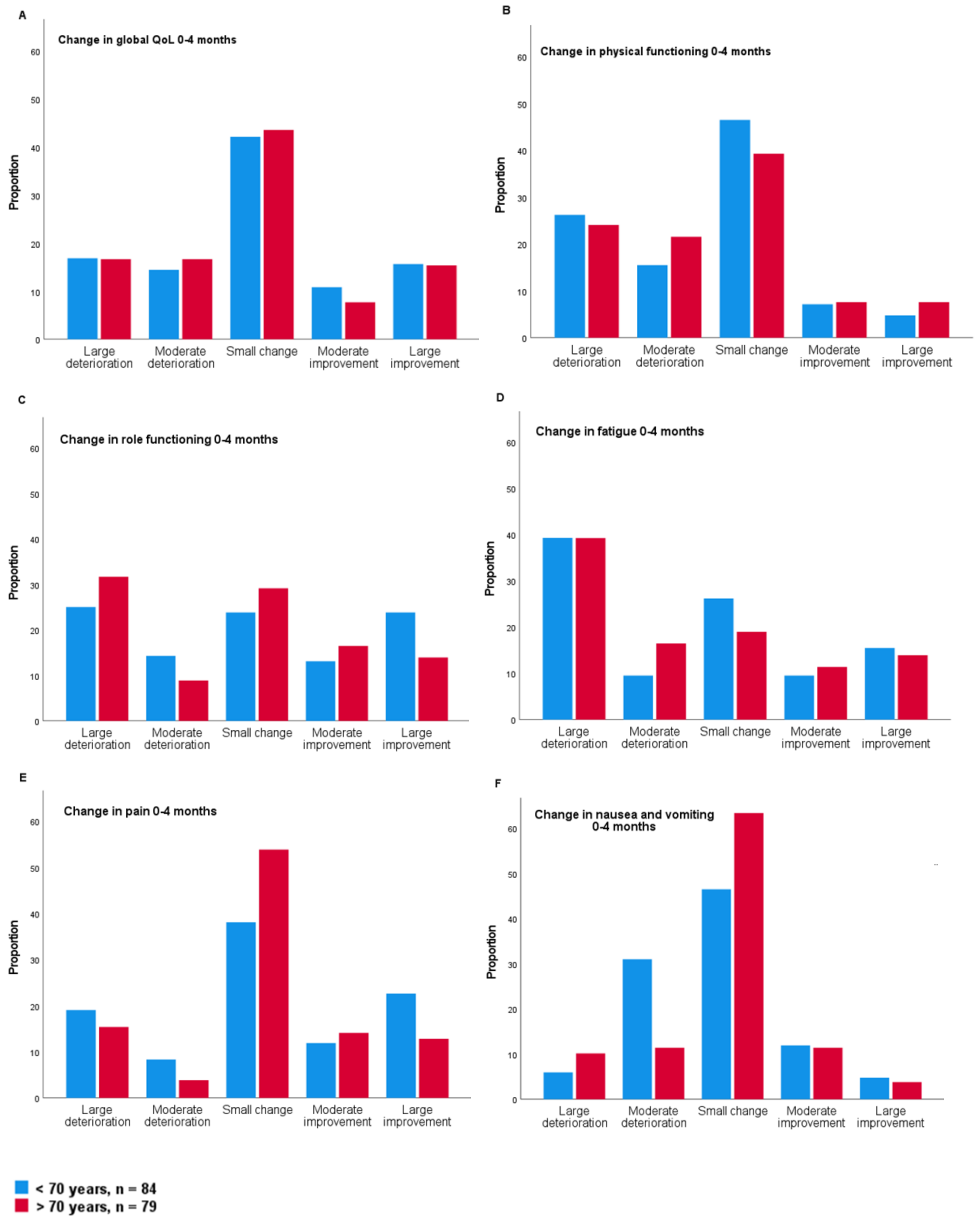

Fig. 5. Individual changes in A) global quality of life, B) physical functioning, C) role functioning, D) fatigue, E) pain and F) nausea and vomiting from baseline to month four divided by age groups, and grouped according to the five categories; large and moderate deterioration, small change, moderate and large improvement. A difference in scores of > 20 is considered a large, from 10 – 20 a moderate deterioration/improvement, and < 10 points a small change. The y-axis represents the percentage for each age group.

Table 8. Effect on change in selected HRQoL domains and survival according to initiation of chemo-break or continued treatment from months 6 - 8 among patients not showing progressive disease at month 6.

	Ongoing treatment from month 6 – 8	Chemo-break from month 6 – 8	p**
Mean difference in HRQoL from month 6 – 8	n = 24 Mean [95% CI]	n = 33 Mean [95% CI]	
Change in functioning scales*			
Global QoL	-11.5 [-19.3 – -3.6]	8.3 [0.9 – 15.9]	**<0.001**
Physical functioning	-6.0 [-11.8 – -0.3]	4.8 [0.2 – 9.4]	**0.003**
Role functioning	-9.7 [-22.5 – 3.1]	4.5 [-4.0 – 13.1]	0.052
Change in symptom scales*			
Fatigue	5.8 [-3.8 – 15.4]	-13.5 [-22.5 – -4.5]	**0.005**
Pain	6.9 [-4.8 – 18.7]	0.0 [-6.8 – 6.8]	0.268
Nausea/vomiting	7.6 [1.8 – 13.5]	-4.5 [-7.6 – -1.5]	**<0.001**
Survival, months	Median [95% CI] 20.8 [16.1 – 25.5]	Median [95% CI] 23.6 [16.3 – 30.8]	0.730

CI, confidence interval; QoL, quality of life; HRQoL, health-related quality of life
**Positive difference on the functioning scales indicates improved function, while positive difference on the symptom scales indicates worsening of symptoms.*
*** Mean difference in HRQoL in the two groups compared with the two-sample t-test. Survival compared with the Log Rank test.*

5. Discussion

The aim of the present thesis was to gain increased insight in the feasibility of a PE intervention during chemotherapy for CRC, how patients experience PE during chemotherapy, and how chemotherapy affects HRQoL among patients with CRC. The following sections present a discussion of the main findings from the three papers, methodological issues related to the study designs, sample sizes, choice of outcome measures and validity of the findings. Finally, conclusions of the thesis are presented before future research within the field is proposed.

5.1. Feasibility of exercise intervention during adjuvant chemotherapy

We found a high willingness to participate (63%). This is higher than in similar studies which have reported willingness of 33 - 49% (135-139). Possible reasons could be the non-randomized design and that the treating oncologists providing information had a positive attitude towards the study. The latter was not the case in one of the above mentioned studies, experiencing that the clinicians were hesitant to refer patients (139). In the present study, it was the physicians that recruited participants, possibly contributing to the higher willingness. The importance of clinicians referring patients to PE intervention has also been described in another non-randomized pilot study with supervised aerobic exercise during adjuvant chemotherapy for CRC, demonstrating a high willingness to participate of 64% (233). In that study, participants could choose their allocation to intervention or control, while in our study, all patients where to take part in the PE intervention.

Despite the high willingness to participate, the inclusion rate was only 43% among eligible patients. Long travel distance was a major barrier, as it made oncologists not asking for participation, and it made patients decline recruitment. This demonstrates the need to accommodate supervised PE closer to where patients live, especially in a country like Norway where people live scattered in more rural areas, often with long travel distances to the hospital.

The dropout rate in the present study was high with seven out of 19, although there were only four who chose to drop out; two before and two after the intervention started. Accounting only for these, the dropout rate was 21%, which is in line with similar studies, reporting

dropout rates between six and 30% (135, 136, 138, 233).

In the present study, high attendance and adherence to the supervised PE were demonstrated with median rates of 85 and 97% respectively. This is comparable to other studies reporting attendance rates of 61 – 89% (135, 138, 139, 233). One likely reason for the high attendance and even higher adherence when a participant first met to a session, was that the intervention was supervised in a one-to-one manner. Systematic reviews and meta-analyses of RCTs with various cancer types have shown that supervised PE has a greater effect on several endpoints than unsupervised, and this could be explained by a higher compliance to supervised PE (79, 234). Scheduled appointments being crucial for both motivation, attendance and adherence to PE, was also found in our qualitative work (235).

Even though the high adherence to supervised PE, the planned increase in intensity of aerobic exercise did not seem feasible as the participants reported slightly lower RPE during the last intervention period (week 17–24), and the goal of achieving intervals of 4 times 3–4 min was only reached in one-third of the participants. During the course of adjuvant chemotherapy, patients will typically experience increased fatigue and decreased cardiorespiratory fitness (236, 237). Contrary to this, the above mentioned non-randomized pilot study by Zopf et al. from 2022 demonstrated a significant increase in cardiorespiratory fitness (relative VO2peak improved by 3.57 ml/kg/min [95% CI, 1.90–5.25; $p < 0.001$]) among CRC patients participating in a supervised aerobic exercise program lasting six months during the period of adjuvant chemotherapy (233). The intervention consisted of twice a week supervised 30 min of cycling on a stationary bicycle with an intensity similar to our study, corresponding to Borg´s RPE scale 13-15 (‘Somewhat hard’ – ‘hard’), in addition to three session per week of home-based 15 min walking. In the present study, VO2peak has not been measured.

There was no temporal relationship between the SAEs and the PE intervention, and it is most likely that the SAEs reported were related to the chemotherapy, although this needs to be confirmed in an RCT. Though, in the literature so far, PE interventions during adjuvant chemotherapy for CRC seem safe (125).

5.2. CRC patients´ experiences with supervised exercise during adjuvant chemotherapy

Scheduled appointments with a physiotherapist gave an opportunity to structure life with cancer and served as an important external motivational factor. Additionally, participants perceived positive effects from exercising, such as improved muscle strength, reduction in sensory neuropathic symptoms, and improvement in mental health. Common hopes and expectations were improvement of endurance and strength, to achieve better tolerance and efficacy, and counteract negative effects of chemotherapy.

Structuring of life with cancer aligns with previous research, exploring women's experiences engaging in supervised PE during treatment for early-stage breast cancer (238, 239). Commitment to scheduled appointments, serving as an external motivational factor, is also described as part of palliative cancer patients' experiences of participation in a PE program (240).

To have supervised PE with regular appointments was crucial, as the participants could not see how they would have been able to perform the same amount of PE without this arrangement, which is in accordance with Backman et al. (239). The preference for supervised PE with individual attention from exercise staff has also been described by others (152, 153).

The participants experienced several positive effects from exercising during adjuvant chemotherapy, both physically and mentally. This has been demonstrated in other studies, but mainly in breast cancer, since most studies on PE interventions have been performed in this patient group (238, 239, 241, 242). There are noticeable differences between these two patient groups, as median age at diagnosis is approximately 10 years higher in CRC (9), and the surgical and adjuvant treatments are different. Our findings thus indicate that positive effects can be achieved in older patient groups as well.

The present study only explored the experiences of those willing to engage in a PE program during adjuvant chemotherapy, and we have no information of those who declined. A more negative attitude toward PE among patients declining participation in a PE study among colon cancer patients receiving adjuvant chemotherapy has been described (139). Further, it has been reported that adjuvant chemotherapy is a major barrier to PE among CRC patients (146). Also in the present study, barriers to PE were related to side effects from chemotherapy, but

these were overcome through the scheduled sessions, individual adjustments, and by an inner motivation developing from positive experiences participating in the PE intervention.

In a Danish study, 25 and 8 patients with breast- and colon cancer respectively, identified as inactive pre-diagnosis, and who had entered a randomized feasibility study of 12-week PA intervention during adjuvant chemotherapy, were interviewed at baseline and 12 weeks after enrolment. A change in attitude towards exercise was described, from being non-exercisers to exercisers. In line with our findings, patient perceptions of the bodily, emotional and social benefits of PE were also emphasized (152).

5.3. Changes in HRQoL during the first year of palliative chemotherapy

The present study demonstrates that older patients with mCRC did not experience more deterioration in the six selected HRQoL domains than their younger counterparts during the first year of palliative chemotherapy. However, almost 40% of both younger and older patients experienced a major deterioration in fatigue after four months of treatment. Displaying individual changes provides a more visual image of the great variance between individuals, as opposed to only displaying the changes in mean values over time. The latter method is often employed in similar studies (197, 199, 202, 225, 243). In addition, a significant part of the individual patients (both younger and older) experienced large deteriorations in physical- and role functioning after four months as well. These findings call for measures to mitigate the expected decline in HRQoL, for instance by early incorporation of tailored palliative rehabilitation and to closely monitor all patients and provide sufficient supportive care. A multimodal intervention consisting of for instance PE, nutritional, cognitive and psychosocial support, would need to be tested in a controlled study. Additionally, use of geriatric assessments in older patients could aid adjustments in treatment plans, and possibly contribute to less toxicity and improved HRQoL (244, 245). This was not (and still is not) routinely in use during the study period.

Several meta-analyses have compared efficacy and tolerability of drugs between younger and older, but rarely reported HRQoL data. The studies conducted conclude that the elderly have similar survival benefits and tolerability of various first line treatments, with the reservation that these studies only included the fittest elderly (246, 247). There are only a few studies exploring age differences in HRQoL during palliative chemotherapy for CRC. The

retrospective analysis of the CAIRO and CAIRO2 RCTs compared global QoL between age groups (248). In line with our results, they found no differences between younger and older patients. However, only fit patients with ECOG PS 0 and 1 were included in these studies, and global QoL was the only domain reported. Previously, it has been demonstrated that global QoL, in contrast to physical functioning, is little affected by toxicities of treatment (205, 249). Another study comparing fit older with younger CRC patients (PS 0-1) starting first-line chemotherapy plus cetuximab, did not find any difference in the younger and older patients´ changes in the HRQoL domains from baseline to week eight or twelve (250).

Despite the elderly had generally lower PS at baseline and reported lower physical functioning, they did not experience more decline in the selected HRQoL domains than the younger patients. An explanation may be that the elderly more often received milder monotherapy regimens, and it is reasonable to believe that they more often had dose reductions, reflecting real-world clinical practice. Regardless the treatment regimens, survival was not different in the two age groups, though there were other differences between the groups that might affect survival in the younger negatively, such as non-resection of the primary, previous treatment and extent of disease.

Compared to baseline, small improvements in mean scores were observed in both groups for emotional functioning, insomnia and appetite loss one year after start of palliative chemotherapy. This is in line with other studies who found decreasing degree of worrying and anxiety among CRC patients, as time progressed after start of chemotherapy (202, 251). In the same period, both groups reported reduced cognitive functioning, a known side-effect of chemotherapy (252-254).

At all measurement points during the first year after start of palliative chemotherapy, younger patients reported more pain than older patients. This might be explained by a larger proportion of the younger having their primary tumour intact, or it could be more directly related to age. Some studies have demonstrated that younger cancer patients report more pain than older (255-257), while Bevilacqua et al. did not find any difference in pain among younger and older cancer survivors (258). In the general population normative data for the EORTC QLQ-C30, older males report less pain than the younger, but this is not seen among females (259). Males were in majority among the elderly in our study.

As expected, patients introduced to a two month chemo-break, compared to those on

continuous treatment from month six, experienced improvements in several HRQoL domains. Some studies have found more toxicity, but no difference in physical functioning and overall health with continuous vs. intermittent treatment (191, 195). The CAIRO3 trial reported statistically significant differences between the groups regarding several of the HRQoL domains, but in contrast to the present study, the differences described were too small to be considered clinically significant (194). In line with our findings, the COIN trial found significant benefits from intermittent- vs. continuous therapy for role- and social functioning, but unlike our study, not for physical functioning and global QoL (192). A possible explanation for the greater positive impact of a chemo-break seen in our study, is that in the real-life setting the patients are frailer and thus benefit more from a chemo-break compared to participants in an RCT.

5.4. Methodological considerations

This thesis is built upon studies from two different patient populations; CRC patients during adjuvant chemotherapy and CRC patients during palliative chemotherapy, using different study designs; interventional and observational, and using different research methods; quantitative and qualitative. In the present feasibility study, additional to quantitative measurements, qualitative methods were utilised in a selection of the patients to explore experiences of engaging in PE during adjuvant chemotherapy for CRC. This between-method triangulation (260) was considered suitable to get a comprehensive understanding of PE for this patient group.

5.4.1. Study design

When preparing for the present feasibility study, the plan was to run a future RCT, investigating whether an individual and supervised PE intervention during adjuvant chemotherapy for CRC could reduce the anticipated development of CIPN and CRF. At that time, there were limited experience with this type of interventional study, and a pilot study seemed sensible to evaluate key feasibility aspects before taking on a full-scale RCT. The choice of a non-randomised feasibility study over a randomised pilot study was a pragmatic one, as our main aim was to test the feasibility of the intervention and test procedures, not the

(preliminary) effect of PE, which would require more participants. Even so, the single arm study was performed as it could have been the interventional arm in an RCT, with all the test procedures performed before a potential randomization and before start of treatment. We did no attempt to have blinded, independent study personnel to perform physical tests, due to limited resources. The pre-post design was to explore changes in self-reported CIPN and fatigue during the intervention period.

The premises for the qualitative study in paper II were largely laid by the present feasibility study, as participation in the qualitative study was dependent on recruitment to the feasibility study. This was one of the reasons for choosing individual interviews instead of interviews in focus groups, even though the interaction between participants in the latter could provide insights of a different nature than what individual interviews offer (209). In the present study, focus groups would not be feasible, since there could be long time periods between inclusions of new participants, and there were a limited number of patients participating in the PE intervention at any given time. Additionally, individual interviews gave logistic advantages, in terms of interviews being held in concordance with the participants´ other appointments at the hospital. The longitudinal design performing interviews before, during and after the intervention period, gave an opportunity to explore both expectations to and experiences with the PE intervention, and to evaluate potential changes over time.

The original idea for the mCRC study arose over a decade ago, and came (among others) from the concern that new, expensive treatments were implemented in general oncological practice based on results from RCTs with study populations not necessarily representative for the whole patient population, and that there was a lack of high quality research in relation to symptom relief, physical and psychological functioning and overall quality of life among patients with CRC in the palliative phase. An observational study design to assess HRQoL in a real-world population of patients with mCRC was considered highly relevant.

5.4.2. Sample size

Due to the feasibility design, no formal sample size calculation was performed for the FAKT feasibility study. It was planned to enrol 20 participants, as this was a number expected to be included within a year, and considered to be sufficient in evaluating feasibility and estimating sample size for a future RCT. It turned out inclusion took longer time, and a pragmatic choice

of closing further inclusion after 19 patients was made, after a long period of slow inclusion rate.

In our observational study, the sample size was given by the already collected data and restricted by the inclusion criteria chosen (commencing first line palliative chemotherapy for CRC, and having filled in the baseline questionnaire).

Discussing sample size in qualitative work is more complicated. Coming from a tradition of quantitative research, estimating or planning for sample size in advance of a project is the usual way to go, where power calculations determine which sample size is necessary to demonstrate effects of a certain magnitude from an intervention. This does not apply for qualitative interviews, and no similar standards for assessment of sample size exist (228). A commonly used concept for sample size in qualitative studies is 'saturation'. This concept has been criticised and found problematic by several (228, 229, 261). It has its origin in one specific methodology in Grounded Theory, but has been inconsistently applied in studies based on other analytic approaches, without clearly defining how saturation is accomplished (228, 229). Still, saturation has been identified as the most commonly used justification for sample size in qualitative health research (262), and it is often held as a criterion for quality in quality checklists (263-265).

The sample size in the present qualitative study was already given when the FAKT feasibility study closed further inclusion. However, the planned randomized FAKT study was commencing, and we chose to continue recruiting participants from the interventional arm in this RCT to our qualitative study, to increase depth and richness of the data set. Based on the research group´s agreement that the collected data contained sufficient information to provide answers to the research question and provide new knowledge to the research field, inclusion was stopped. In dialog with editor of the journal the study was published in, we ended up stating that 'information redundancy had been achieved', which was considered an acceptable justification for sample size.

5.4.3. Outcome measures

Choice of the different PROMS and rationale for using PROMS have been covered in previous sections. Ideally, we could have measured changes in CIPN with objective measures

in addition to PROMS. In clinical practice, receiving referral of patients to adjuvant chemotherapy, we usually have a short time frame (1-2 weeks) until chemotherapy should commence, according to guidelines. After conferring with our colleagues at the neurological department, organizing objective measures would not be possible without postponing start of treatment, which would be unethical. Another issue is that quantitative neurological testing does not necessarily reflect the patients´ symptoms (266).

The main purpose of the feasibility study was to inform the future RCT. Hence, the objectives in a pilot/feasibility study should differ from those in an RCT, by stipulating the issues of uncertainty to be addressed in the future trial (267). We have focused on reporting the feasibility measures, especially those related to the PE intervention during adjuvant chemotherapy for CRC as defined in the methods section, not the results of the various physical tests. The aim of exploring changes in selected outcome measures was mainly to estimate sample size for the future RCT.

5.4.4. Validity

Internal validity

When studying causal relationships, internal validity refers to which extent an observed result represents the truth in the studied population, and is not influenced by other factors or variables. Performing RCTs reduces many of the threats to internal validity. Internal validity can also be asking whether a study investigates what it is meant to (268). Neither of the three papers in the present thesis were designed for or meant to establish any causality. Threats to internal validity in observational studies exploring causality are (among others) related to confounding factors. These can be attenuated using different statistical methods (among others) and by various selection strategies. In the present observational study in paper III, the number of participants were too low to reliably establish any causality, and we focused on presenting the results descriptively. Paper III aimed to describe changes in HRQoL the first year of palliative chemotherapy for CRC. The choice of instrument measuring HRQoL is crucial for enhancing internal (and external) validity. The cancer specific EORTC QLQ-C30 used in the present study, has well documented psychometric properties and has been extensively evaluated and validated (168).

Missing data imposes a threat to internal (and external) validity, meaning there exists a meaningful data value which could have been, but was not recorded. In paper III, 59 participants from the mCRC study were not included in the present study, due to missing base line form. Additionally, questionnaires were missing on the following time points through the 12 months observation period, which is common in longitudinal HRQoL studies. This means that the results could have looked different, given that all questionnaires had been returned. Even so, the compliance rate of returning QLQ-C30 was high, and the drop-out rate in the two age groups was equal. Of those still alive after six and twelve months, 84 and 78%, respectively, returned the questionnaire. This is higher than other observational studies of patients with mCRC (199, 202, 207). After one year, only 53% of the original study population returned the QLQ-C30, and the main reason for not returning was death. This might bias the comparison with baseline, since the healthiest survive to answer the questionnaire after one year.

Unfortunately, adherence to unsupervised PE was only registered in half of the participants in paper I. Apart from that, missing data was not an issue in the feasibility study with nearly 100% completion rates of both the physical tests and questionnaires. Choosing appropriate feasibility measures is essential in order to assure we investigate what we intend to and necessary to inform a future RCT. These are defined and described in the methods sections in paper I and are in line with recommendations for feasibility studies for research on PE (269).

External validity

External validity asks whether the findings from a study will apply for similar patients outside the study setting, if they are generalizable to a broader population. Selection of patients and the specific study settings, are main threats to external validity (270). Broad inclusion criteria were employed in the present studies, aiming to have study populations representative for the whole population of interest. The feasibility study included participants between 18 and 80 years, whereas some other PE interventional studies have excluded older age (129, 138). The mCRC study aimed to include all newly diagnosed with metastatic or non-resectable CRC above 18 years of age in the health region of Mid-Norway in a given time-period.

In the feasibility study, 11 out of the 30 asked, declined participation, reporting having other plans, too much going on or long travel distance. Long travel distance was also the main reason for not asking for study participation among eligible patients. We have not registered

any clinical or demographic data of the non-included patients, as that would be outside what was given ethical approval of, and regardless, it would be unethical to record such data without patient consent. Hence, we do not know if the non-included differ from the included, which in turn could have altered the results given a larger inclusion rate. Given the non-randomized design, we do not know if a randomized design will reduce the willingness to participate, also posing a threat to external validity. The PE intervention was designed to easily being implemented in clinical practise, aiming to enhance external validity.

To our knowledge, the present observational study is the first to compare changes in HRQoL between younger and older from a real-world unselected cohort of patients with mCRC the first year after start of first line palliative chemotherapy. This being a 'real-life' population is reflected by the six selected HRQoL domain scores being worse in both groups compared to similar patient populations in RCTs and in the general population (225, 243, 259).

A screening log over those not included in the mCRC study was only systematically registered in one of seven hospitals (St. Olav´s hospital). This poses a threat to external validity. At St. Olav´s hospital, approximately 85% of all potential patients (newly diagnosis of metastatic or non-resectable CRC) were included, which can be said to be fairly high. Major reasons for non-participation were declined inclusion, advanced disease and not able to consent or missed out. Another limitation is the timing of the questionnaires regarding administration of chemotherapy, as the HRQoL scores greatly can vary through a treatment cycle (202, 271). This was not standardized in the present study.

Are the findings from the observational study conducted between 2014 and 2018 still relevant today? I would say they definitely are, since the treatment of mCRC has not changed that much since that period. Still, combination chemotherapy is the preferred first line choice today, but EGFR antibody is more often added to the chemotherapy back bone than VEGR antibody, compared to the population from our observational study.

Can the findings from the adjuvant and the palliative settings be relevant for each other? Demonstrating that PE interventions are feasible in the adjuvant setting, might also apply in the palliative setting. As demonstrated in an observational study from Oslo, symptoms and complaints in a population in a palliative vs. adjuvant setting commencing chemotherapy, are similar (201). The chemotherapy given in the adjuvant and palliative settings are similar (12), and the increased symptom burden during the chemotherapy paths in both settings have been

demonstrated in the mentioned Oslo study. Lack of energy was the most occurring symptom six months after commencing chemotherapy, and palliative patients scored significantly higher compared with curative patients (202). In the present feasibility study in paper I, physical fatigue slightly improved after three months of adjuvant chemotherapy and participation in the PE intervention, whereas a major proportion of the palliative population in paper III experienced a large deterioration in fatigue after four months of treatment. Naturally, these two populations are not comparable, but the findings from paper I and II hold promise that it is possible to mitigate the anticipated fatigue from chemotherapy.

Trustworthiness

In qualitative research, alternative standards for quality assurance have been proposed. Lincoln and Guba introduced the term trustworthiness in 1985, defined as the extent to which an inquirer can persuade audiences that his or her findings are 'worth paying attention to', and encompasses the four criteria of credibility, transferability, dependability and confirmability (260, 272). Quantitative analogues to these four criteria are suggested to be internal validity, external validity, reliability and objectivity, respectively (260). Relevance, validity and reflexivity as overall standards for qualitative inquiry have been proposed by others (268). Some of these terms in relation to our work in paper II will be discussed below.

To achieve credibility, it is important to include patients who have experiences of the phenomenon under study, hence participants that were about to, or were participating in the supervised PE intervention during adjuvant chemotherapy for CRC were consecutively recruited to the present qualitative study. Being transparent by providing clarity regarding all stages of the study (who the participants were, how they were selected, how the data were collected and analysed, how the conclusions were derived) is also emphasized as one of the indicators of quality, both for qualitative and quantitative studies (260). Patient characteristics regarding age, sex, self-reported levels of PA, marital-, employment-, and educational status are provided in the paper, displaying a wide variety, and thus might contribute to transferability, though restricted to those actually willing to engage in PE during treatment.

Data collection consisted of interviews which were audio recorded and transcribed. Having three different interviewers, provided both potential advantages and disadvantages. Different backgrounds (physiotherapist, oncologist and psychologist) might entail that the interviewers focused on different aspects of the topic under research, contributing to a richer data set, but

also with a risk that important aspects were missed out. The interview guide would contribute to the most important topics being covered. Former experience with the research method might also have affected the richness of the collected data, and that was a reason for the experienced qualitative researcher in the research group doing a major part of the interviews. None of the interviewers were involved in supervising the PE intervention nor in the medical treatment given, and hopefully the participants did not feel obliged to give a skewed description of their experiences. There is a possibility that a positive attitude towards PE among the interviewers could have influenced the interviewees, but also important to bear in mind, is that the participants likely had a more positive attitude towards PE than those declining participation, as described by van Wart et al. (139). The interview guide was designed to reveal both positive and negative experiences from PE. Performing the interviews while participants still were under intervention, reduced the risk of recall bias (273). Half of the interviews were transcribed by a student outside the research group, a couple by the PhD candidate, and the rest by a secretary experienced in transcribing. The PhD candidate listened through all the recorded interviews and corrected obvious mistakes.

Describing the analytical method and process in sufficient detail, contributed to dependability. Having several researchers participating in the analytical process doing initial coding and participating in regular meetings discussing themes, might also contribute to enhance dependability and reflexivity (268). Members of the research group had different backgrounds and thus brought different perspectives to the discussions, strengthening the analysis. Bringing the transcribed interviews back to the participants to check for accuracy, or taking the final analysis back to the participants to check whether they felt the analysis represented their experiences (i.e. member-checking), were not performed. Views on, and practice of member-checking differ in the qualitative community (209, 212). For this project we found it inexpedient. Several of the participants wanted feedback on study results when the project was completed, which they will be provided.

6. Conclusions

This thesis has aimed to provide increased knowledge of the feasibility of a PE intervention during adjuvant chemotherapy, how patients experience such an intervention, and how HRQoL is affected during palliative chemotherapy for CRC patients. The thesis includes three papers answering the following research questions:

Paper I:

1. What is the feasibility of a PE intervention during adjuvant chemotherapy for CRC?

- Overall, we found that a combined supervised and home-based PE intervention in CRC patients receiving adjuvant chemotherapy was feasible and safe, with a high willingness to participate, attendance and adherence to the PE intervention, and completion of study specific tests. The planned increase in intensity of aerobic exercise from the first to the second period seemed not feasible. The drop-out rate before entering intervention was high. There is a need to accommodate supervised PE intervention closer to patients' homes.

Paper II:

2. What are the expectations to and experiences with participating in an individually tailored and supervised PE program during adjuvant chemotherapy for CRC?

- Common expectations were improvement of endurance and strength, and counteracting negative effects of chemotherapy. Scheduled appointments gave structure to daily life and served as an external motivational factor. The individual adjustments of PE gave a sense of security and helped improving adherence, especially when feeling depressed or fatigued. Experienced positive effects from exercising, both mentally and physically, contributed to inner motivation and inspired continued exercising after the study period. We recommend supervised and individually tailored PE during adjuvant chemotherapy for this patient group.

Paper III:

3. With key focus on global QoL, physical- and role functioning, fatigue, pain, nausea and vomiting - How is HRQoL changing in older (> 70 years) compared with younger CRC patients the first year of palliative chemotherapy in a real-life population?

- Older patients did not experience more deterioration in selected HRQoL domains than younger during the first year of palliative chemotherapy, but a major part of both younger and older patients experienced a large deterioration in fatigue and physical function four months after start of palliative chemotherapy. Self-reported HRQoL was mostly maintained or improved after one year, except for cognitive functioning.

4. What is the impact of a chemo-break on HRQoL?

- Patients introduced to a chemo-break, compared to those on continued treatment from month six, experienced significant improvements in global QoL, physical- and role functioning, fatigue, and nausea/vomiting after a two month treatment-free period. This positive impact of a chemo-break seems to be larger in a real-life population than in patients included in RCTs.

7. Future perspectives

Relative to the prevalence of CRC, PE interventions during both adjuvant and palliative chemotherapy in CRC patients have received little scientific attention, and more studies are warranted. PROMS have gained increased attention the last decades, both within the framework of an RCT, but also in the real-world setting.

The present feasibility study was conducted as a preparation for a future RCT, aiming to investigate the impact of a PE intervention during adjuvant chemotherapy, consisting of both supervised and homebased combinations of aerobic endurance-, strength-, and balance training, on self-reported CIPN and fatigue. Based on experiences from the feasibility study, several adjustments were made in the upcoming RCT: Supervised PE has been organized closer to participants´ homes engaging physiotherapists in the communities, there has not been planned for any increase in the intensity of aerobic endurance exercise, which has been kept on a moderate level, and a self-reported activity diary was employed for documentation of unsupervised PE, among others. The FAKT RCT, conducted as a National multicenter study, has completed inclusion, and results are awaiting.

As previously discussed, engaging patients with CRC in PE intervention has proven challenging for several investigators. In our qualitative interview study, only those willing to participate in PE during adjuvant chemotherapy were included. Hence, we know little of the perspectives of those not interested in such a PE intervention. Conducting a qualitative study among patients not interested in PE, could provide knowledge valuable for engaging more patients with CRC in physical activity in their different disease trajectories.

In our real-world observational study of mCRC patients receiving palliative chemotherapy, a major proportion of the patients experienced large deteriorations in several of the HRQoL domains a few months after commencing treatment. This is a major concern, since one of the main treatment goals with palliative chemotherapy is improved or preserved HRQoL in addition to prolongation of life. Measures to mitigate these deteriorations are warranted. Geriatric assessments are still not in routinely use, and individual treatment plans are based on clinical judgements. Implementing geriatric assessments, perhaps within the frame of a research project, might improve how we treat older, frail patients in the future. Additionally, digital surveillance of patients is a promising field, and research on this area could also

contribute to better adjust the balance between toxic treatments, often resulting in troubling side-effects, and the goal of disease control and prolonged time to progression.

There is increasing evidence that PE (both during and after chemotherapy) in the curative setting has positive impacts on several HRQoL outcomes (2, 75, 126, 127), and evidence in the palliative setting is evolving (82, 83, 274). We have demonstrated that a PE intervention during adjuvant chemotherapy for CRC is feasible, and a study on a PE intervention among the palliative CRC population might provide knowledge whether such an intervention could mitigate the anticipated decline in HRQoL after commencing palliative chemotherapy.

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9. Appendix

Contents

”Borg-skala”

Borg	Nivå	Opplevelsen	Økt-type
20	**”Svært anstrengende”**	Det er få minutter til du må stoppe.	
19			
18			
17	**”Meget anstrengende”**	Du puster kraftig, og kan kun svare med enkeltord.	**Hard økt**
16			
	”Snakkegrensen”		
15	**”Anstrengende”**	Du kan snakke, men må ta pauser for å trekke pusten.	**Medium økt**
14		Du kan synge, men det høres ikke spesielt pent ut…	
13	**”Litt anstrengende”**	Du kan snakke relativt uanstrengt, men det er litt slitsomt å synge.	**Lett økt**
12	**”Ganske lett”**		
11			
10	**”Meget lett”**	Du kan snakke helt uanstrengt, og du kan synge med.	**Oppvarming Nedtrapping**
9			
8			
7			
6	**”Hvile”**	Før og etter trening	

Mnd: ☐☐ PID: ☐☐☐☐

EORTC QLQ-CIPN20

Endel pasienter opplever av og til at de har noen av følgende symptomer eller problemer. Vær vennlig å angi i hvilken grad du har hatt disse symptomene eller problemene i løpet av den siste uka. Sett kryss for det svaret som best beskriver din tilstand.

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**En del**	**Svært mye**
31. Har du hatt kribling i fingre eller hender?	☐	☐	☐	☐
32. Har du hatt kribling i tær eller føtter?	☐	☐	☐	☐
33. Har du hatt nummenhet i fingre eller hender?	☐	☐	☐	☐
34. Har du hatt nummenhet i tær eller føtter?	☐	☐	☐	☐
35. Har du hatt ilende eller brennende smerte i dine fingre eller hender?	☐	☐	☐	☐
36. Har du hatt ilende eller brennende smerte i dine tær eller føtter?	☐	☐	☐	☐
37. Har du hatt kramper i dine hender?	☐	☐	☐	☐
38. Har du hatt kramper i dine føtter?	☐	☐	☐	☐
39. Har du hatt problemer med å stå eller gå p.g.a. vanskeligheter med å føle bakken under dine føtter?	☐	☐	☐	☐
40. Har du hatt vanskelig for å skille mellom varmt og kaldt vann?	☐	☐	☐	☐
41. Har du hatt vanskeligheter med å skrive p.g.a.at du har hatt problemer med å holde en penn?	☐	☐	☐	☐
42. Har du hatt vanskeligheter med å håndtere små gjenstander med fingrene (f. eks. kneppe små knapper)?	☐	☐	☐	☐
43. Har du hatt vanskeligheter med å åpne et glass med skrukork eller en flaske p.g.a. kraftløshet i hendene?	☐	☐	☐	☐
44. Har du hatt vanskeligheter med å gå p.g.a. at føttene dine falt nedover (droppfot)?	☐	☐	☐	☐
45. Har du hatt vanskeligheter med å gå i trapper eller reise deg fra en stol p.g.a. kraftløshet i bena?	☐	☐	☐	☐
46. Har du blitt svimmel når du har reist deg fra en sittende eller liggende stilling?	☐	☐	☐	☐
47. Har du hatt uklart syn?	☐	☐	☐	☐
48. Har du hatt vanskelig for å høre?	☐	☐	☐	☐

Mnd: ☐☐ PID: ☐☐☐☐

I løpet av den siste uka:

Vennligst svar på følgende spørsmål kun dersom du kjører bil

	Ikke i det hele tatt	Litt	En del	Svært mye
49. Har du hatt vanskeligheter med å bruke pedalene?	☐	☐	☐	☐

Vennligst svar på følgende spørsmål kun dersom du er mann

	Ikke i det hele tatt	Litt	En del	Svært mye
50. Har du hatt vanskeligheter med å få eller opprettholde en ereksjon?	☐	☐	☐	☐

Mnd: ☐☐

Fatigue

PID: ☐☐☐☐

Vi vil gjerne vite om du har følt deg sliten, svak eller i mangel av overskudd den siste måned. Vennligst besvar alle spørsmålene ved å krysse av for det svaret du synes passer best for deg. Vi ønsker at du besvarer alle spørsmålene selv om du ikke har hatt slike problemer. Vi spør om hvordan du har følt deg i det siste og ikke hvordan du følte deg for lenge siden. Hvis du har følt deg sliten lenge, ber vi om at du sammenligner deg med hvordan du følte deg sist du var bra. Sett kun ett kryss for hvert spørsmål.

Har du problemer med at du føler deg sliten?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Trenger du mer hvile?	☐ *Nei, mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Føler du deg søvnig eller døsig?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Har du problemer med å komme i gang med ting?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Mangler du overskudd?	☐ *Ikke i det hele tatt*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Har du redusert styrke i musklene dine?	☐ *Ikke i det hele tatt*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Føler du deg svak?	☐ *Mindre enn vanlig*	☐ *Som vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Har du vansker med å konsentrere deg?	☐ *Mindre enn vanlig*	☐ *Som vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Forsnakker du deg i samtaler?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Er det vanskeligere å finne det rette ordet?	☐ *Mindre enn vanlig*	☐ *Ikke mer enn vanlig*	☐ *Mer enn vanlig*	☐ *Mye mer enn vanlig*
Hvordan er hukommelsen din?	☐ *Bedre enn vanlig*	☐ *Ikke verre enn vanlig*	☐ *Verre enn vanlig*	☐ *Mye verre enn vanlig*

Hvis du føler deg sliten for tiden, omtrent hvor lenge har det vart? (ett kryss)

- Mindre enn en uke ☐
- Mindre enn tre måneder ☐
- Mellom tre og seks måneder ☐
- Seks måneder eller mer ☐

Hvis du føler deg sliten for tiden, omtrent hvor mye av tiden kjenner du det? (ett kryss)

- 25% av tiden ☐
- 50% av tiden ☐
- 75% av tiden ☐
- Hele tiden ☐

Vennligst kontroller at du har besvart alle spørsmålene

Mnd: ☐☐ **FYSISK AKTIVITET** PID: ☐☐☐☐

1. Under arbeid (lønnet eller ulønnet) eller vanlige daglige gjøremål- Hvordan vil du beskrive aktivitetsnivået ditt de siste 7 dagene?

☐ For det meste stillesittende aktiviteter
☐ Aktiviteter som krever at du går mye
☐ Aktiviteter hvor du går og løfter mye
☐ Tungt kroppsarbeid

Med mosjon mener vi at du for eksempel går tur, går på ski, svømmer eller driver trening/idrett.

2. Hvor ofte mosjonerte du de siste 7 dagene? *(Ta et gjennomsnitt)*

☐ Aldri
☐ Sjeldnere enn en gang i uka
☐ En gang i uka
☐ 2-3 ganger i uka
☐ Omtrent hver dag

3. Hvor lenge holder du på hver gang? *(Ta et gjennomsnitt av de siste 7 dagene)*

☐ Mindre enn 15 minutter
☐ 15 – 29 minutes
☐ 30 minutter til en time
☐ Mer enn en time

4. På en skala fra 6-20, hvor hard var aktivitetene du vanligvis utførte når du mosjonerte/trente *(tenk på de siste 7 dagene)?*

☐ 6
☐ 7 Meget, meget lett
☐ 8
☐ 9 Meget lett
☐ 10
☐ 11 Ganske lett
☐ 13 Litt anstrengende
☐ 14
☐ 15 Anstrengende
☐ 16
☐ 17 Meget anstrengende
☐ 18
☐ 19 Svært anstrengene
☐ 20

Mnd: ☐☐ **EORTC QLQ-C30** PID: ☐☐☐☐

(Versjon 3.0)

Dine initialer: ☐☐☐☐ Dato for utfylling: ☐☐.☐☐.20☐☐

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

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

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

Bla om til neste side

Mnd: ☐☐ PID: ☐☐☐☐

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

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

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

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig Helt utmerket

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

☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7

Svært dårlig Helt utmerket

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Intervjuguide for semistrukturert intervju med deltagere i FAKT-studien

- Innledning med bakgrunn for studien.
- Informasjon om gjennomføring av intervjuet og hvordan det blir behandlet i etterkant
- Bekreftelse på samtykkeerklæring
- Dokumentasjon av informantens kjønn, alder, jobb/student/sykemeldt
- Varighet: 30-60 minutter

Intervjuguide, før oppstart

Intervjuguiden tar utgangspunkt i deltagernes erfaringer rundt disse områdene:

- Tidligere erfaring med trening
- Andre personers erfaringer, anbefalinger, historier ift cellegiftbehandling
- Egen motivasjon for å skulle trene (fysisk form, velvære, psykisk helse, normalitet)
- Symptomer, plager og bivirkninger
- Logistikk

- Hva er din tidligere erfaring med trening?
- Hva tror du dette kan gi deg av fordeler og/eller ulemper i tiden som kommer?
- Hvilket inntrykk har du fra før om hvordan man har det under cellegiftbehandling?
- Kan du si noe om hvordan du tror dette påvirker deg i fasen du er i nå?
- Hva er det du ønsker å oppnå med treningen?
- Hva tenker du om det å trene også om du har plager, symptomer og/eller bivirkninger?
- Har du noen tanker om hvordan du skal håndtere disse eventuelle utfordringene?
- Hva tenker du om det praktiske rundt å delta? Tid, sted osv.

Intervjuguide, midtveis

Intervjuguiden tar utgangspunkt i deltagernes erfaringer rundt disse områdene:

- Egen motivasjon for å skulle trene fram til nå (fysisk form, velvære, psykisk helse, normalitet) Endret seg fra oppstart
- Symptomer, plager og bivirkninger
- Treningen: type trening, individuelt, intensitet, dose, fysioterapeutens rolle
- Logistikk

- Hva har vært motivasjonen for å delta fram til nå?
- Har motivasjonen for å delta endret seg siden oppstart? Eventuelt hvordan?
- Hvilke opplevelser har du så langt i forhold til å trene med eventuelle plager, symptomer og bivirkninger som har oppstått?
- Hvis bivirkninger har vært tilstede, hva har vært din strategi for å trene likevel?
- Hva synes du om treningene så langt?
- Hva ved treningen tenker du burde endres for at du skulle være 100% fornøyd?
- Hvordan har det praktiske rundt treningen fungert for deg med tanke på tidspunkt, sted osv.?

Intervjuguide, sluttfase

Intervjuguiden tar utgangspunkt i deltagernes erfaringer rundt disse områdene:

- Egen motivasjon for å skulle trene siste halvdel (fysisk form, velvære, psykisk helse, normalitet) Endret seg underveis
- Symptomer, plager og bivirkninger
- Treningen: type trening, individuelt, intensitet, dose, fysioterapeutens rolle
- Logistikk

- Hva har vært motivasjonen for å delta på treningen i behandlingsperioden?
- Har motivasjonen for å delta endret seg underveis? Eventuelt hvordan?
- Hvilke opplevelser har du i forhold til å trene med eventuelle plager, symptomer og bivirkninger som har oppstått?
- Hvis bivirkninger har vært tilstede, hva har vært din strategi for å trene likevel?
- Hva synes du om treningene?
- Hva ved treningen tenker du burde endres for at du skulle være 100% fornøyd?
- Hvordan har det praktiske rundt treningen fungert for deg med tanke på tidspunkt, sted osv.?

Paper I

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ORIGINAL ARTICLE

Physical exercise during adjuvant chemotherapy for colorectal cancer—a non-randomized feasibility study

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Abstract

Background Colorectal cancer (CRC) is the third most common cancer worldwide, and a large proportion of the patients receive adjuvant oxaliplatin-based chemotherapy. Most of these experience chemotherapy-induced peripheral neuropathy (CIPN), affecting quality of life. Evidence to advise exercise to reduce CIPN is limited. The primary aim of this study was to investigate the feasibility of an exercise intervention and data collection among CRC patients during adjuvant chemotherapy.

Material and methods This non-randomized feasibility study included CRC patients admitted to adjuvant chemotherapy to an intervention consisting of supervised aerobic endurance, resistance, and balance exercises twice a week at the hospital in addition to home-based exercise once a week. A physiotherapist supervised the patients, and the intervention lasted throughout the period of adjuvant chemotherapy (12–24 weeks). Participants performed physical tests and filled in questionnaires at baseline, 3, 6, 9, and 12 months.

Results and conclusion Nineteen (63%) of 30 invited patients consented. A major barrier to recruit or consent to participation was long travel distance to the hospital. The completion rate of questionnaires and physical tests were near 100%. Seven participants dropped out, five before the intervention started. Median attendance to supervised exercise was 85%. There were no serious adverse events related to the intervention. Except for a planned higher intensity of endurance exercise, we found the intervention feasible and safe. Based on experiences in this study, some adjustments have been made for an upcoming randomized trial, including the supervised exercise taking place close to participants' homes.

Trial registration NCT03885817, March 22, 2019, retrospectively registered.

Keywords Colorectal cancer · Physical exercise · Adjuvant chemotherapy · Neuropathy · Oxaliplatin

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Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide with 1.8 million new cases each year [1]. Adjuvant chemotherapy is a standard treatment for stage III and some high-risk stage II colon cancer [2]. In addition, postoperative chemotherapy is considered after surgery for stage IV CRC and after resection of locally advanced rectal cancer. Chemotherapy can cause several short- and long-term side effects, which may have major negative impacts on patients' quality of life [3–5]. Chemotherapy-induced peripheral neuropathy (CIPN) is a frequent side effect from oxaliplatin, which is used in the adjuvant treatment of CRC, with more than 90% of the patients exposed to the compound experiencing CIPN [6].

According to recent guidelines, there is strong evidence to advise cancer patients to carry out aerobic exercise alone or in combination with resistance training at moderate intensity,

both during and after treatment, to improve several cancer-related health outcomes [7]. Also, there are exercise guidelines for cancer survivors based on guidelines for the general population with both moderate-intensity and vigorous physical activities [8]. Notably, current recommendations are mainly based on evidence from clinical trials conducted in breast or prostate cancer patients. Less is known about the effects of higher-intensity aerobic exercise during cancer treatment, and studies on this topic are scarce. Independent of outcomes, few randomized controlled trials (RCTs) have investigated the effects of exercise during adjuvant chemotherapy among CRC patients, and in available studies, the sample sizes are small [9]. To our knowledge, there are no trials exploring the effects of a combination of supervised and home-based aerobic endurance, resistance, and balance exercises for this patient group. For the outcome CIPN, there is less knowledge concerning the effect of exercise, and recently published consensus statements and reviews conclude that the evidence is still insufficient [7, 10, 11].

Before the performance of a full-scale RCT to evaluate the effects of an exercise intervention during adjuvant chemotherapy for CRC, issues of recruitment and retention need to be properly addressed. In addition, exploration of preliminary efficacy (changes) in patient-reported CIPN and fatigue is necessary for the estimation of sample size in the future RCT. On this background, the primary aim of the current study was to evaluate the feasibility of an exercise intervention and data collection among patients during adjuvant treatment for CRC by tracking willingness to participate, inclusion and dropout rate, attendance and adherence to the intervention, safety, and completion rate of questionnaires and physical testing. The secondary aim was to explore post-intervention changes in CIPN and fatigue.

Material and methods

Trial design

This was as a single-centre, non-randomized interventional feasibility study with a pre-post design performed at St. Olav's hospital in Trondheim, Norway. Fourteen months after commencement of the trial, a collaborative hospital (alesund hospital) was invited to participate in the study to prepare this hospital for the future RCT.

Participants

The eligibility criteria were radical resection for stage II–IV CRC within the last 3 months and scheduled for adjuvant chemotherapy (Resection for synchronous metastases was allowed.), age 18–80 years, performance status 0–2 according to the Eastern Cooperative Oncology Group [12], ability to conduct the intervention based on the treating physician's assessment, and ability to understand Norwegian language. The exclusion criteria were serious comorbidity contraindicating physical exercise and treatment for other cancers during the 5 past years, except for basal cell carcinoma of the skin and cervical carcinoma in situ.

During the recruitment period, the consulting oncologists screened all patients referred to adjuvant chemotherapy after surgery for CRC for eligibility. The treating oncologist provided oral and written information at the first consultation, and a study coordinator obtained written informed consent within a few days.

Intervention

The intervention was an individually tailored and supervised exercise programme including progressive aerobic endurance, resistance, and balance exercises. A physiotherapist, certified in giving exercise for cancer patients, supervised the exercise sessions twice a week at a specialized outpatient training facility for cancer patients located within the hospital area. In addition, the participants were encouraged to perform one weekly, unsupervised exercise session with endurance and balance exercises in their home setting. The exercise intervention lasted throughout the period of adjuvant treatment.

Each exercise session consisted of 10-min warm-up, 20-min aerobic endurance, 15-min resistance, and 15-min balance exercises. Participants performed the warm-up and endurance exercise on a treadmill. Endurance exercise was standardized as a gradual approach to intervals of 4 min (Table 1). The Borg's scale [13] was used to instruct the participants regarding intensity of the endurance exercise and to map the participants' rate of perceived exertion (RPE). The physiotherapist recorded RPE after warm-up and following each interval. On a scale from 6 (no effort) to 20 (maximal effort), the participants reported how strenuous the exercise was (RPE). For progression, the intensity of the interval training was increased during the intervention period; from 12–14 ('somewhat hard') on Borg's scale in weeks 1–16 to 14–16 ('hard') from week 17.

The resistance exercises were aimed at large muscle groups and followed a period plan that involved individually tailored progression according to standardized training principles (Table 1). During the first 2 weeks, the focus was adaptation, learning of technique, and intensity management. In weeks 3–8, participants performed the exercises with submaximal intensity (low resistance, up to 12 repetitions in three series) to account for any postoperative limitations (e.g., avoiding high abdominal pressure and pain provocation). In weeks 9–16, exercise load was adjusted based on the weight the participant managed to lift a maximum of 10 times and repeated in three series. In the last period (weeks 17–24), intensity was increased by reducing the number of repetitions (6–8) and

Table 1 Endurance and resistance exercise

Aerobic endurance exercise		
Period/exercise	Duration	Borg's scale
Week 1–2		
Walking on treadmill[1]	1 × 5 min	12–14
Week 3–8		
Intervals of uphill walking	4–6 × 2 min	12–14
Week 9–16		
Intervals of uphill walking	3–4 × 3 min	12–14
Week 17–24		
Intervals of uphill walking	4 × 3–4 min	14–16
Resistance exercise		
Period/exercise	Period	Repetitions (reps)
Week 1–8	Week 1	1 × 12 reps
Knee extension	Week 2	2 × 12 reps
Sitting chest press	Week 3–8	3 × 12 reps
Standing rowing		
Seat raise		
Week 9–24	Week 9–16	3 × 10 reps
Leg press	Week 17–24	3 × 8 RM[2]/4 × 6 RM
Oblique seated chest press with manuals		
Standing rowing		
Lying on back, one leg alternately lowering		

[1] Getting accustomed to the treadmill

[2] RM = repetition maximum

increasing the number of series (3–4) to work up to maximum strength. In line with individually adapted progression, manual weights, elastic bands, and various exercise equipment were used.

Balance training consisted of a set of exercises, lasting 15–20 min, to be performed on various surfaces (floor, cushions, or Bosu balls). Individual tailoring was based on the physiotherapist making a selection from a standardized pool of exercises with increasing difficulty from static to dynamic balance, and progress was monitored in the two weekly supervised sessions.

Outcomes

Primary outcomes

The rate of consenting participants among those invited for participation defined the feasibility outcome *willingness to participate*. *Inclusion rate* was defined as the number of included participants among eligible participants identified, and *dropout rate* was defined as the number of participants who withdrew from the study among consenting participants. This latter group was termed 'dropouts', and the rest were termed 'completers'.

Attendance to supervised exercise was calculated as the number of performed sessions divided by the number of planned sessions. The physiotherapist registered whether the participant met and why he/she did not meet. *Adherence to supervised exercise* was analysed by comparing the content of each session when a participant met with the exercise programme according to protocol. The physiotherapist registered the duration of the warm-up and the endurance exercise, the number and duration of each interval and intensity, the different resistance exercises and number of repetitions, and whether the participant performed the balance exercise. Looking at each component, adherence to endurance, resistance, and balance exercises was analysed, respectively. *Attendance to unsupervised exercise* was calculated by dividing the number of performed unsupervised exercise sessions with the number of unsupervised exercise sessions according to protocol, and it was the physiotherapist that registered whether the home training was done.

Safety, recorded as all serious adverse events (SAEs), was registered from the participants who started the intervention until 1 month after the end of the intervention. In addition, any adverse event occurring *during* supervised exercise was noted.

The feasibility of the data collection was measured by the *completion rate of questionnaires and physical testing*. The participants filled in questionnaires at baseline, after 3, 6, 9, and 12 months, and they performed the physical tests at baseline, after 3 and after 6 months. The questionnaires used were The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [14], EORTC QLQ—Chemotherapy-Induced Peripheral Neuropathy 20 (CIPN20) [15], and The Fatigue Questionnaire (FQ) [16]. Physical tests were 'Modified Shuttle walk', 'Sit-to-stand', 'Tandem stance', and 'Unipedal stance' [17–20]. Demographic variables, clinical characteristics, patient-reported physical activity, and sick leave were also assessed.

Secondary outcomes

Secondary outcomes were changes in patient-reported CIPN and fatigue between baseline (T_0) and 3 months after inclusion (T_1). CIPN was assessed by the 9-item EORTC QLQ-CIPN20 sensory subscale [15]. Each item is rated on a scale from 1 ('not at all') to 4 ('very much'). Fatigue was assessed by FQ which contains 13 questions. Each question is rated on a scale from 0 ('not at all' or 'less than usual') to 3 ('much worse than usual').

Adjuvant chemotherapy and change in assessments

According to the national guidelines at the time this study started, adjuvant chemotherapy for CRC should start within 4–8 weeks postoperatively and last for 24 weeks [2]. Younger patients (< 70 years) should receive combination chemotherapy with intravenous (IV) fluorouracil/calcium folinate or oral capecitabine in combination with IV oxaliplatin. The same

guidelines recommended monotherapy with capecitabine or IV fluorouracil/calcium folinate to the elderly patients (> 70 years) [2]. After commencing this study, new recommendations regarding duration of adjuvant chemotherapy was published [21]. As a result, some participants received 12, not 24 weeks of adjuvant treatment. These participants performed physical tests at baseline and after 3 months.

Sample size

It was estimated that 20 participants could be recruited within a year at St. Olav's hospital, and this number was considered to be sufficient in evaluating whether the intervention and test procedures were feasible and in estimating the sample size for the larger randomized trial.

Analytical methods

To estimate adherence to supervised endurance exercise, the total number of minutes of warm-up plus intervals performed for every session was divided by the minimum number of minutes of warm-up and intervals according to the protocol. Similarly, adherence to supervised resistance exercise was estimated by looking at the number of resistance exercises and repetitions performed for every session compared with the protocol. Adherence to supervised balance exercise was estimated by dividing the number of performed supervised balance training by the number of performed supervised sessions.

The raw score (*RS*) in CIPN was calculated by the sum of each item's score (1–4) divided by the number of items. $RS = (I_1 + I_2 + \ldots + In)/n$. A linear transformation of the *RS* to 0–100 gives the score (*S*), where higher *S* indicates worse CIPN. $S = ((RS-1)/3) \times 100$ [22]. For each participant, *S* at T_0 is subtracted from *S* at T_1 to calculate the change in CIPN.

FQ measures physical fatigue (PF) (scores 0–21) and mental fatigue (MF) (scores 0–12). Higher score indicates more fatigue [16]. For each participant, PF and MF scores at T_0 are subtracted from PF and MF scores at T_1 to calculate the changes in PF and MF.

Continuous variables are reported by median values, range, and standard deviation (SD). The statistical analyses performed were descriptive statistics using the IBM SPSS Statistics, version 25.

Numbers analysed

Exploring attendance and adherence to the intervention and completion rate of physical tests and questionnaires after baseline, only completers were included. All consenting participants were included when analysing completion rates for baseline testing and questionnaires. Only participants who filled in in CIPN20 and FQ at T_0 and T_1 were included in analysing changes in patient-reported CIPN and fatigue.

Results

Recruitment

From December 2016 to November 2018, 52 potential participants were identified at the Cancer Clinic, St. Olav's hospital. One participant was identified and recruited from alesund hospital. Nine patients did not fulfil the inclusion criteria for reasons described in Fig. 1. Fourteen patients were identified as eligible, but not asked to participate. The major reason for not asking was long travel distance to the hospital. After including 19 of the planned 20 participants, the study was closed due to a long period of slow recruitment, and the planned RCT was commencing.

Baseline data

Table 2 presents baseline demographics and clinical characteristics. Participants received adjuvant chemotherapy for a period of 12 to 24 weeks, with median starting 6 weeks after surgery.

The completers had a lower median age than the dropouts (58 vs. 69 years). A higher proportion of the completers were married or had a partner (9 of 12 vs. 2 of 7) and had higher education than the dropouts (10 of 12 vs. 1 of 7).

Outcomes

Willingness to participate and inclusion and dropout rates

Nineteen among the 30 eligible participants that were invited to take part consented, giving a willingness to participate of 63%. Figure 1 lists reasons for declining participation. With 19 included among 44 eligible participants, the inclusion rate was 43%. Five of the 19 participants never started the intervention. Two participants were hospitalized shortly after the first course of chemotherapy with serious complications, and further adjuvant chemotherapy was stopped. Two participants withdrew consent shortly after inclusion, reporting having 'too much going' and having transportation issues, respectively. The fifth dropout was not contacted. Two of 14 participants dropped out after one and four exercise sessions, respectively. One reported pre-existing back pain got worse, and the other did not show up after the first session despite repeated proposals of new appointments. Total dropout rate was 37% (7 of 19).

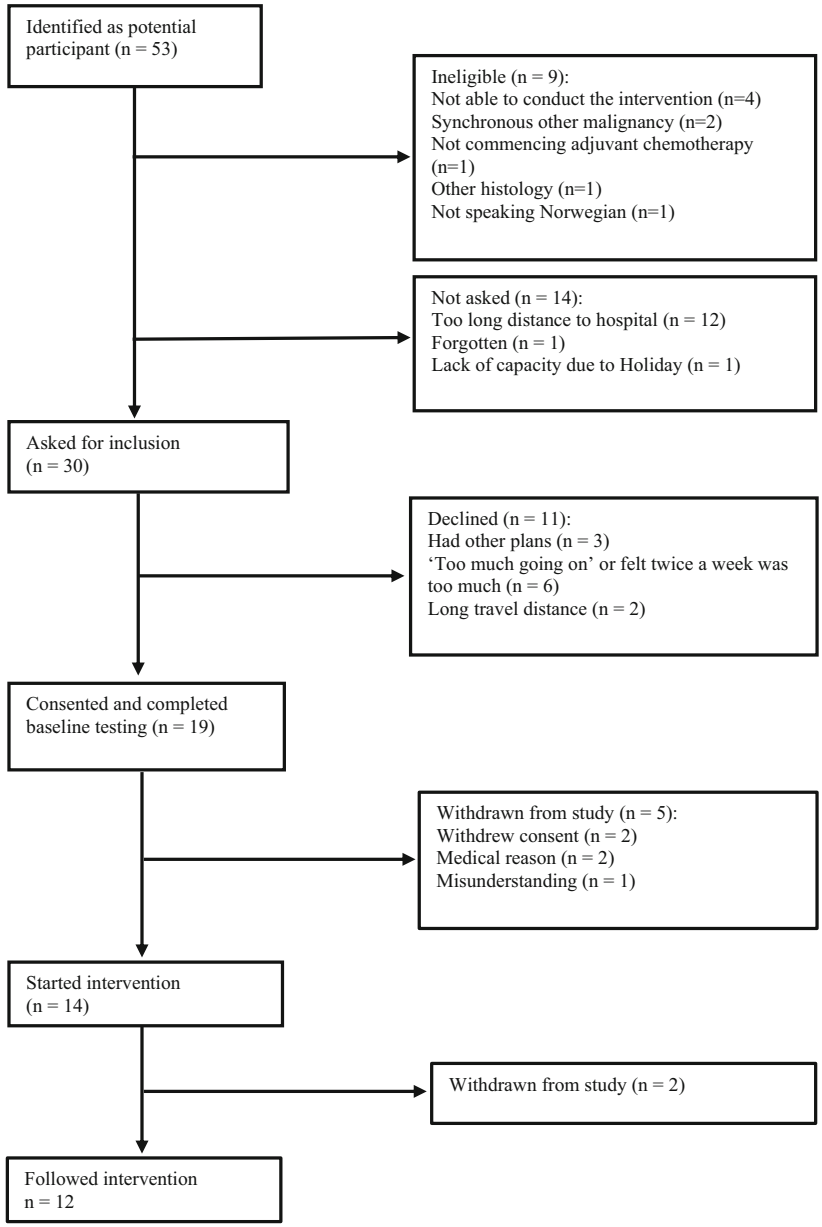

Fig. 1 Participant flow

Attendance and adherence to the intervention

Table 3 summarizes attendance and adherence to the supervised exercise. The median rate of attendance to supervised exercise was 85%. Attendance rate was above 77% in 10 of 12 completers. For the two remaining participants, the rate was 33% and 54%, respectively. Reasons for not meeting to a session were that the participant was not feeling well (33%), being hospitalized (15%), being out of town (8%), and other reasons (4%). In 40% of the cases, the reason was unknown, and the participant with the lowest rate of performed sessions accounted for two-thirds of these cases. The median adherence to supervised endurance, resistance, and balance exercises was 96, 95, and 100%, respectively.

Table 2 Baseline demographics and clinical characteristics for completers and the dropouts

	Completers	Dropouts
No. of patients	12	7
Age, years, median [range]	57.5 [33, 78]	69 [43, 80]
Males	7	3
Females	5	4
ECOG PS		
0	7	2
1	4	5
2	1	0
Comorbidity (Charlson comorbidity)		
None	9	5
Cerebrovascular disease (prior TIA or stroke)	2	1
Prior peptic ulcer	1	0
Connective tissue disease	0	1
Stoma		
Yes	0	2
No	12	5
Type of surgery		
Laparoscopy	8	2
Open	4	5
Stage		
III	10	5
IV	2	2
Adjuvant treatment planned		
Combination chemotherapy	11	4
Monotherapy	1	3
Time from surgery to start chemotherapy, days, median [range]	42 [32, 58]	45 [36, 57]
Marital status		
Living alone	3	5
Married/partner	9	2
Employment		
Working	9	1
Partly working/partly disabled	0	1
Retired	3	5
Education		
Elementary or high school	2	6
College/university	10	1

The intensity of the endurance exercise was slightly lower in the second period (week 17–24) with a median of 14 in the first (week 1–16), and a median of 13.5 in the second period. Only four participants achieved intervals of 4 times 3–4 min.

Attendance to the unsupervised exercise was systematically registered only in the second half of the completers. Median attendance rate to unsupervised exercise among these six participants was 59% (41.7–87.5).

Safety

No adverse events were registered *during* supervised exercise sessions. Two thromboembolic events occurred, where one was a deep vein thrombosis of the lower leg shortly after hospitalization due to an infection. The participant had not been to any supervised exercise the past 10 days before this incident. The other was an incident of pulmonary embolism. The participant received combination chemotherapy 6 days before the first symptoms of pulmonary embolism and did the last supervised exercise 10 days before diagnosis. Both participants were successfully treated ambulatory with anticoagulation and resumed exercise.

Six of 14 participants had one or two admissions to hospital. There were four admissions due to infection, with one due to neutropenic fever. Two admissions were because of chemotherapy-induced enterocolitis, one was with generalized cramps after administration of chemotherapy, and one was because of painful and disabling cramps of the legs after administration of oxaliplatin.

Completion rate of questionnaires and physical testing

All 19 participants completed the physical tests according to protocol at baseline. Eighteen of 19 completed the baseline questionnaires, in which one was filled in 2 days after commencing chemotherapy. At 3, 6, and 12 months, all 12 completers returned the questionnaires, with the QLQ-C30 missing in one participant at 12 months. At 9 months, 11 of 12 were completed, with the CIPN20 and FQ missing in one participant. The 12 completers performed all physical tests.

Changes in patient-reported CIPN and fatigue

Table 4 reports changes in CIPN, PF, and MF from T_0 to T_1. The symptoms of CIPN increased from T_0 to T_1 with a median increase of 14.8 on a scale from 0 to 100. PF decreased one point on a scale from 0 to 21, and MF increased one point on a scale from 0 to 12.

Discussion

This study investigated the feasibility of a combined supervised and home-based exercise intervention in CRC patients receiving adjuvant chemotherapy. We found a high willingness to participate, attendance and adherence to the exercise intervention, and completion rate of study specific tests. A

Table 3 Attendance and adherence to supervised exercise

	According to protocol	*N*	Median	Range	SD
Planned sessions (number)	48	12	44	[22, 46]	7.6
Performed sessions (number)		12	37.5	[12, 46]	11.1
Attendance to supervised exercise (%)		12	85.4	[33.3, 100]	19.9
Adherence to supervised endurance exercise (%)[1]		12	95.8	[81.6, 100]	6.9
Borg's scale week 1–16	12–14	12	14	[12, 16]	1.1
Borg's scale week 17–24	14–16	10	13.5	[12, 16]	1.5
Adherence to supervised resistance exercise (%)[1]		12	94.5	[76.5, 100]	6.5
Adherence to supervised balance exercise (%)[1]		12	100	[86.5, 100]	4.3
Did participants achieve 4 times 3–4-min intervals?	*N*				
Yes	4				
No	6				
Not applicable[2]	2				

[1] Adherence to the exercise programme when a participant met

[2] Adjuvant chemotherapy and the intervention lasted less than 17 weeks

high proportion dropped out before the start of intervention, and a major barrier for inclusion was long travel distance to participate in supervised exercise.

A high fraction (63%) of the patients were willing to participate. This is higher than in similar studies which have reported willingness to participate between 37% and 49% [23–26]. One possible reason for the high willingness could be the non-randomized design, where all participants could take part in physical exercise. Also the fact that the treating oncologists providing information had a positive attitude towards the study may have contributed to the high willingness. Contrary to our findings, Waart et al. reported difficulties in recruiting patients with colon cancer to an exercise study during adjuvant chemotherapy, experiencing that the clinicians were hesitant to refer patients [26].

Despite the high willingness demonstrated, the inclusion rate was only 43% among eligible patients. Long travel distance was a major barrier, as it made oncologists not asking for participation and patients to decline recruitment. In retrospect, long travel distance should have deemed a potential participant ineligible. However, this was not defined pre-trial, but left to be decided upon by the treating oncologist.

More than one-third of the participants dropped out after inclusion, a higher dropout rate than similar studies, reporting between 6% and 22% [23–25]. However, the majority of the dropouts happened before the start of intervention, mainly due to conditions not controlled by the participants. With the low sample size in this study, small numbers may have large impact on percentage and not necessarily reflecting the expected dropout rate in a larger study.

The attendance and adherence to the supervised exercise were high. A median attendance rate to supervised exercise of 85% is comparable to other studies reporting between 61% and 89% [23, 24, 26]. One likely reason for the high attendance was that the exercise intervention was supervised. Systematic reviews and meta-analyses of RCTs with various cancer types have shown that supervised exercise has a greater effect on several endpoints than unsupervised, and this could be explained by a higher compliance to supervised exercise [27, 28]. When a participant met, adherence to the exercise intervention in our study was close to 100%. A physiotherapist, experienced with patients with cancer, supervised the exercise in a one-to-one manner, and this has likely contributed to the high attendance and adherence.

According to protocol, the intensity of the aerobic endurance exercise should gradually increase during the intervention period. This seemed not feasible as the participants reported slightly lower RPE during the last intervention period (week 17–24). The goal of achieving intervals of 4 times 3–4 min was only reached in one-third of the participants. During the course of adjuvant chemotherapy, patients will typically experience increased fatigue and decreased cardiorespiratory fitness [29, 30]. According to the experience of the present feasibility study, we believe that interval training with increasing intensity is not feasible for the majority of the patients during adjuvant treatment.

One limitation of the present study is the lack of systematically reporting of the unsupervised exercise. Based on the available data, compliance to the unsupervised exercise could be interpreted as lower than the supervised. In a future RCT, a self-reported activity diary will be preferred for documentation of unsupervised exercise. Another limitation is the non-

Table 4 Individual changes in patient-reported chemotherapy-induced peripheral neuropathy and fatigue

		CIPN[1]			PF[2]			MF[3]		
	N	Median	Range	SD	Median	Range	SD	Median	Range	SD
T_0[4]	10	0.5	[0, 33.3]	10.3	16.0	[6.0, 24.0]	6.3	4.5	[4.0, 8.0]	1.3
T_1[5]	10	20.4	[0, 44.4]	13.0	15.0	[7.0, 25.0]	5.5	5.5	[4.0, 10.0]	2.1
T_1–T_0	10	14.8	[-3.7, 25.9]	9.6	− 1.0	[− 6.0, 13.0]	5.9	1.0	[0, 5.0]	1.6

[1] European Organization for Research and Treatment of Cancer Quality of Life Questionnaire–Chemotherapy-Induced Peripheral Neuropathy 20 sensory subscale (score 0–100)

[2] Physical fatigue from Fatigue Questionnaire (score 0–21)

[3] Mental fatigue from Fatigue Questionnaire (score 0–12)

[4] Baseline

[5] After 3 months

randomized design. We do not know if a randomized design would reduce the willingness to participate. The participants in this study were a selective group willing to attend the exercise intervention. It is reasonable to believe that those willing to participate had a more positive attitude towards exercise than those declining, like Waaet et al. found in their study [26]. Strategies to improve recruitment to interventional studies are needed, and this study did not address that. Because of the higher dropout rate than anticipated, a larger sample size could have strengthened the study. Regarding data collection, we have demonstrated that this was feasible with nearly 100% completion rates of both the physical tests and questionnaires.

There was no temporal relationship between the SAEs and the exercise intervention, and it is most likely that the SAEs reported were related to the chemotherapy, although this needs to be confirmed in an RCT. There were two (14%) thromboembolic events among the 14 participants. In comparison, an adjuvant study comparing two different chemotherapy regimens in CRC reported an incidence rate of thromboembolism of around 6% [6]. With the small sample size in our study, a higher rate of thromboembolism might just be by chance, and no conclusion can be drawn.

As expected, we found that symptoms of CIPN increased from baseline to 3 months after inclusion, as we do not expect exercise to fully prevent development of CIPN. It remains to be established in an RCT if the degree of CIPN developed can be reduced among those randomized to an exercise intervention compared with a control group. Zimmer et al. found that worsening of CIPN could be prevented among metastatic CRC patients receiving palliative chemotherapy randomized to a multimodal exercise programme in a small RCT [31].

To conclude, this study has demonstrated that a combination of supervised and home-based aerobic endurance, resistance, and balance exercises in CRC patients receiving adjuvant chemotherapy was feasible and safe, with the exception of a planned increased intensity of the aerobic endurance exercise which was not feasible for the majority. Based on our experiences from this feasibility study, we have made some adjustments in the ongoing RCT regarding the intervention and data collection, including physiotherapists supervise participants in their local community close to their homes [32], and the endurance exercise is kept on a moderate intensity and with a duration according to general recommendations [33].

Authors' contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Line Merethe Oldervoll, Arne Wibe, Guro Birgitte Stene, Signe Nilssen Stafne, Eva Hofsli, and Ingunn Hatlevoll. The first draft of the manuscript was written by Ingunn Hatlevoll, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability Data can be provided at request.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethics approval This study was approved by the Regional Committee for Medical and Health Research Ethics of Northern Norway (Record no. 2015/1050/REK nord) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

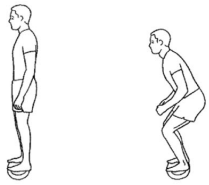
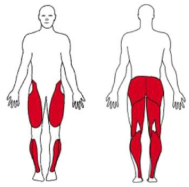
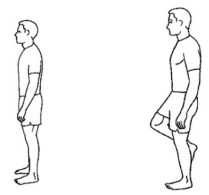
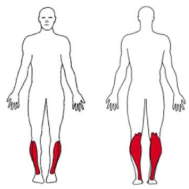
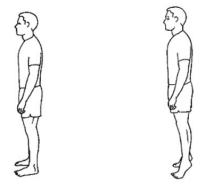
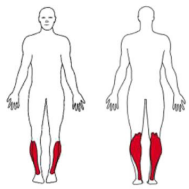
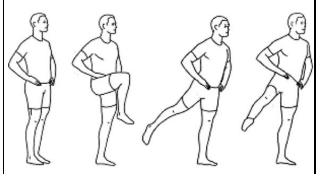
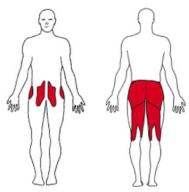
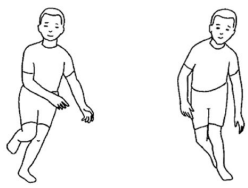
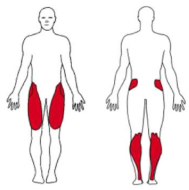
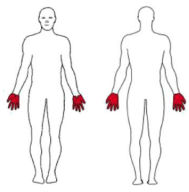
Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent for publication Not applicable.

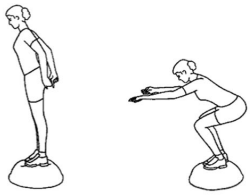
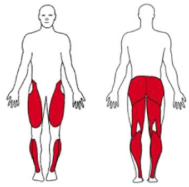
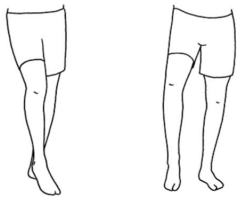
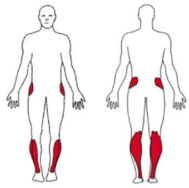
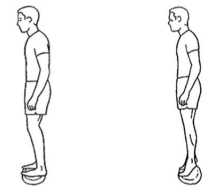
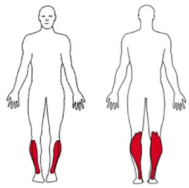
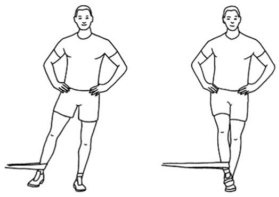
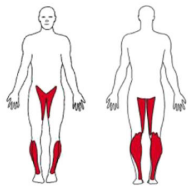
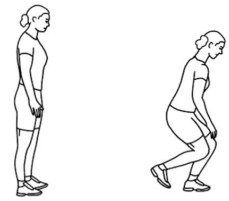
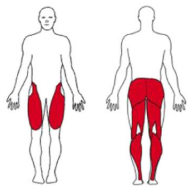
Code availability Not applicable.

Appendix. Illustrations of balance and resistance exercises, with permission from ExorLive

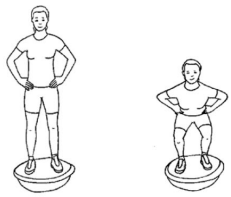
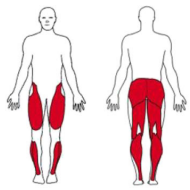
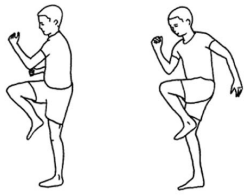
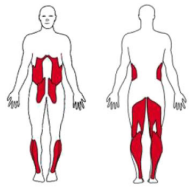
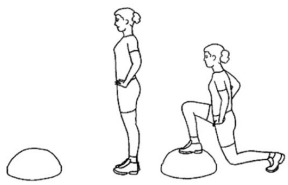
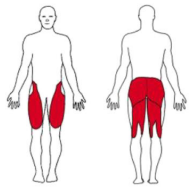
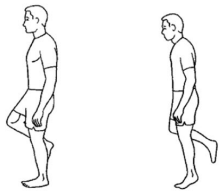
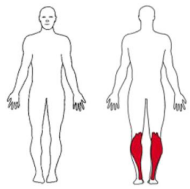
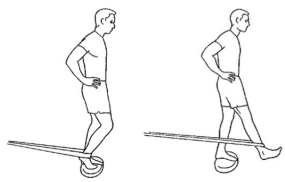
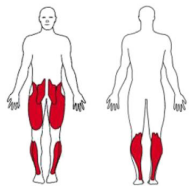
Balanseprogram nivå 1

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
Balansepute: knebøy			3 set x 10 rep	Stå på balanseputen. Bøy ned til ca. 90 grader i knærne og press opp igjen. Hold ryggen rett og blikket fram. Alternativt kan sittestillingen holdes i noen sekunder før du presser opp igjen.
Stå på ett ben			4 rep	Stå på ett ben, med lett bøy i kneet og rett rygg. Forestill deg at det blåser og at du svaier som et strå i vinden. Forsøk å stå slik til du blir trøtt i benet. Øvelsen kan gjøres vanskeligere ved at du lukker øynene. Bytt til motsatt ben og gjenta.
Tåhev			3 set x 10 rep	Stå på gulvet med ca hoftebreddes avstand mellom føttene. Løft hælene og press opp til tåstående. Vend tilbake til utgangsstillingen og gjenta. Øvelsen kan gjøres med eller uten støtte.
Ettbensstående balanse			10 rep	Stå på ett ben med hendene i siden. Løft motsatt ben opp ved å bøye i hoften. Beveg det deretter strakt bakover og strekk i hoften, og beveg deretter strakt ben ut til siden. Kom rolig tilbake til utgangsstilling og gjenta. Hold deg stabil i overkropp og bekken slik at det kun er benet som beveger seg. 10 repetisjoner på hvert ben, eller
Hinking sidelengs			10 rep	Stå på venstre fot. Ta ett hink til venstre og ett hink til høyre side. Bytt fot.
Klemme en ball			10 rep	Hold en liten myk ball i hånden. Klem rundt ballen slik at du bøyer fingrene. Hold spenningen litt og strekk deretter fingrene ut igjen.

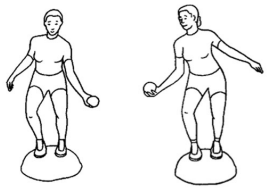
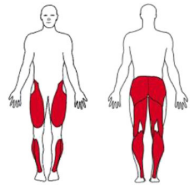
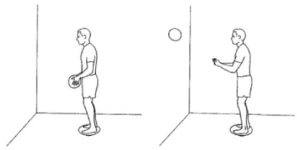
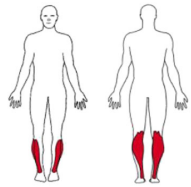
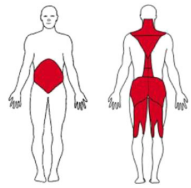
Balanseprogram nivå 2

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
BOSU: Knebøy			3 set x 10 rep	Stå med parallelle føtter med litt avstand på toppen av BOSU-en. Bøy i knær og hofter og sving armene fram foran kroppen. Pass på å holde ryggen rett og at nakken er i en naturlig forlengelse av ryggen. Se på skrå ned og framover. Pass også på å ha kne over tå. Før armene tilbake samtidig som du strekker deg
Skriv navn med foten			4 rep	Stå på ett bein. Skriv navnet ditt med foten i luften. Gjenta på motsatt bein.
Balansepute: tåhev			3 set x 10 rep	Stå på balanseputen og hold balansen. Løft hælene og press opp til tåstående. Senk tilbake og gjenta øvelsen. Støtt deg gjerne mot noe i starten.
Ettbens balanse m/strikk			10 rep	Stå på ett ben med hendene i siden og fest en strikk rundt ankelen på benet du ikke står på. Beveg benet strakt vekselvis foran og bak standbenet.
Sideveis hink fremover			10 rep	Hink fra side til side vekselsvis fot, tre skritt av gangen. Pass på at kne og tå peker samme retning.

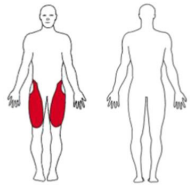
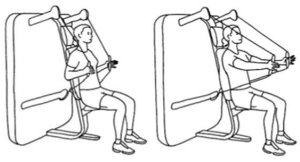
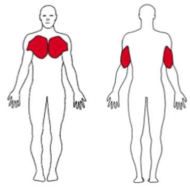
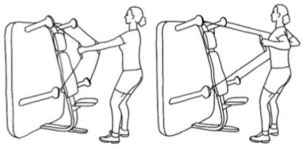
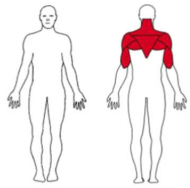
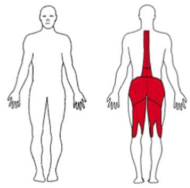
Balanseprogram nivå 3

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
Knebøy på BOSU opp ned			3 set x 10 rep	Snu BOSU-en opp ned. Stell deg på BOSU`en med cirka hoftebreddes avstand mellom bena og hoftetak med hendene. Gjør en knebøy ned til 90 grader og returner til startstilling.
Kne mot albue-gange frem			3 set x 10 rep	Gå fremover på en rett linje. Når du tar et steg fremover, løfter du vekselvis knærne opp mot motsatt sides albue.
BOSU: Utfall i 4 tellinger			10 rep	Stå et lite steg bak BOSU-en. Plasser en fot på toppen. Ta en dyp knebøy mot BOSU-en, ved at du bøyer i knærne og senker kroppen ned og litt framover. Pass på at du har knær over tær og rett rygg. Strekk opp igjen og skyv deg tilbake til utgangsstillingen. Foten skal være på BOSU-en under hele øvelsen.
Ettbens tåhev			10 rep	Stå på ett ben. Løft hælen og press opp til tåstående. Hold stillingen i 10-15 sek. Hold blikket framover og unngå å kikke ned mens du gjør øvelsen. Øvelsen kan gjøres vanskeligere ved at du lukker øynene. Bytt ben og gjenta.
Balansepute: stående benspark m/strikk			10 rep	Stå på balanseputen med strikken festet rundt den ene ankelen. Hold balansen mens du bøyer i både kne og hofte på det aktive benet. Utfør et benspark slik at du strekker kneet maksimalt. Gjenta øvelsen med det andre benet.

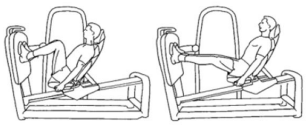
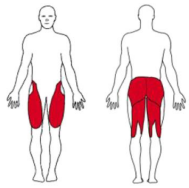
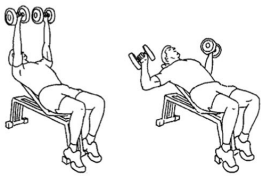
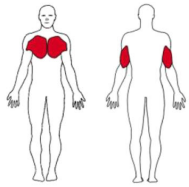
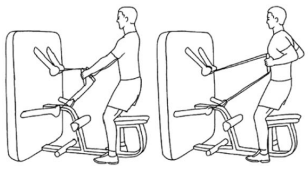
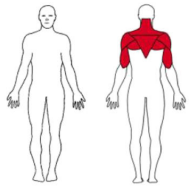
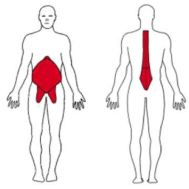
Balanseprogram nivå 4

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
BOSU: Knebøy m/vektball			10 rep	Stå med parallelle føtter på toppen av BOSU-en. Bøy i kne og hofter. Pass på å holde ryggen rett og at nakken er i en naturlig forlengelse av ryggen. Bli i knebøy og kast ballen fra den ene hånden til den andre. Strekk tilbake til utgangsstillingen. Gjenta annenhver side. Gjør det vanskeligere med å følge ballen
Vippebrett: kast en ball			3 set x 10 rep	Stå på vippebrettet og forsøk å holde balansen mens du kaster ballen mot en vegg eller til en annen person. Prøv å unngå at kanten av brettet berører gulvet. Øvelsen er enklere desto større avstand du har mellom føttene.
BOSU: Firfotstående diagonal arm- og benstrekk			3 set x 10 rep	Stå på alle fire på BOSU-en. Stabiliser mage- og korsryggregionen. Strekk vekselvis den ene armen og det motsatte benet til de er i forlengelse av kroppen. Hold noen sekunder før du vender tilbake til utgangsstillingen og gjentar til motsatt side. Pass på å holde korsryggen i nøytralstilling under

Styrkeøvelser - Periode 1

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
Kne ekstensjon			Ryggstøtte: Ankelpute:	Sørg for å ha god støtte i korsryggen. Press anklene mot ankelputen og strekk benene maksimalt ut. Markér gjerne sluttstillingen og senk rolig tilbake.
Press: sittende brystpress				Sitt med lave skuldre, ta tak i håndtakene og hold dem i brysthøyde tett inntil kroppen. Press fram til armene er strake, og før noe langsommere tilbake til brystet.
Press: stående roing				Stå oppreist med en naturlig svai i ryggen med ansiktet mot apparatet. Ta tak i håndtakene med strake armer og slipp skuldrene frem. Start bevegelsen ved å trekke skuldrene nedover og bakover og trekk håndtakene mot brystet. Slipp armene rolig tilbake til utgangsstilling.
Liggende seteløft				Ligg på ryggen med bøyde knær. Knip setet sammen og løft bekkenet og nedre del av ryggen fra underlaget. Hold i 3-5 sek. Hvil tilsvarende.

Styrkeøvelser - Periode 2

Øvelse	Illustrasjon	Treningsfokus	Øvelsesdata	Kommentar
Skråsittende benpress			3 set x 10 rep	Plasser benene på fotbrettet i skulderbreddes avstand. Ha ca. 90 grader i knærne. Stram opp i mage- og korsryggregionen og press opp til benene er nesten strake. Vend tilbake til startstillingen og gjenta.
Skrå brystpress			3 set x 10 rep	Ligg på ryggen med føttene i gulvet og hold hantlene på strake armer over brystet. Senk hantlene i en svak bue mot utsiden av skuldrene og press tilbake til startstillingen med noe større hastighet. Unngå å svaie for mye i korsryggen.
Low Pull: stående roing			3 set x 10 rep	Stå oppreist med en naturlig svai i ryggen med ansiktet mot apparatet. Ta tak i håndtakene på apparatet med strake armer og slipp skuldrene frem. Start bevegelsen ved å trekke skuldrene nedover og bakover og beveg håndtakene ned mot brystet. Slipp armene rolig tilbake til utgangsstilling.
Ryggliggende ettbens senk			3 set x 10 rep	Ligg på ryggen med 90° i hofte og knær. Plassér fingrene på innsiden av hoftekammen. Trekk navlen inn. Pust ut, senk høyre fot og strekk benet ut. Trekk inn navlen så mye som mulig. Pust inn og bøy og hev benet opp til utgangsstillingen igjen. Unngå økt svai i korsryggen. Ikke senk benet lenger ned enn at du klarer å holde

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Paper II

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ORIGINAL ARTICLE

WILEY

Colorectal cancer patients' experiences with supervised exercise during adjuvant chemotherapy—A qualitative study

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Background: Colorectal cancer (CRC) is a common cancer worldwide, with increasing numbers surviving and living with long-term side effects from treatment. Physical exercise during or after treatment may have several beneficial effects, but knowledge of CRC patients' reflections on exercising during adjuvant therapy is limited. The aim of this study was to explore the experiences of CRC patients participating in a supervised exercise program during adjuvant chemotherapy.

Methods: This study included CRC patients participating in two intervention studies with individually tailored and supervised combinations of endurance, resistance, and balance exercises during adjuvant chemotherapy. Semi-structured interviews performed at the beginning, during, and immediately after the intervention period from 15 participants were analyzed using thematic analysis.

Results: Four main themes identified were "structuring life with cancer," "motivation to exercise," "training experiences," and "effects of exercise." Scheduled appointments gave structure to daily life and served as an external motivational factor. The individual adjustments of exercise gave a sense of security and helped improving adherence, especially when feeling depressed or fatigued. Common expectations were improvement of endurance and strength and counteracting negative effects of chemotherapy. Experienced positive effects from exercising, both mentally and physically, contributed to inner motivation and inspired continued exercising after the study period.

Conclusion: This study offers important insights into CRC patients' experiences of participating in a physical exercise program during adjuvant chemotherapy. Based on our findings, we recommend supervised and individually tailored physical exercise during adjuvant chemotherapy to this patient group.

KEYWORDS
adjuvant chemotherapy, colorectal cancer, physical exercise, qualitative study, supervised exercise

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1 | INTRODUCTION

Colorectal cancer (CRC) is a growing health burden worldwide, as the incidence rates are expected to increase 60% by 2030.[1] During recent years, modern treatment principles for CRC have become more complex with improved surgical techniques, radiotherapy, and systemic therapies, and thus, more people are surviving their cancer.[2] However, such comprehensive toxic regimens are followed by complications and long-term side effects. Fatigue and chemotherapy-induced peripheral neuropathy are common side effects of oxaliplatin-based chemotherapy used in adjuvant treatment for CRC. These and other side effects have major negative impact on patients' quality of life.[3-5]

Physical activity (PA) is associated with reduced risk of developing colon cancer and improved survival from CRC.[6,7] Furthermore, it has been demonstrated beneficial effects of physical exercise both during and after cancer treatment on cancer-related health outcomes, but this has mainly been studied in breast- and prostate cancer.[8] Since the first randomized controlled trial (RCT) studying the effects of physical exercise on quality of life in CRC survivors was published in 2003,[9] only a few studies have included patients with CRC receiving adjuvant chemotherapy in physical exercise interventions.[10,11] Recruiting patients with CRC to PA seems difficult,[12,13] and information about CRC patients' expectations and reflections of undergoing a physical exercise program during adjuvant chemotherapy is limited.[14,15] The aim of this study was to explore the experiences of patients with CRC participating in an individually tailored and supervised exercise program during adjuvant chemotherapy.

2 | MATERIAL AND METHODS

2.1 | Study design

This was an explorative qualitative study using individual, semi-structured interviews at different time-points during adjuvant chemotherapy among CRC patients who participated in physical exercise interventions during treatment.

2.2 | Participants

Fifteen participants were recruited from our non-randomized feasibility study and our ongoing RCT, "Physically Active during Cancer Treatment".[16,17]

The major eligibility criteria were radical resection for stage II–IV CRC *and* scheduled for adjuvant chemotherapy (resection for synchronous metastases was allowed.), age 18–80 years, ability to conduct the intervention based on the treating physician's assessment, and ability to understand Norwegian language. Exclusion criteria were medical conditions contraindicating physical exercise and treatment for other invasive cancers during the five past years.

All CRC patients referred to adjuvant chemotherapy were screened for eligibility by the consulting oncologists. At the first consultation, the treating oncologist provided oral and written information to the patient, and a study coordinator obtained written informed consent the following days. Information about the qualitative study was repeated before starting the interviews. The study was approved by the Regional Committee for Medical and Health Research Ethics of Northern Norway (Record no. 2015/1050/REK nord).

2.3 | Physical exercise intervention

The intervention started when commencing adjuvant chemotherapy and lasted throughout the treatment period (ie, 12–24 weeks). It consisted of an individually tailored combination of supervised and home-based aerobic endurance, resistance, and balance exercises built on results from exercise tests and earlier experience with physical exercise. The resistance exercises were supervised, while the endurance- and balance exercises were both supervised and unsupervised. Choice of exercises and dosage was individually adjusted based on progression. A detailed description of the intervention can be found in our previous work.[16]

The participants met with a physiotherapist at the hospital the same week or the week after starting the first course of chemotherapy and were introduced to the exercise program. Written information with illustrations of the exercises to be performed at home was handed out. Participants in the RCT were equipped with a heart rate monitor to guide the intensity and duration of the aerobic endurance exercise. A physiotherapist, located either at a specialized outpatient training facility for cancer patients, or in the municipal health service, supervised the participants twice a week through the whole intervention period.

To assess self-reported PA level, a questionnaire for patient-reported PA developed for use in the North Trondelag Health Study (HUNT) was used.[18] This is a three-item questionnaire on leisure-time PA regarding frequency, intensity, and duration (three–five alternatives) giving rise to a PA index, placing the participants in three different levels of activity, from low to high[18] (Table 1).

TABLE 1 Patient characteristics

No. of patients	15
Age, years, median [range]	65 [43–80]
Males	8
Females	7
Stoma	
Yes	2
No	13
Type of surgery	
Laparoscopy	7
Open	8
Stage[a]	
III	13
IV	2
Adjuvant treatment planned	
3 months oxaliplatin-capecitabine	4
6 months oxaliplatin-capecitabine	8
6 months capecitabine	3
Marital status	
Living alone	7
Married/partner	8
Employment	
Working	7
Partly working/partly disabled	2
Retired	6
Education	
Elementary or high school	6
College/university	9
Self-reported physical activity	
Low level of activity	7
Medium level of activity	4
High level of activity	4

[a]Stage according to TNM Classification of Malignant Tumours, 8th edition.

2.4 | Adjuvant chemotherapy

Adjuvant chemotherapy consisted of oral capecitabine alone or in combination with intravenous oxaliplatin, depending on patients' age, and with start 4–8 weeks postoperatively. Duration of adjuvant treatment was 24 weeks for monotherapy and 12–24 weeks for combination chemotherapy.[19]

2.5 | Data collection

Interviews took place at study start ($n = 13$) and after 12 ($n = 10$) and 24 ($n = 6$) weeks. Participants only receiving 12 weeks of intervention were not interviewed at 24 weeks, participants dropping out of the intervention had only baseline interviews, and those entering the qualitative study later did not have baseline interviews. The interviews were scheduled in concordance with the patients' other appointments and held in a private room at the hospital.

Semi-structured interviews were used to explore participants' expectations to and experiences with participation in the physical exercise program, based on interview guides (Table 2). The interviews lasted 20–45 min, were audio recorded, and transcribed verbatim. Three researchers conducted the interviews. One physiotherapist having long experience with cancer patients (SAS), one oncologist (IH), and one being an experienced qualitative researcher (JAS). JAS supervised the two other interviewers, considered as novices in the field of qualitative research. None of the interviewers were involved in supervising the exercise intervention or the medical treatment.

From January 2018 to October 2020, 29 interviews distributed among 15 participants at St. Olav's University

TABLE 2 Interview guide

At baseline
What is your previous experience with exercise?
What do you think this can give you in terms of advantages and/or disadvantages in the future?
What is your impression on how people experience chemotherapy?
Can you say something about how you think this affects you in the phase you are in now?
What do you wish to achieve with the exercise?
What do you think about exercising even if you have ailments, symptoms, and/or side effects?
Do you have any thoughts on how to deal with these possible challenges?
What do you think about the practicalities of participating? Time, place, etc.
At 12 and 24 weeks
What has been your motivation for participating in the exercise until now? /during the treatment period?
Has the motivation to participate changed since the start? / along the way? Possibly how?
What experiences have you had in relation to exercising with any ailments, symptoms, and side effects that have occurred?
If side effects have been present, what has been your strategy for exercising anyway?
What do you think about the training (so far)?
Is there anything about the exercise program you think should be different in order to be 100% satisfied?
How has the practicality of the training worked for you in terms of time, place, etc.?

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Hospital, Trondheim ($n = 14$) and Aalesund Hospital ($n = 1$) were performed. Patient characteristics are summarized in Table 1. Five patients from the feasibility study dropped out shortly after inclusion due to medical ($n = 2$) and administrative ($n = 1$) reasons or their changed minds ($n = 2$). Five patients from the feasibility study and five from the RCT followed the intervention and provided interviews at 12 and 24 weeks.

2.6 | Analytical methods

Thematic analysis with an inductive approach, as described by Braun and Clarke, was used.[20] It consists of six phases: 1. Familiarizing yourself with your data, 2. Generating initial codes, 3. Searching for themes, 4. Reviewing themes, 5. Defining and naming themes, and 6. Producing the report. All authors read all the interviews. In addition, the first author listened through all the interviews at least once. All authors contributed in phase 1–3. In phase 4–6, the first and second authors were mainly involved, all authors took part in discussions regarding the analysis, read through, and approved the final report. Codes and themes were generated during the research process, in line with the explorative nature of the study. Although the initial design was to explore relevant themes in a pre-post fashion, the prolonged therapeutic period for a minority of the participants also allowed for elements of a longitudinal analysis, as described by Saldaña.[21] Inclusion was stopped after 15 participants, based on the research group's agreement that information redundancy had been achieved, and no new codes were generated through continued interviewing.

3 | RESULTS

Patients with CRC experienced that an individually tailored and supervised exercise program during adjuvant chemotherapy provided structure to life with cancer, motivation to exercise, training experiences, and effects of exercise.

3.1 | Structuring life with cancer

Overall, the patients saw inclusion in the study as being offered a number of benefits. In addition to hoping for positive effects of physical exercise, study participation represented an opportunity to structure their lives as cancer patients through scheduled appointments and commitments to themselves and other people.

> *"But I'm pretty sure that if you're a little down, and you might be that when you get a serious diagnosis, then I think it's so important to have regular appointments, in that way you have to do things." (Female, 65)*

Being on sick leave, the need to and importance of filling the days was recognized.

> *"If I'm not going to work I need something to fill the days. It's been OK during the Olympics, but that won't last. ...Otherwise I think it will be a bit dismal to sit and wait for the rest of the people to return at four or five." (Male, 57)*

Similar statements were emphasized repeatedly throughout the study. It helped them to structure their day and gave them something to look forward to. To become isolated was a concern, and signing up for the study represented a good opportunity to avoid this. Advantages from getting out instead of sitting indoors doing nothing was another benefit.

> *"The fine thing is that you are getting out of the house no matter how bad you feel." (Female, 65)*

Having appointments helped them to get up and out when feeling depressed or tired. This was acknowledged as critical at times when exercising by themselves was found challenging and was particularly important toward the end of the treatment period.

> *"In particular now towards the end, if I hadn't had this commitment it would have been heavier to get this done on my own. As I say it is difficult to get out of the chair and get started, and in this way it is important to have a steady appointment." (Male, 78)*

Getting the chance to participate in the study led to feelings of gratitude, accompanied by a wish that more patients would be offered the same opportunity.

> *"Well, it's the total package, and I'm grateful for that, to be part of this.....No, it has been positive [to participate in the study], it has. If I hadn't, I would probably just sit at home, and probably been in a lot more pain than I am now." (Male, 67)*

3.2 | Motivation to exercise

Although all participants demonstrated a motivation for exercise by joining the study, both skepticism and insecurity toward participation were revealed initially. There

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was skepticism as to whether the program was too oriented and focused on disease, hence serving as a reminder of the diagnosis, whether the body could handle it if one exercised too much, but also having to meet with a physiotherapist. The insecurity was about not knowing how one would react to the treatment and whether daily commitments would be manageable.

> *"So I was a little skeptical having to show up and see a physiotherapist, but I clearly see the need to exercise your muscles after an operation and during such a serious treatment course." (Male, 62)*

To exercise intuitively made sense, as a realization of the necessity of keeping both body strength and flexibility. The threat of losing strength during the treatment period gave a motivation to potentially rebuild what was lost. Exercise was also a way to counteract the anticipated breakdown of the body due to chemotherapy.

> *"But I see that exercising might be good for your body while you break it down, because it's kind of breaking down the body to heal, isn't it? And if you exercise, you then manage to weigh up a bit of that, the breakdown, I think." (Male, 71)*

Faith in exercise was expressed, as being good for both physical and mental health, including a hope that exercise may increase the efficacy of chemotherapy.

> *"It is as if I have this picture that exercise and chemotherapy...it is important to get the chemotherapy into action" (Female, 61)*

Exercise motivation came from both external and internal sources, and there were factors bolstering motivation while others threatened it. An inner motivation was demonstrated through a strong desire to exercise and not skip out when tired.

> *"I've felt very strongly that I should do the training. Skipping the training because I've been tired was not relevant for me." (Male. 68)*

A crucial external motivation for exercising both regularly and efficiently came through the appointments with the physiotherapist. It made the participants feel obliged to attend even when feeling sick and weak from chemotherapy.

> *"It must be some of the best things that has happened, it's kind of something that has kept me going... towards...you know? I am, I think I'm pretty good at structuring myself, but when you get tired and lazy, it's okay to have someone outside yourself, who sort of is with you and, yes..." (Female, 53)*

If an exercise session was canceled for some reason, and participants were supposed to exercise by themselves, postponing or skipping parts of the program presented a temptation that not all were able to resist.

> *"There was one time when the physiotherapist was absent, so I had to do the exercises by myself. It then came right away: It started with me feeling out of shape, thinking like – Maybe I'll rather do it tomorrow....." (Female. 61)*

Motivation was also threatened by exercises they did not like or found boring, and when they felt fatigued. An inner struggle between going to the gym and the desire to rest was experienced, especially at times when even simple activities of daily living was a struggle.

> *"Yes, resistance exercising is <u>really</u> boring. It can't be denied, but it kind of has to be done. I'm still doing it. I feel it does me good, but it is not fun." (Female, 61)*

It could take a huge effort to get to the gym, but a motivation in such instances would be earlier experience of symptoms decreasing during and after exercise. Knowing that they could rest with a clear conscience afterward bolstered motivation further.

> *«...and the feeling that you're actually getting weaker and weaker, and things are getting heavier and heavier, it's a bit hard. At the same time, physically, I see that I have progress in my exercises, I'm actually getting stronger, the balance actually gets a little better, and it gives a positive experience....but I think maybe I'm sitting more in my recliner, but with a better conscience in a way." (Male, 57)*

Supervision by a physiotherapist provided motivation to perform a little extra, and to complete all the exercises, even the boring ones. Guidance from a physiotherapist to adjust the exercising according to variations in their physical function also gave a sense of security.

> *"I think it's important there are professionals who have..., you feel confident in what they instruct, and..., do not push me a lot, but I feel that they help me exert more than I might do on my own." (Female, 58)*

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A desire to contribute to research, to prove that exercise works, was a motivational factor for one.

> *«...and I say to M [the physiotherapist] that now, M, I'm not only running for me, I'm running for your project, so you get more means [laughing], so people can realize that this works." (Female, 53)*

With time, an ambition to continue exercising without supervision after the study period also emerged reflecting a change from outer to inner motivation.

> *"One day when one of the instructors were ill, I noticed that I was really lazy, so it is important for me that there is somebody there. (Female, 53, week 12)*

> *"But the last time she was absent I did it all by myself.... I realized that in June she is not going to be there anymore, so I was starting to realize that I have to this on my own." (Female, 53, week 24)*

3.3 | Training experiences

Previous experience with physical exercise varied among participants from training at a fitness center several times a week, to hardly having done any physical activity except sporadic outdoor walks. Training intensity varied across the lifespan; often originating in organized sports in childhood, while family life and work took time away from training in adulthood. A common feature was their appreciation of walking outdoors, to and from the workplace, or in the nature in their leisure time.

> *"I've always been in activity. Do a lot of walking in the country side...Used to do aerobics three times a week, and climbing hilltops, and I had a dog I used to walk twice a day...." (Female, 71)*

> *"I have exercised very little, exercised a bit in the 90's, but otherwise it has been some walks and stuff." (Male, 68)*

Variations in both physical fitness and in how they responded to exercise were observed regularly, in and between individuals. After recovering from surgery, chemotherapy could give a setback. Their physical fitness could also vary within each chemotherapy cycle, as an activity mastered with ease one day felt impossible another. Generally, exercising felt harder toward the end of the treatment period.

> *"So I didn´t realize, that the Monday after [the last tablet], I didn´t realize it was then I was most tired, and the next Friday I could climb the ceiling, if you know what I mean." (Female, 53)*

Participants exercised regularly, as prescribed. Concerns for health-related obstacles to exercise, as well as non–health-related obstacles like family logistics or slippery ground during wintertime, were mentioned prior to commencing the study, but did to little extent influence the exercising. The only major obstacle to turning up for a training session was intercurrent illness with infection. A factor contributing to this high exercise fulfillment was individual adjustments made by the staff to accommodate orthopedic complaints or when a participant was not feeling well.

> *"Yes, they certainly did [adjust the exercise according to variations in shape]. They were very sensitive to that. It was facilitated, and I tried, of course, to stretch myself a bit, as far as possible, but they were considerate." (Female, 58)*

Use of a heart rate monitor was introduced as a motivational factor for exercise, with varied success. Experiences differed from sporadic use of the watch and just learning the basics (start, stop, and monitoring heart rate) to carefully monitoring each exercise session and going through them on the smart phone afterward. In one case, it also inspired one participant to exercise beyond what was considered beneficial under the circumstances.

> *"I have gotten a lot out of it [the heart rate monitor]. I have an app on my smart phone, so every time I exercise, I read the results from the app, because there is some motivation in it...Sometimes I have been too eager and trained too hard. I am pleased there and then, but the day after I have a minor backlash." (Male, 62)*

3.4 | Effects of exercise

Prior to entering the program, participants hoped that the exercise would improve their endurance and strength, and to regain their pre-cancerous physical status. Being able to resume activities they had been capable of before, and to

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be able to return to work after the treatment period, were also among their hopes. These hopes were paired with a belief that staying in good shape would make the treatment more tolerable, and possibly reduce long-term side effects from the chemotherapy.

> *"I'm actually in the situation that I look forward to this, because I've felt that my shape has gotten worse when I have done nothing, so I will try to roughly get back in shape, even though I've had cancer, because I think that's possible if you believe in it." (Male, 64)*

Despite the fluctuant setbacks described above, continued improvements were a common effect from the program. Feelings of increased energy, and of being in better shape right after a workout than before, were often described. Still, for others, insecurity persisted as to whether endurance had improved. Tiredness was a regular experience after a training session, but most often in terms of feeling tired in a good way. Toward the end of the study period, the perceived physical fitness diverged, ranging from feeling in better shape than for a long time, to feeling major fatigued.

> *"I then noticed that when I started exercising, I got better. I felt better when I left, in a way." (Female, 58)*

Being physically active and exercising affected the participants' mental health positively. Reported effects ranged from reducing symptoms of depression to a feeling of joy or happiness during and after exercise. Losing weight while engaging in the exercise program was described as a bonus by a participant considering himself as overweight.

> *"To be honest, I think it helps you mentally as well. It definitely does. Because getting out and being in movement; that helps a lot." (Female, 65)*

Symptoms from peripheral sensory neuropathy often diminished after commencing exercise and getting warm, and this could last for several hours after the session. Increased muscle strength was experienced both through being able to increase the load during strength exercise, and the feeling of regaining lost muscle mass. Being able to keep in shape and keeping their strength, despite receiving chemotherapy, led to feelings of satisfaction.

> *"It's like I get paid for it when I finish the intervals, feels like I've gotten something out, it doesn't tingle so much anymore, and the burning in my hands can suddenly completely disappear,..." (Male, 57)*

4 | DISCUSSION

This study offers important insights into CRC patients' experiences of participating in an individually tailored and supervised physical exercise program during adjuvant chemotherapy. Scheduled appointments with a physiotherapist gave an opportunity to structure life with cancer and served as an important external motivational factor. Furthermore, participants perceived positive effects from exercising, as improved muscle strength, reduction in sensory neuropathic symptoms, and improvement in mental health. Common expectations and hopes were improvement of endurance and strength, to achieve better tolerance and efficacy, and counteract negative effects of chemotherapy.

Structuring of life with cancer aligns with previous research, exploring women's experiences engaging in supervised exercise during treatment for early-stage breast cancer.[22,23] Commitment to scheduled appointments, serving as an external motivational factor, is also described as part of palliative cancer patients' experiences of participation in a physical exercise program.[24]

To have supervised exercise with regular appointments was crucial, as the participants could not see how they would have been able to perform the same amount of exercise without this arrangement, which is in accordance with Backman et al.[23] The preference for supervised exercise with individual attention from exercise staff was also found among CRC survivors participating in an exercise rehabilitation program performed after chemotherapy, and among physically inactive breast and colon cancer patients initiating PA while undergoing adjuvant chemotherapy.[15,25]

Our participants experienced several positive effects from exercising during adjuvant chemotherapy, both physically and mentally. This has been demonstrated in other studies, but mainly in breast cancer.[15,22,23,26,27] There are noticeable differences between these two patient groups, however, as median age at diagnosis is approximately 10 years higher in CRC,[28] and the surgical and adjuvant treatments are different. Our findings thus indicate that positive effects can be achieved in older patient groups as well.

Generally, the participants were positive toward exercise. This might not be surprising, as they chose to participate in the study. We did not explore the experience of those declining participation, but Wart et al. found a more negative attitude toward exercise among patients declining participation in a physical exercise study among colon cancer patients receiving adjuvant chemotherapy.[13] It has been reported that adjuvant chemotherapy is a major barrier to PA among CRC patients.[29] In the present study, barriers were related to side effects from chemotherapy,

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but these were overcome through the scheduled sessions, individual adjustments, and by an inner motivation developing from positive experiences participating in the exercise intervention.

A strength of our study was that the interviews were performed both at the beginning, during and right after the intervention, allowing to explore both expectations to and experiences with the exercise intervention, and to evaluate potential individual changes over time in a longitudinal manner.[21] Performing the interviews while participants still were under intervention, reduced the risk of recall bias.[30] Contributions by the whole research team doing initial coding and participating in regular meetings discussing themes have strengthened the quality of our data analysis.

Given the explorative nature of this study, no theoretical framework was applied to guide our analysis, which was more data-driven. The participants were given the opportunity to tell about their experiences in their own words, providing insights to the experiences of performing physical exercise after major surgery and receiving toxic chemotherapy. Social cognitive theory-based PA behavior change interventions seem promising in improving PA level among cancer survivors, but that was beyond the scope of the present study.[31]

The inclusion of participants both willing and unwilling to engage in physical exercise during adjuvant chemotherapy would have broadened the scope of our study. An expansion of this scope, to also encompass patients refraining from training, should be encouraged in the future research. Though we would argue that our study population represents a wide variety regarding age, sex, marital-, employment-, and educational status, levels of PA, and former experience with PA, and hence, most likely our results are representative for patients with CRC commencing adjuvant chemotherapy and being willing to engage in supervised exercise.

5 | PERSPECTIVES

The literature is scarce on effects of exercise during treatment for patients with CRC.[11] In our previous work, we have demonstrated the feasibility of an exercise intervention during adjuvant treatment for CRC.[16] To our knowledge, this is the first qualitative study reporting CRC patients' experiences participating in an individually tailored combination of supervised and home-based aerobic endurance, resistance, and balance exercises during adjuvant chemotherapy.

Based on our findings, we recommend supervised and individually tailored physical exercise when prescribing exercise to this patient group during adjuvant chemotherapy. This is also supported by a meta-analysis demonstrating that the effects on quality of life and physical function were significantly larger for supervised than unsupervised exercise.[32]

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. SAS, JAS, and IH did the interviews. During data analysis, all authors contributed in phase 1–3. JAS and IH were mainly involved in phase 4–6. All authors took part in discussions regarding the analysis, read through, and approved the final analysis. IH wrote the first draft of the manuscript. All authors commented on previous versions of the manuscript, and read and approved the final manuscript.

ETHICS APPROVAL

This study was approved by the Regional Committee for Medical and Health Research Ethics of Northern Norway (Record no. 2015/1050/REK nord) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors declare that they have no conflicting interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Paper III

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Do older patients with colorectal cancer experience more deterioration in health-related quality of life during the first year of palliative chemotherapy? – A prospective real-world observational study.

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Abstract

Purpose: The primary aim was to evaluate changes in health-related quality of life (HRQoL) in a real-life population among younger (< 70 years) and older patients with metastatic colorectal cancer (mCRC) the first year of palliative chemotherapy. The secondary aims were to assess the impact of chemo-break on HRQoL and to report overall survival (OS).

Methods: Patients with newly diagnosis of mCRC, ≥ 18 years, and scheduled for first line palliative chemotherapy, were included in this multicentre longitudinal observational study. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (0-100) was filled in at baseline and every second month, and >20 points change was considered to be of a large clinical magnitude. Treatments, patient- and tumour characteristics were prospectively registered.

Results: Totally 214 patients were included, and 146 were alive after one year. Four months after start of treatment, large deteriorations in fatigue and physical functioning were reported by 40% and 25% of the patients, respectively. Changes in global QoI, physical- and role functioning, fatigue, pain, and nausea/vomiting were not significantly different between the age groups and reached baseline levels after one year. Patients on chemo-break reported significant improvements in several HRQoL domains. Median OS was 17.5 months [95% CI 14.4-20.5] with no difference between younger and older patients.

Conclusion: Older patients did not experience more deterioration in HRQoL than younger patients during the first year of palliative chemotherapy. Measures to mitigate the deteriorations in fatigue and physical functioning observed during the first months of palliative treatment are warranted.

Trial registration: NCT02395224 , March 23, 2015, retrospectively registered.

Keywords: Aged, colorectal neoplasms, Quality of life, treatment break, palliative care

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths worldwide [1]. In Norway, CRC is the second most common cancer, and approximately half of the patients develop metastatic disease, either upfront or later in their disease trajectory [2]. Most of these patients will be treated with palliative intent [3].

The main treatment goals of unresectable metastatic CRC (mCRC) are prolongation of life, symptom relief, and maintenance of quality of life (QoL). Knowledge of treatment effects from different regimens is mainly derived from randomized controlled trials (RCTs) which most often constitute highly selected patients who may not be representative for the whole patient population. Participants in RCTs are often younger and with better performance status (PS) [4]. Still, treatment guidelines are based on such trials. While median age at diagnosis of CRC is approximately 72 years [2], the median age of participants in RCTs for palliative chemotherapy in CRC typically is 10 years younger [5]. Since older patients are underrepresented in RCTs, there have been concerns whether these patients will tolerate palliative chemotherapy as good as younger patients.

When investigating new chemotherapy regimens for unresectable CRC in RCTs, the strategy often is treatment to progression or unacceptable toxicity [6-8]. Unlike this, the clinical practice in Northern Europe is to introduce a chemo-break in a stop-and-go manner or maintenance therapy with a milder regimen to let patients recover from side effects of treatment [9]. Without establishing a final consensus, several trials have explored whether maintenance or intermittent treatment is preferable regarding efficacy and tolerability [10-14]. Sonbol et al. concluded in a meta-analysis that there is no clear overall survival (OS) benefit with either strategy, but a maintenance strategy is preferred [15]. Norwegian guidelines recommend considering a chemo-break four to six months after start of first line palliative chemotherapy for mCRC [3].

Shared decision-making is advocated in situations where several rational choices exist [16,17]. However, more information from real-life populations regarding effects and side-effects from different treatment regimens is needed for patients to make well-informed choices on receiving chemotherapy, withholding treatment, or introducing a chemo-break. Information about long term health-related quality of life (HRQoL) will enable patients and physicians to make sensible treatment plans.

The primary aim of the present study was to describe changes in HRQoL in a real-life population of patients with mCRC the first year after introduction of palliative chemotherapy, comparing younger vs. older, with key focus on global QoL, physical- and role functioning, fatigue, pain, and nausea/vomiting. Secondary aims were to evaluate the impact of chemo-break on HRQoL and to report OS.

Material and methods

Trial design

The present study used data from a prospective observational study of newly diagnosed patients with mCRC in central Norway (mCRC-study) [18]. The aim of the mCRC-study was to evaluate treatment and patient care given to unselected "real-life" patients during their disease trajectories. Data regarding patient- and tumour characteristics, the different treatments with responses, and patient reported outcomes (PROMs) were prospectively collected.

Participants

To be eligible for inclusion in the mCRC-study, patients had to be newly diagnosed with metastatic or non-resectable CRC, ≥18 years of age, and provide written informed consent. Eligible participants were identified when referred to the local oncological department. From September 2014 to

November 2018, 354 patients were included from all seven hospitals in the health region of central Norway. Only patients who had filled in the baseline questionnaire and were scheduled to start first line palliative chemotherapy, were included in the present study.

Outcomes

Clinical data were registered by health personnel in an electronic case report form. Registered data relevant for the present study included patient demographics, chemotherapy regimen, primary tumor- and metastatic site, stage of disease, baseline blood tests (such as CRP, albumin and CEA), modified Glasgow Prognostic Score [19], and tumor mutational- and microsatellite instability (MSI) status. Eastern Cooperative Oncology Group (ECOG) performance status (PS) was assessed by the treating clinician.

HRQoL

HRQoL was assessed using the cancer specific European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30), version 3.0 [20]. This is a self-reported questionnaire aggregating 30 items, constituting five functioning scales, three symptom scales, six single items and one overall QoL scale covering the past week. The two items assessing overall health and QoL are scored on a categorical scale from 1 to 7 giving rise to global QoL, and the rest of the items are scored from 1 (not at all) to 4 (very much). Higher scores on the functioning and global QoL scales indicate better functioning, while higher scores on the symptom scales and single items indicate more symptoms.

Participants filled in the QLQ-C30 using pen and paper. Questionnaires were filled in at inclusion and every second month thereafter, indefinitely. The questionnaires were handed out to patients by study personnel at inclusion, and were mailed, with a prepaid return envelope, to the patients from the study office at all other time points.

Statistical considerations

HRQoL scores were transformed into a scale from 0 to 100, as described in the EORTC scoring manual [21]. Changes or differences in QoL scores of >20, 10-20, and 5-10 points were considered to be of large, moderate, and small clinical magnitude, respectively [22]. Comparing means of different QoL scores between groups or over time, a threshold of 5-10 was considered the minimally important difference (MID) [23]. No imputation of missing data was performed. A two-sided p-value of <0.05 was considered statistically significant.

At baseline and after 12 months, all domains from the QLQ-C30 are presented according to age group, comparing younger (<70 years) vs. older (≥70 years). Describing changes in HRQoL, the key six domains are global QoL, physical- and role functioning, fatigue, pain, and nausea/vomiting. The domains were chosen based on what clinicians often experience is affected by cancer and its treatments, and thus often reflected in clinical studies in this patient population [24].

To evaluate the impact of a chemo-break, the time period between months six and eight was chosen, since clinical guidelines often recommend to consider a chemo-break after six months of treatment [3,25]. To be eligible for this analysis, patients had to have returned questionnaires at both time points, and to be on treatment and not having progressive disease at month six.

OS was calculated from start of first line palliative chemotherapy to time of death of any cause or censored at cut-off date.

Statistical analyses performed were mainly descriptive, mean scores were compared between groups with the two-sample t-test, and for the survival analyses the Kaplan-Meier method was used. The Log Rank test was used comparing survival between groups. Patient baseline characteristics were described with median and range (continuous variables) or with numbers and percentages (categorical variables), and compared between groups with the Pearsons Chi-Square

test, which was also used comparing individual changes from baseline to month four and twelve. The analyses were performed using IBM SPSS Statistics version 28.

Ethics

The mCRC-study was approved by the Norwegian Data Protection Authority (Reference no. 36627 13 / 01039-6 / CGN), and the present study was approved by the Regional Committee for Medical and Health Research Ethics of Middle Norway (Reference no. 216433). Written informed consent was obtained from all individual participants included in the study.

Results

Recruitment

Among the 354 patients in the mCRC-study, 214 patients were included in the present study. Reasons for exclusion were: 'treatment with curative intent' (n=39), 'never started palliative chemotherapy' (n=28), 'never returned any questionnaires or baseline form missing' (n=59), 'included after chemotherapy was given' (n=6) and 'withdrew consent' (n=8).

Baseline data

Younger patients had better PS, and a larger proportion had their primary tumour intact compared to the older patients (42% vs. 25%). A larger proportion of the older patients (73% vs. 62%) had not received earlier curative intended chemotherapy. Ninety-eight percent of the younger, compared to 73% of the older patients were scheduled for combination chemotherapy. The addition of a monoclonal antibody was more often given to the younger patients (80% vs. 59%). Mutational- and MSI status were evenly distributed between the groups, as well as sex, tumour location, and other socio-demographic factors (Table 1).

Return of HRQoL-questionnaire at different time points

The completion rate of QLQ-C30 among those alive to answer was 100, 88, 87, 84, 83, 80 and 78% from baseline to month 12, respectively. There were no difference in completion rates between the two age groups. Major reasons for not returning a form were death, dropping out of returning, or missed time points. After one year, 146 of the originally 214 patients were still alive. Detailed information on number of patients with completed EORTC QLQ-C30 questionnaires at different time points and reasons for not returning a questionnaire is presented in figure 1.

Baseline HRQoL in younger and older patients

At baseline, younger patients reported significant worse global QoL, more pain and financial difficulties, but better physical functioning than older patients. Younger patients had numerical worse scores for insomnia, role- and social functioning, but these scores were not significantly different between the two groups (Table 2). Except for pain, the differences between mean scores in the two age groups were of a small clinical magnitude, but above the threshold for MID. Mean score for pain was 11 points higher in the younger group.

Changes in HRQoL the first year after start of first line palliative chemotherapy

Younger patients reported better physical functioning but more pain at all time points through the first year (Figure 2). Both groups experienced a decline in physical functioning, increased fatigue, and less pain from baseline to four months after introduction of chemotherapy. The two groups underwent similar changes in the six selected HRQoL domains through the first year of palliative chemotherapy. Compared to baseline, mean scores for these domains were on the same level one year after initiation of chemotherapy, except for the younger patients experiencing improvement in pain (Table 2).

After 12 months, using a threshold of 5-10 for the MID, an improvement in role- and social functioning (younger), emotional functioning, insomnia and appetite loss (both groups), and a deterioration in cognitive functioning (younger) and dyspnoea (older) were reported. Except for financial difficulties, there was no significant difference between the groups after one year (Table 2).

The worst mean scores for both fatigue and physical functioning were found four months after start of treatment. In this period, almost 40% of the patients in both groups experienced large deteriorations in fatigue, 25-30% experienced large deteriorations in physical- and role functioning, while on the other hand, large improvements were seen in global QoL (16%), role functioning (19%), and pain (18%) (Figure 3). There was no significant difference between the two age groups regarding individual changes from baseline to month four except for nausea/vomiting, where a larger proportion of the younger patients experienced a moderate deterioration (31 vs. 11%, p=0.035).

Except for fatigue, the majority of the patients belonged to the group with a small change in the selected domains after 12 months (Supplementary Figure 1). Notably, 24 and 38% (not significant) of the younger and older patients, respectively, reported large deteriorations in fatigue one year after start of palliative chemotherapy.

Impact of chemo-break

There were 57 patients eligible to evaluate the impact of a chemo-break between month six and eight, of whom 33 had initiation of chemo-break at month six, while 24 patients had ongoing treatment in the same period. A larger proportion of females, those receiving irinotecan- and VEGFR antibody based therapy, and having RAS and BRAF wild type tumour, had initiation of a chemo-break at month six (Supplementary Table 1). There was no significant difference in age between the groups.

The group on continuous treatment had significant worsening of global QoL, physical- and role functioning, fatigue, and nausea/vomiting from month six to eight, compared to those on a

chemo-break, who demonstrated improvements in the same domains in this period (Table 3). The differences in scores between the groups ranged from 11-20 in these domains. There were no significant differences regarding change in pain in the same period or in median OS between the two groups.

Overall survival

By September 19th 2022, after a minimum observation time of 46 months (range 46-96), 204 of the 214 patients had deceased, with seven and three patients still alive among the younger and older patients, respectively. Median OS in the whole population was 17.5 months [95% CI 14.4-20.5], with no significant difference between younger and older patients, being 17.4 [95% CI 12.6-22.2] vs. 18.1 months [95% CI 13.7-22.5], respectively (p=0.464) (Figure 4).

Discussion

This observational study with real-life data demonstrates that older patients with mCRC did not experience more deterioration in the six selected HRQoL domains than younger patients during the first year of palliative chemotherapy. However, almost 40% of both younger and older patients experienced a major deterioration in fatigue after four months of treatment. After one year, the mean scores of HRQoL in the domains selected were unchanged compared to baseline in both groups. Younger patients reported significant more pain at all time points, but better physical functioning than the older patients. Patients on chemo-break experienced significant improvements in several HRQoL domains, in particular global QoL and fatigue. There was no difference in survival between younger and older patients.

There are few studies comparing HRQoL between younger and older patients with CRC during first line palliative chemotherapy. Several meta-analyses and pooled analyses of RCTs in this setting have compared efficacy and tolerability of drugs between younger and older, but rarely

reported HRQoL data. The studies conducted conclude that older patients have similar survival benefits and tolerability of various first line treatments, with the reservation that these studies included only the more fit older patients [26,27]. A few studies have explored HRQoL differences, and a retrospective analysis of the CAIRO and CAIRO2 RCTs compared global QoL between age groups [28]. In line with our results, they found no differences between younger and older patients. However, only fit patients with ECOG PS 0 and 1 were included, and global QoL was the only domain reported. Previously, it has been demonstrated that global QoL, in contrast to physical functioning, is little affected by toxicities of treatment [29,30]. Another study, comparing fit older with younger patients (PS 0-1), reported no different changes in any of the HRQoL domains from baseline to week eight or twelve for patients with CRC starting first-line chemotherapy plus cetuximab [31]. To our knowledge, the current study is the first to compare changes in HRQoL between younger and older from a real-world unselected cohort of patients with mCRC. Despite the older patients had generally lower PS and reported lower physical functioning, they did not experience more decline in the selected HRQoL domains than their younger counterparts. An explanation may be that the older patients more often received milder monotherapy regimens, and it is reasonable to believe that they more often had dose reductions. Regardless the treatment regimens, survival was not different in the two age groups, though there were other differences between the groups that might affect survival in the younger negatively, such as resection of the primary, previous treatment and stage of disease.

It is worth noting that a significant part of the individual patients experienced large deteriorations in fatigue, physical-, and role functioning after four months. This finding calls for measures to mitigate the expected decline in these HRQoL domains, for instance by early incorporation of rehabilitation and to closely monitor all patients and provide sufficient supportive care. It is well documented that physical exercise, both during and after chemotherapy in the curative setting, has a positive impact on several HRQoL outcomes such as fatigue and physical functioning [32], and evidence in the palliative setting is evolving [33]. Additionally, use of geriatric

assessments in older patients could aid adjustments in treatment plans, and possibly contribute to less toxicity and improved HRQoL [34,35]. This was not routinely in use during the study period. Information regarding the risk of decline in several HRQoL domains and possible measures to reduce them, should be provided the patients in the process of shared decision making.

Compared to baseline, small improvements in mean scores were observed in both groups for emotional functioning, insomnia and appetite loss one year after start of palliative chemotherapy. This is in line with others who found decreasing degree of worrying and anxiety among patients with CRC, as time progressed after start of chemotherapy [36,37]. In the same period, both groups reported reduced cognitive functioning, a known side-effect of chemotherapy [38-40].

Younger patients reported more pain at all time points the first year. This might be explained by a larger proportion of the younger having their primary tumour intact, or it could be more directly related to age. Some studies have demonstrated that younger patients with cancer report more pain than older patients [41,42], while Bevilacqua et al. did not find any difference in pain among younger and older cancer survivors [43]. In the general population normative data for the EORTC QLQ-C30, older males report less pain than the younger, but this is not seen among females [44]. Males were in majority among the older patients in the present study.

Not surprisingly, patients introduced to a chemo-break, compared to those on continued treatment from month six, experienced improvements in several HRQoL domains after a two month treatment-free period (global QoL, physical- and role functioning, fatigue, and nausea/vomiting). Other studies investigating chemo-break described more toxicity, but no difference in physical functioning and overall health with continuous vs. intermittent treatment [10,14]. The CAIRO3 trial reported statistically significant differences between the groups regarding several of the HRQoL domains, but in contrast to the present study, the differences they described were too small to be considered clinically significant [13]. In line with our findings, the COIN trial found significant benefits from intermittent- vs. continuous therapy for role- and social functioning, but unlike our study, not

for physical functioning and global QoL [11]. A possible explanation for the greater positive impact of a chemo-break seen in the present study, is that in the real-life setting the patients are frailer and thus benefit more from a chemo-break compared to participants in an RCT.

A strength of the present study is that it provides real-life data with PROMs from an unselected cohort of patients with mCRC starting first line palliative chemotherapy from an entire region of Norway, reflected by the six selected HRQoL domain scores at baseline being worse in both groups compared to similar patient populations in RCTs and in the general population [24,44,45]. Another strength is the high compliance rate of returning QLQ-C30, and that the drop-out rate in the two age groups was equal. Of those still alive after six and twelve months, 84 and 78%, respectively, returned the questionnaire. This is higher than other observational studies of patients with mCRC [36,46,47]. After one year, only 53% of the original study population returned the QLQ-C30, the main reason for not returning was death. This might bias the comparison with baseline, since the healthiest survive to report after one year. A limitation is the timing of the questionnaires regarding administration of chemotherapy, as the HRQoL scores greatly can vary through a treatment cycle [36,48]. This was not standardized in the present study. Additionally, only participants returning the baseline questionnaire were included, and this might compromise the generalisability.

From this study on a real-life population of patients with mCRC, it might be concluded that older patients do not experience more deterioration in selected HRQoL domains than younger during the first year of palliative chemotherapy, indicating that age alone should not exclude patients from treatment. Self-reported HRQoL was mostly maintained or improved after one year, except for cognitive functioning. No survival difference between the two age groups was observed in spite of less intensive treatment regimens in the older group. The positive impact of chemo-break on selected HRQoL domains seems to be larger in a real-life population than in patients included in RCTs. In our opinion, more attention should be paid to mitigate the major deterioration in fatigue and physical functioning observed during the first months of treatment.

Statements and Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Authors' contributions

Eva Hofsli, Are Korsnes Kristensen, Tora Skeidsvoll Solheim, Arne Wibe, Line Merethe Oldervoll and Ingunn Hatlevoll designed the study. Hege Elvebakken, Are Korsnes Kristensen, Eva Hofsli and Ingunn Hatlevoll were involved in data collection and registration. Øyvind Salvesen, Are Korsnes Kristensen and Ingunn Hatlevoll were responsible for data analysis. The first draft of the manuscript was written by Ingunn Hatlevoll, and all authors critically reviewed the draft and approved the final version for submission.

Ethics approval

This study was approved by the Regional Committee for Medical and Health Research Ethics of Middle Norway (Reference no. 216433) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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Table 1. Patient baseline characteristics.

Characteristic		**< 70 years** **n = 110**	**≥ 70 years** **n = 104**	
Age	Years	Median (range) 62 (27 - 69)	Median (range) 75 (70 – 89)	
		n (%)	n (%)	p*
Sex	Male	63 (57.3)	65 (62.5)	0.44
	Female	47 (42.7)	39 (37.5)	
Highest education	Elementary school	30 (27.3)	39 (37.5)	0.26
	High school	44 (40.0)	38 (36.5)	
	College or university	36 (32.7)	27 (26.0)	
Living situation	Living alone	22 (20.0)	25 (24.0)	0.48
	Living with others	88 (80.0)	79 (76.0)	
ECOG performance status	0	61 (55.5)	38 (36.5)	**0.008**
	1	41 (37.3)	48 (46.2)	
	2	8 (7.3)	18 (17.3)	
Modified Glasgow prognostic score	0	57 (51.8)	59 (56.7)	0.73
	1	37 (33.6)	30 (28.8)	
	2	16 (14.5)	15 (14.4)	
CEA > 5	Yes	85 (77.3)	84 (80.8)	0.53
	No	25 (22.7)	20 (19.2)	
Location of primary tumour	Right colon	42 (38.2)	50 (48.1)	0.34
	Left colon	31 (28.2)	24 (23.1)	
	Rectum	37 (33.6)	30 (28.8)	
Presence of liver metastases	Yes	68 (61.8)	70 (67.3)	0.40
	No	42 (38.2)	34 (32.7)	
Primary tumour resected	Yes	64 (58.2)	78 (75.0)	**0.009**
	No	46 (41.8)	26 (25.0)	
Stage of disease	Synchronous	79 (71.8)	66 (63.5)	0.19
	Metachronous	31 (28.2)	38 (36.5)	
Received chemotherapy before	No	68 (61.8)	76 (73.1)	**0.024**
	> 12 months ago	16 (14.5)	19 (18.3)	
	6-12 months ago	16 (14.5)	4 (3.8)	
	< 6 months ago	10 (9.1)	5 (4.8)	
First line palliative treatment	Monotherapy**	2 (1.8)	28 (27.0)	**<0.001**
	Oxaliplatin based combination	7 (6.4)	12 (11.5)	
	Irinotecan based combination	91 (82.7)	59 (56.7)	
	Oxaliplatin + irinotecan	10 (9.1)	5 (4.8)	
Additional monoclonal antibody	EGFR antibody	19 (17.3)	11 (10.6)	**0.003**
	VEGFR antibody	69 (62.7)	50 (48.1)	
	None	22 (20.0)	43 (41.3)	
Tumour mutation status	RAS/BRAF wild type	27 (24.5)	31 (29.8)	0.12
	RAS mutation	56 (50.9)	45 (43.3)	
	BRAF mutation	24 (21.8)	18 (17.3)	
	Not tested	3 (2.7)	13 (12.5)	
MSI status	MSI	6 (5.5)	9 (8.6)	0.50
	MSS	74 (67.3)	63 (60.6)	
	Not tested	30 (27.2)	32 (30.8)	

ECOG, Eastern Cooperative Oncology Group; MSI, microsatellite instable; MSS, microsatellite stable.

*The two groups compared with Pearsons Chi-Square Test.

** Including pyrimidine analogues and PD-1 blocker.

Table 2. HRQoL at baseline and after 12 months comparing younger and older patients.

	< 70 years	≥ 70 years	p **	< 70 years	≥ 70 years	p **
Time	**Baseline**			**After 12 months**		
	n = 110	n = 104		n = 58	n = 56	
Age (years)	62 (median)	75 (median)		60 (median)	76 (median)	
HRQoL	Mean (95% CI)	Mean (95% CI)		Mean (95% CI)	Mean (95% CI)	
Functioning scales*						
Global QoL	57 (52-61)	64 (60-68)	**0.026**	59 (53-65)	63 (56-69)	0.460
Physical functioning	79 (76-83)	73 (69-77)	**0.024**	77 (72-83)	70 (64-76)	0.055
Role functioning	58 (51-64)	65 (58-71)	0.15	63 (56-71)	61 (53-69)	0.691
Emotional functioning	76 (73-80)	80 (76-84)	0.15	82 (76-87)	85 (80-90)	0.327
Cognitive functioning	84 (80-88)	85 (81-89)	0.679	78 (72-85)	81 (76-87)	0.695
Social functioning	61 (56-67)	69 (63-74)	0.051	66 (59-73)	69 (62-76)	0.540
Symptom scales and single items*						
Fatigue	42 (37-47)	41 (36-46)	0.797	42 (36-48)	44 (38-51)	0.622
Nausea and vomiting	8 (5-11)	8 (5-11)	0.990	7 (4-9)	8 (3-12)	0.657
Pain	29 (23-35)	18 (13-23)	**0.008**	21 (14-28)	15 (9-21)	0.201
Dyspnoea	23 (18-28)	20 (15-25)	0.343	22 (14-31)	29 (21-37)	0.187
Insomnia	33 (28-39)	26 (20-31)	0.078	26 (19-34)	20 (12-28)	0.251
Appetite loss	29 (23-36)	26 (19-33)	0.470	21 (14-29)	19 (11-28)	0.852
Constipation	21 (15-26)	23 (17-29)	0.666	20 (13-27)	21 (13-28)	0.768
Diarrhoea	26 (20-31)	22 (18-28)	0.473	24 (19-30)	24 (17-31)	0.910
Financial difficulties	8 (5-12)	3 (0.4-5)	**0.015**	12 (6-18)	4 (1-8)	**0.019**

CI, confidence interval; QoL, quality of life; HRQoL, health-related quality of life.

*Higher scores on the functioning scales indicate better function, while higher scores on the symptom scales and single items indicate more symptoms.

**Mean scores in age groups < and ≥ 70 years compared with the two-sample t-test.

Table 3. Effect on change in selected HRQoL domains and survival according to initiation of chemo-break or continued treatment from months 6 - 8 among patients not showing progressive disease at month 6.

Mean difference in HRQoL from month 6 – 8	Ongoing treatment from month 6 – 8 n = 24 Mean [95% CI]	Chemo-break from month 6 – 8 n = 33 Mean [95% CI]	p**
Change in functioning scales*			
Global QoL	-11.5 [-19.3 – -3.6]	8.3 [0.9 – 15.9]	**<0.001**
Physical functioning	-6.0 [-11.8 – -0.3]	4.8 [0.2 – 9.4]	**0.003**
Role functioning	-9.7 [-22.5 – 3.1]	4.5 [-4.0 – 13.1]	0.052
Change in symptom scales*			
Fatigue	5.8 [-3.8 – 15.4]	-13.5 [-22.5 – -4.5]	**0.005**
Pain	6.9 [-4.8 – 18.7]	0.0 [-6.8 – 6.8]	0.268
Nausea/vomiting	7.6 [1.8 – 13.5]	-4.5 [-7.6 – -1.5]	**<0.001**
Survival, months	Median [95% CI] 20.8 [16.1 – 25.5]	Median [95% CI] 23.6 [16.3 – 30.8]	0.730

CI, confidence interval; QoL, quality of life; HRQoL, health-related quality of life

*Positive difference on the functioning scales indicates improved function, while positive difference on the symptom scales indicates worsening of symptoms.

** Mean difference in HRQoL in the two groups compared with the two-sample t-test. Survival compared with the Log Rank test.

Supplementary Table 1. Patient baseline characteristics according to continuous treatment or chemo-break months 6 – 8.

Characteristic	Ongoing treatment from month 6-8 n = 24	Chemo-break from month 6-8 n = 33	p*
Age	Median (range)	Median (range)	0.23
Years	71 (41 – 87)	65 (27 – 79)	
	n (%)	n (%)	
Sex			**0.01**
Male	19 (79.2)	15 (45.5)	
Female	5 (20.8)	18 (54.5)	
ECOG performance status			0.19
0	11 (45.8)	23 (69.7)	
1	11 (45.8)	8 (24.2)	
2	2 (8.3)	2 (6.1)	
Modified Glasgow prognostic score			0.85
0	12 (50.0)	14 (42.4)	
1	10 (41.7)	16 (48.5)	
2	2 (8.3)	3 (9.1)	
CEA > 5			0.80
Yes	19 (79.2)	27 (81.8)	
No	5 (20.8)	6 (18.2)	
Location of primary tumour			0.74
Right colon	13 (54.2)	15 (45.5)	
Left colon	4 (16.7)	8 (24.2)	
Rectum	7 (29.2)	10 (30.3)	
Presence of liver metastases			0.41
Yes	15 (62.5)	24 (72.7)	
No	9 (37.5)	9 (27.3)	
Primary tumour resected			0.14
Yes	17 (70.8)	17 (51.5)	
No	7 (29.2)	16 (48.5)	
Stage of disease			0.68
Synchronous	17 (70.8)	25 (75.8)	
Metachron	7 (29.2)	8 (24.2)	
Received chemotherapy before			0.69
No	19 (79.2)	24 (72.7)	
> 12 months ago	2 (8.3)	5 (15.2)	
6-12 months ago	3 (12.5)	3 (9.1)	
< 6 months ago	0 (0)	1 (3.0)	
First line palliative treatment			0.084
Monotherapy**	5 (20.8)	3 (9.1)	
Oxaliplatin based combination	3 (12.5)	0 (0)	
Irinotecan based combination	15 (62.5)	27 (81.8)	
Oxaliplatin + irinotecan	1 (4.2)	3 (9.1)	
Addition with monoclonal antibody			0.22
EGFR antibody	3 (12.5)	4 (12.1)	
VEGFR antibody	11 (45.8)	22 (66.7)	
None	10 (41.7)	7 (21.2)	
Tumour mutation status			0.14
RAS/BRAF wild type	3 (12.5)	13 (39.4)	
RAS mutation	14 (58.3)	13 (39.4)	
BRAF mutation	6 (25.0)	5 (15.2)	
Not tested	1 (4.2)	2 (6.1)	

ECOG, Eastern Cooperative Oncology Group. *The two groups compared with Pearsons Chi-Square Test. **Including pyrimidine analogues and PD-1 blocker.

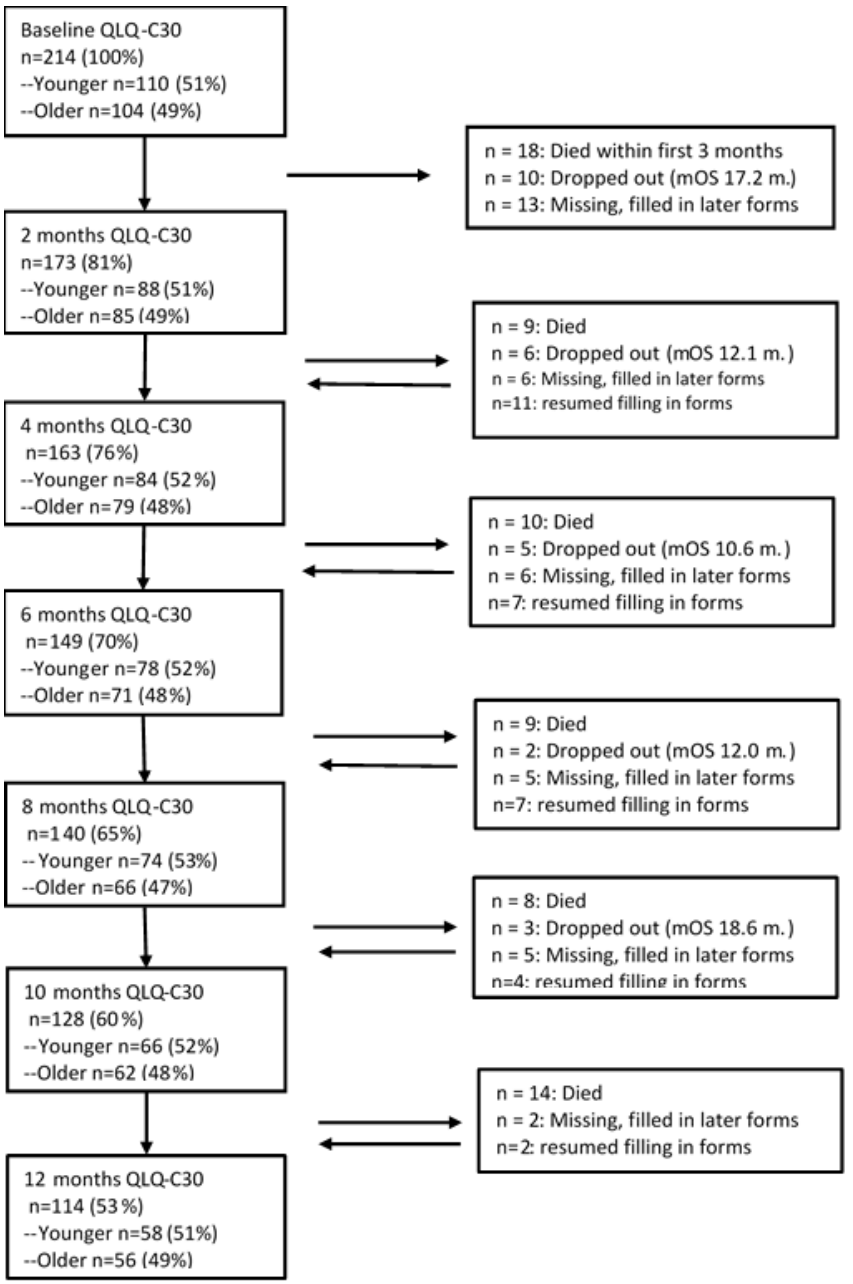


Fig. 1. Number of patients with completed EORTC QLQ-C30 questionnaires at different time points and reasons for not returning a questionnaire. EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; mOS, median overall survival.

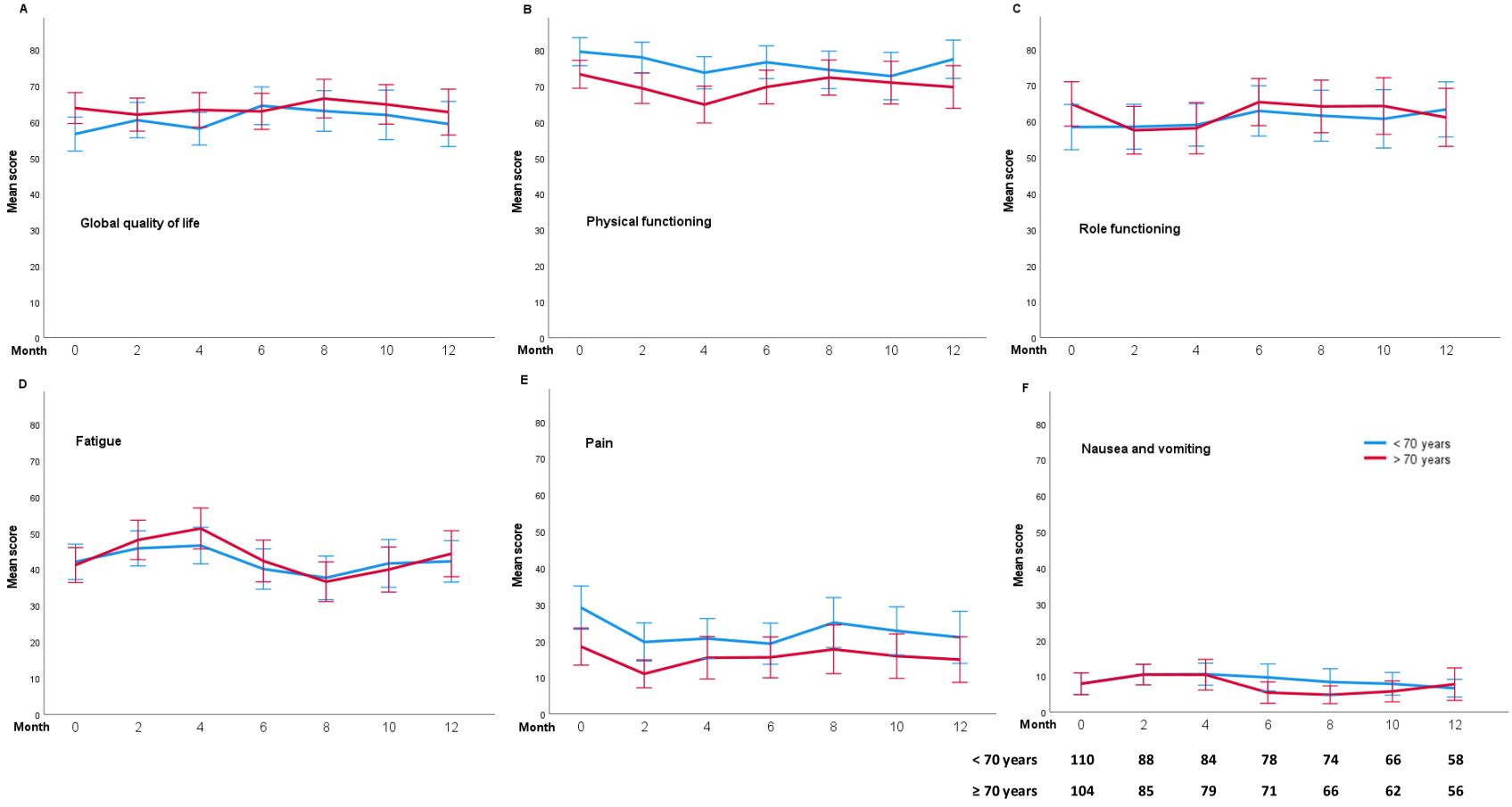


Fig. 2. Mean scores of A) global quality of life, B) physical functioning, C) role functioning, D) fatigue, E) pain and F) nausea and vomiting, according to age group, from baseline through 12 months after start first line palliative chemotherapy. The error bars represent 95% confidence intervals. A higher score on the functioning scales indicates better function, while a higher score on the symptom scales reflects more symptoms. Lower right displays how many returned the questionnaire at each time-point.

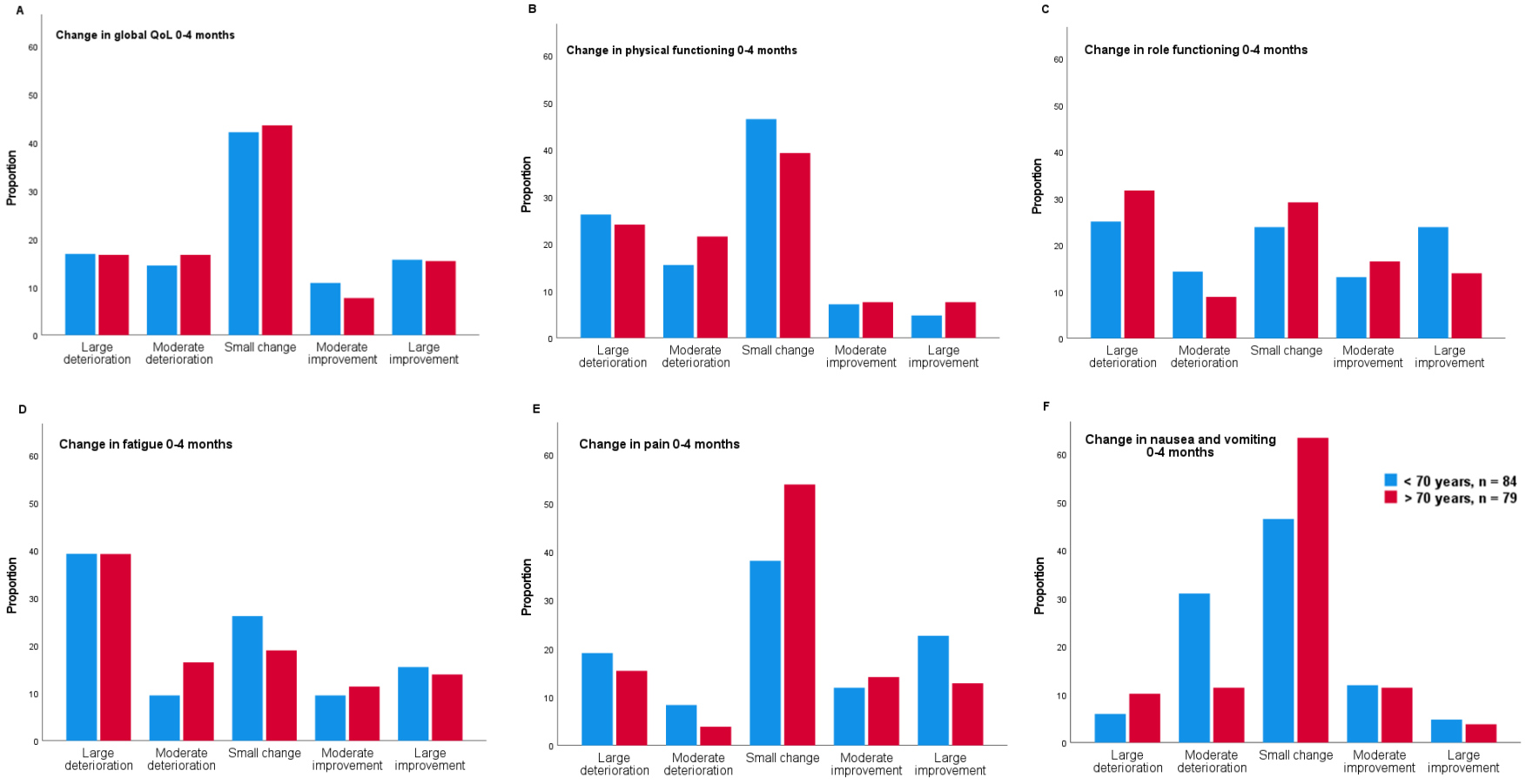


Fig. 3. Individual changes in A) global quality of life, B) physical functioning, C) role functioning, D) fatigue, E) pain and F) nausea and vomiting from baseline to month four divided by age groups, and grouped according to the five categories; large and moderate deterioration, small change, moderate and large improvement. A difference in scores of > 20 is considered a large, from 10 – 20 a moderate deterioration/improvement, and < 10 points a small change. The y-axis represents the percentage for each age group.

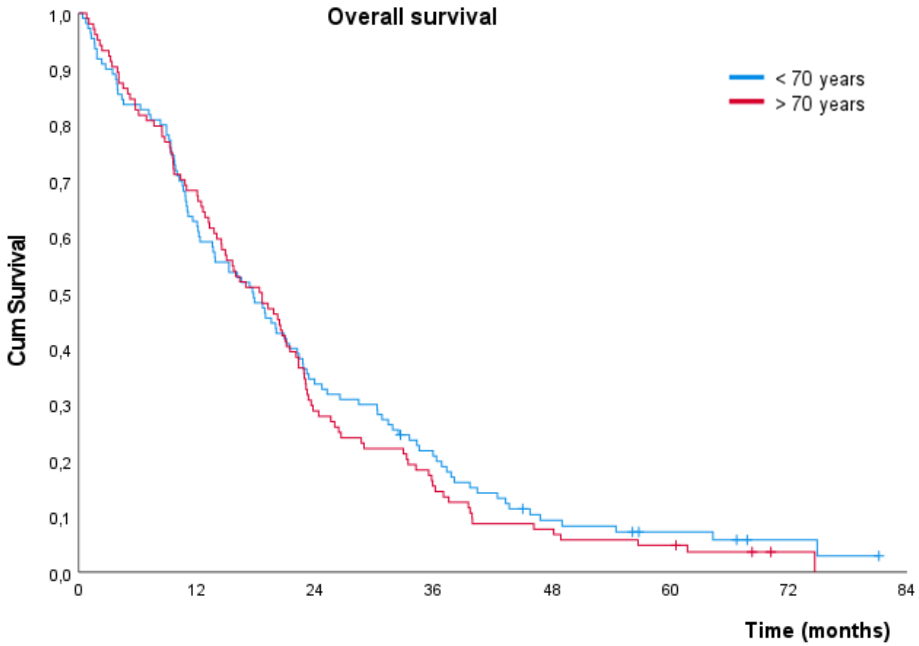
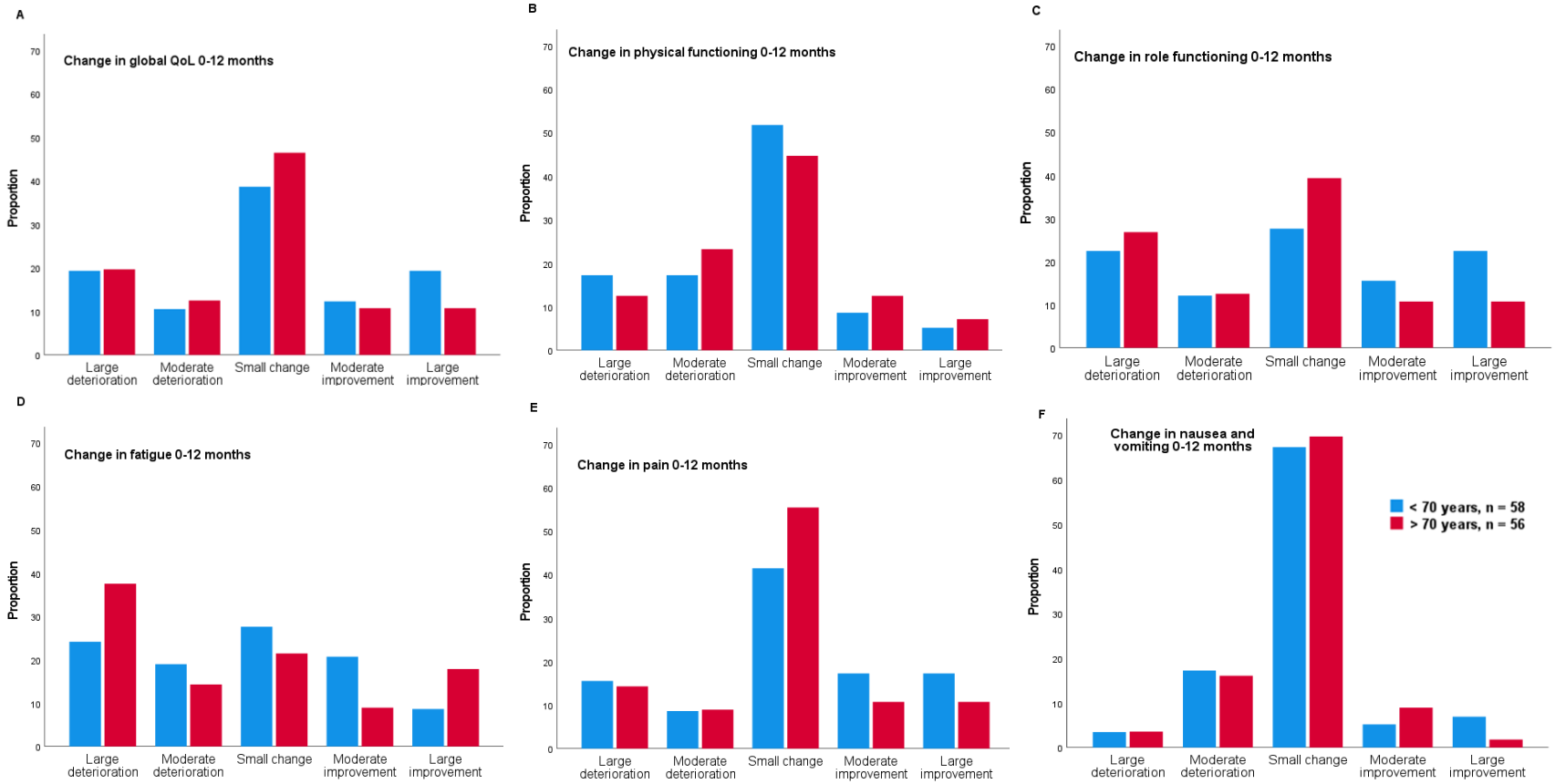


Fig. 4. Kaplan-Meier plot for overall survival per age group.



Supplementary Fig. 1. Individual changes in A) global quality of life, B) physical functioning, C) role functioning, D) fatigue, E) pain and F) nausea and vomiting from baseline to month 12 divided by age groups, and grouped according to the five categories; large and moderate deterioration, small change, moderate and large improvement. A difference in scores of > 20 is considered a large, from 10 – 20 a moderate deterioration/improvement, and < 10 points a small change. The y-axis represents the percentage for each age group.

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