Master's thesis

NTNU
Norwegian University of Science and Technology
Faculty of Medicine and Health Sciences
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The association between patient-reported and physician-reported chemotherapy-induced peripheral neuropathy, and physical activity among patients with colorectal cancer under adjuvant treatment

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Abstract

Background: Increasingly more people are living with late effects after cancer treatment. Colorectal cancer patients are often treated with oxaliplatin, which is neurotoxic and can cause chemotherapy-induced peripheral neuropathy (CIPN). The burden of symptoms from CIPN can result in limitations in the daily life and physical activity. There are several assessment methods for CIPN, both physician-reported and patient-reported, which can lead to inconsistent prevalence.

Purpose: To explore the association between physician-reported and patient-reported CIPN, and if the burden of symptoms from CIPN affects level of physical activity.

Methods: Prospective study using data from a single-armed pilot study were patients were offered a supervised exercise training intervention during adjuvant treatment for colorectal cancer. CIPN was documented with patient-report (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN; EORTC QLQ-CIPN20) and physician-report (National Cancer Institute Common Terminology Criteria for Adverse Events; CTCAE). Physical activity was assessed with a questionnaire regarding frequency, type and intensity enabling to calculate whether study participants met the Norwegian national guidelines for physical activity or no (150 minutes of moderate activity or 75 minutes of high intensity activity a week). Self-reports on CIPN and physical activity were collected at five time points: baseline, 3 months, 6 months, 9 months and 12 months after inclusion, and physician-reports on CIPN at baseline, 3 months and 6 months. Data were analysed in SPSS by Kendall rank tau b correlation and Mann-Whitney U test.

Results: In total, 19 of 30 colorectal cancer patients that were eligible for study participation agreed to participate. Six of the participants were later excluded, leaving 13 participants with complete data. There was a significantly moderate positive correlation between patient-reported and physician-reported CIPN symptoms (p=.002). The median symptoms of CIPN increased during the treatment period, then decreased after 6 months. Further, there was no significant difference in the burden of symptoms from CIPN between those who met the national guideline for physical activity and for those who did not.

Conclusion: There was a moderate positive association between physician-reported and patient-reported symptoms of CIPN under treatment for colorectal cancer, and the burden of

symptoms did not differ for those who met the national recommendations for physical activity and for those who did not.

Abstrakt

Bakgrunn: Flere mennesker lever med senskader etter kreftbehandling. Tarmkreftpasienter blir ofte behandlet med oxaliplatin, som er nevrotoksisk og kan forårsake cellegift-indusert perifer nevropati (CIPN). Flere kartleggingsmetoder for CIPN er brukt, både legerapporterte og pasientrapporterte. Dette kan føre til inkonsistente resultater vedrørende forekomst og alvorlighetsgrad. Symptombyrden fra CIPN kan også resultere i begrensninger i hverdagslivet og fysisk aktivitet.

Formål: Å undersøke assosiasjonen mellom lege-rapportert og pasient-rapportert CIPN, og om symptombyrden av CIPN påvirker fysisk aktivitet.

Metode: Prospektiv kohortestudie som bruker data fra en enarmet pilotstudie av tarmkreftpasienter under behandling med adjuvant cellegift med fysisk trening som intervensjon. Pasient-rapportert CIPN ble kartlagt med The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN (EORTC QLQ-CIPN20) og selvrapportert fysisk aktivitet med 3 spørsmål fra Helseundersøkelsen i Nord-Trøndelag (HUNT). Lege-rapportert CIPN ble kartlagt med National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE). I analysen er variabelen selvrapportert fysisk aktivitet implementert som om de møter de Norske nasjonale anbefalingene for fysisk aktivitet eller ikke. Deltagerne fylte ut spørreskjema ved fem tidspunkt: baseline, 3 måneder, 6 måneder, 9 måneder og 12 måneder etter inklusjon, mens legene rapporterte ved baseline, 3 måneder og 6 måneder etter inklusjon. Dataene ble analysert i SPSS med Kendall rank tau b korrelasjon og Mann-Whitney U test.

Resultater: 19 av 30 tarmkreftpasienter som ble forespurt om å delta i studien takket ja. Seks av deltagerne ble senere ekskludert av forskjellige årsaker, som gjorde at 13 deltagere inngikk i studien. Det var en signifikant moderat positiv korrelasjon mellom pasientrapportert og legerapportert CIPN symptomer (p=.002). Median symptombyrde fra CIPN økte under behandlingsperioden, for så å reduseres etter 6 måneder. Det var ingen signifikant forskjell i symptombyrde fra CIPN mellom de som møtte de nasjonale anbefalingene for fysisk aktivitet og de som ikke gjorde det.

Konklusjon: Det er en moderat assosiasjon mellom legerapporter og pasientrapportert symptombyrde av CIPN under behandling for tarmkreft. Deltagerne var i stand til å være fysisk aktiv på tross av moderate symptomer fra CIPN, og symptombyrden er ikke forskjellig fra de som møter de nasjonale anbefalinger for fysisk aktivitet og de som ikke gjør det.

Acknowledgements

This master's thesis was inspired by all the cancer survivors living with late and long-term effects after cancer treatment. The increasing proportion of survivors experiencing late effects made me curious about the evaluation and possible treatments for nerve damage after toxic chemotherapy.

I wish to thank the research group in the FAKT-study for granting me access to the data material, and especially Dr. Ingunn Hatlevoll and PhD Line Oldervoll for professional guidance in the research area. I am grateful for the support and advice from my thesis advisor, PhD Signe Nilssen Stafne. Thank you for the high-quality advice, good availability and for taking time to share your expertise with me.

A master's thesis is a time-consuming project. My employer, Surnadal Kommune, enabled a flexible work life as a fulltime worker the first two years, and a part-time worker this last year. Thank you for the willingness to support me.

Finally, I want to express my appreciation to my loving husband, Nils-Erik, family and friends, for their understanding and support in these years.

Tingvoll, 27 November 2019
Ingrid Kvendset Ulset

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1.Introduction

Increasingly more people survive cancer. Today, more than two-thirds of cancer patients are alive five years after diagnosis compared to 50% in 1980 (1). This positive development is explained by a combination of early diagnosis and improved treatment. Cancer treatment often combines surgery, radiation and chemotherapy (1). The high proportion of survivors is resulting in more people living with mild to severe late effects due to toxicity of cancer treatment. The national cancer-strategy for Norway 2013-2017 is estimating an increase in new cases of cancer in the next years and highlights the importance of actions towards better quality of life for those living with and having survived cancer (2).

Colorectal cancer has a high incidence among cancer types in both male and females. The incidence-rate for colorectal cancer have increased with 2.3% for males and 6.6% for females the last 5 years (1). The choice of treatment depends on several factors like localisation and size of the tumour, metastasising, age, general condition and comorbidities, but often combines surgery with adjuvant chemotherapy. The recommended type of chemotherapy for colorectal cancer is either a combination treatment with oxaliplatin and 5-FU/folinate or capecitabin for patients < 70 years, or monotherapy with 5-FU or capecitabine for patients >70 years (3). Oxaliplatin is a neurotoxic component in adjuvant chemotherapy in colorectal cancer and can cause chemotherapy-induced peripheral neuropathy (CIPN). The toxicity causes axonal and/or demyelisation damage or is damaging the cells in the dorsal root ganglia. The damages often start distally and develop proximally. CIPN is presenting under, after short time or up to years after ended treatment (4-6). A high number of patients develops neurologic symptoms, and CIPN is the most dose-limiting symptom of oxaliplatin (7). Higher accumulative doses of oxaliplatin are associated with chronic peripheral nerve damage (4, 8, 9). More than 50% presents with neuropathic symptoms after treatment with neurotoxic chemotherapy (2-4), and the prevalence increases because of the widespread use and more long-term survivors of cancer. Due to lack of a uniform assessment-method of CIPN the prevalence varies from 10% to 96.2% (10-14). Patients with CIPN are experiencing both painful and non-painful symptoms. Numbness, loss of balance, muscle weakness, clumsiness, fatigue, burning pain, muscle pain and change in sensibility are some of the symptoms reported by patients (4-6, 15-17). Symptoms affect quality of life negatively. However, the impact of symptoms depends on individual characteristics, perception, treatment and dose of medicine (16). The sensorimotor outcomes can result in increased tendency to fall and limitations in the daily life (18-20). Falls can lead to hospitalization, disability and large costs

for the healthcare system and the society. The disability of CIPN can affect the ability to work, which gives both economic and social disadvantages (19, 20). Today, there is no standardised follow-up for patients with CIPN, neither at the hospital nor in the primary health care (1).

It is suggested that CIPN is underreported in clinical trials due to limitations in assessment-methods (10). Both physician-reported and patient-reported assessment-tools are used. Commonly used assessment-methods are National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) (21) for physician-reports and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN (EORTC QLQ-CIPN20) (22) for patient-reports. An approach with only physician-based information is criticized for the exclusion of the patient's perspective (23). Several studies have criticised the validity of CTCAE (24-28) and argue that EORTC QLQ-CIPN20 is more sensitive for sensory symptoms. There are only few studies comparing physician-reported and patient-reported CIPN (7, 29, 30). A study including 538 participants (7) found a strong positive association between physician-reported and patient-reported CIPN. However, the study also found a large range in EORTC QLQ-CIPN20 score for each CTCAE-grade in inter-patient variation. EORTC QLQ-CIPN20 was also more sensitive for changes over time. The participants in the study had a large variation in cancer type, treatment regime and treatment of CIPN, which can affect the results. Data from two randomized placebo-controlled trials for prevention of CIPN which both used EORTC QLQ-CIPN20 and CTCAE as assessment method showed a strong positive association between the scores. Patients with colon-, ovarian-, lung- and other cancer types were included. This study also had more variation in the EORTC QLQ-CIPN20 score (30). A third study with 281 patients with stable CIPN evaluated the patient-reported and physician-reported assessment of sensory scale. The two methods were also highly related in this study (29). Even though the mentioned studies had a strong association and relationship between physician-reported and patient-reported CIPN, none of the data from the physician had a perfect relationship with patients' perception of CIPN severity.

A conversion from EORTC QLQ-CIPN20 to CTCAE score is not reliable on an individual level (30). Since the symptoms of CIPN are experienced on an individual level there is still a need for more knowledge about the usefulness of physician-reported versus patient-reported assessment methods. Physicians and patients may have different perceptions and assessments of CIPN, and this might lead to inconsistent results.

Cancer patients and survivors are like the rest of the population recommended to engage in weekly physical activity a minimum of 150 minutes of moderate-to-strenuous or 75 minutes of strenuous intensity (31-33). CIPN can limit activities of daily life and physical activity (17-19). Unfortunately, there are only a few studies investigating how the burden of symptoms from CIPN affects the ability to be physically active (16, 34). A study from Tofthagen used data from semi structured interviews on patients with CIPN and found that the neuropathic symptoms negatively affects activities of daily and physical activity (16). Not meeting the Dutch physical activity guidelines of 150 minutes of moderate to vigorous physical activity was associated with more CIPN symptoms in a prospective survey among colorectal cancer survivors (34). These studies were conducted on cancer survivors, and significant laps in time of onset of symptoms (up to three years after completed chemotherapy) may bias their description and may not be reflective of their actual experience. There is need for knowledge about how CIPN affects the ability to be physically active under adjuvant cancer treatment.

Based on this I want to study whether there is an association between physician-reported and patient-reported CIPN during a six months adjuvant chemotherapy treatment period, and if the burden of CIPN affect level of physical activity.

1.2 Hypothesis

The research question is based on a null-hypothesis that there is no difference in the burden of symptoms between the physician-reported and the patient-reported CIPN, and that the burden of symptoms does not affect patient-reported physical activity. The following two questions are the base of this master thesis:

a) *Is there an association between physician-reported and patient-reported symptoms of CIPN under adjuvant treatment for colorectal cancer?*
b) *Does the burden of CIPN-symptoms differ for those who meet the national recommendation for physical activity and for those who do not?*

2. Theoretical background

2.1 Colorectal cancer

Colorectal cancer is a common type of cancer in both men and women (1). In the treatment of advanced colorectal cancer, the chemotherapy agent oxaliplatin is considered a central component.

The type of adjuvant chemotherapy for treating colorectal cancer can vary. In this study two different types are used; *capox* and *flox. Capox* is a combination of capecitabin and oxaliplatin. It is given to the patients every third week and consists of eight courses in total for six months. The *flox* combines flourilacil (5FU) and oxaliplatin and is given to the patients every second week. In the course of 6 months, the patients receive a total of 12 courses. Oxaliplatin binds and cross-links strands of DNA, forming DNA adducts thus inhibiting DNA replication and transcription (35). Oxaliplatin is a third-generation platinum and can cause a dose-limiting sensory peripheral neurotoxicity (13). The sensory peripheral neurotoxicity symptoms can be both acute and develop gradually. The acute neurotoxicity occurs in about 85% to 95% of patients, while the progressive cumulative neurotoxicity develops among 10% to 15% of patients receiving cumulative oxaliplatin dose of 780 to 850 mg/m2 (13, 14).

2.2 Acute neurotoxicity

The acute neurotoxicity symptoms of oxaliplatin is distal and/or peripheral paraesthesia and/or dysesthesias (13). These symptoms last only for a few hours or days. In addition, peripheral motor neuropathy symptoms such as muscular contractions, stiffness of muscles in the hands or feet and inability to release grip is presented (11, 12). A higher dose of oxaliplatin increases the risk of the acute neurotoxicity.

2.3 Gradually developing neurotoxicity

Cumulative neurotoxicity symptoms consist of dysesthesias and paraesthesia of the extremities. The symptoms increase in intensity with the cumulative dose (11, 12). A decrease in the severity of symptoms is seen in 75% of the patients within 3 to 5 months after last treatment (12).

2.4 Mechanism of oxaliplatin and CIPN

The precise mechanism of oxaliplatin is unclear, but it is thought to exert their cytotoxic effects through the formation of various types of DNA lesions (36). The CIPN mechanism is thought to be altered ion-channel and receptor activity, oxidative stress injury of the nerves, and inflammation. This is the direct result of the accumulation of oxaliplatin in dorsal root

ganglia cells (14, 37). The damage on dorsal root ganglia cells results in a sensory neuropathy, which leads to axonal degeneration (14).

2.5 Assessment of CIPN

Motor and autonomic symptoms of CIPN may be observed objectively, but sensory symptoms are mainly subjective. To assess and grade the toxicity of CIPN a combination of clinical and paraclinical parameters is commonly used and relies on the judgement of physicians (38).

Several patient-reported outcome measures (PROMs) assessing CIPN are used in clinical studies. Cancer-specific questionnaires that are widely used are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CIPN (EORTC QLQ-CIPN20) (38), the Functional Assessment of Cancer Therapy-General (FACT-G) (39), the MD Anderson Symptom Inventory (MDASI) (40), the Patient-Reported Symptom Monitoring (PRSM) system form (41) and the National Cancer Institute's Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) (42). A physician-reported assessment that often is used for grading CIPN is The National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) (43). In clinical trials the following two assessments are most commonly used to grade CIPN: CTCAE and EORTC QLQ-CIPN20 (38).

The EORTC QLQ-CIPN20 has been developed to elicit patients experience of symptoms and functional limitations related to CIPN. It is self-reported and consists of 20-item questionnaire, with three subscales assessing sensory, motor and autonomic symptoms and functioning during the past week (30). The method uses a 4-point scale: 1 = “not at all”, 2 = “a little”, 3 = “quite a bit” and 4= “very much”. Score ranges: sensory 1 to 36, motor 1 to 32, and autonomic 1 to 12 for men and 1-8 for women (erectile function item is excluded in this study). The scales are linear, with higher scores indicating more symptom burden (44).

The CTCAE is a physician-reported assessment method. It displays grades 0 through 5 with descriptions of severity based on the guideline: Grade 0; No symptoms. Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Grade 2 Moderate; minimal, local or non-invasive intervention indicated. Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL. Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to Adverse

Events. In this study the under groups paraesthesia, peripheral motor neuropathy and peripheral sensory neuropathy are used (21).

2.6 CIPN, physical activity, quality of life and social economics

Physical activity is referred to as all body movement by muscle work that leads to increased energy use. Physical activity is different from exercise, which is defined as physical activity that is planned, structured, repetitive, and purposive in the sense that improvement or maintenance of one or more components of physical fitness is the goal (45). In this study physical activity is the variable assessed. The effect on body physiology from physical activity is dependent on the intensity of the activity. The rule is the higher the intensity, the larger the immediate effect (31).

Among colorectal cancer survivors, physical activity is associated with improved health-related quality of life and less psychosocial challenges (46-50). There is also a positive association between physical activity and colorectal cancer prevention, recurrence and mortality (40). Physical activity is also associated with less fatigue, pain and insomnia (48). However, studies show that only a third of colorectal cancer survivors are physical active at least 30 minutes five days a week (48, 51-55), which was the previous recommendation for physical activity. The burden of symptoms from CIPN may influence the ability to engage in physical activity, but there are few studies on this topic (16, 34). CIPN in combination with low levels of physical activity are negatively associated with health-related quality of life (17, 34).

2.7 Patient pathway

In 2015 a patient pathway was designed to give a well-organized, holistic and predictable pathway for cancer patients (56). The pathway includes assessment, treatment and eventually relapse, rehabilitation, palliative care, communication with patient and next of kin, and specific timelines. There is some information about physical activity, where the need of rehabilitation for each patient should be evaluated by the physician as early as possible. But there is no specific information about recommended type of activity and the frequency, intensity and duration (57, 58).

3. Material and method

3.1 Study design

This is a prospective cohort study using data from a single-armed feasibility study conducted as a preparation for a RCT. Patients planned for adjuvant treatment for colorectal cancer and meeting the inclusion criteria were offered an exercise training intervention. The standardised exercise program was supervised by a physical therapist. Those who consented to the study were assessed on four time points: at baseline, 3 months, 6 months, 9 months and 1 year after inclusion. Patients were recruited from January 2016 to November 2018.

3.2 Participants

Colorectal cancer patients planned for adjuvant chemotherapy following surgery for stadium II and III disease were invited to the study. The patients met to a consult with the oncologist at the cancer outpatient clinic, St.Olavs Hospital, Trondheim University Hospital approximately 3-4 weeks postoperatively. They were given written and oral information about the study. All participants signed a consent form at inclusion (Appendix 5). Start of adjuvant chemotherapy was approximately one week after inclusion in the study. Baseline testing was done before start of adjuvant chemotherapy.

Criteria for inclusion:

1. Receiving curative surgery for colorectal cancer the last 3 months and scheduled for adjuvant chemotherapy.
2. Live nearby St.Olavs Hospital (within 30 minutes' drive).
3. Age18 – 80 years.
4. Able to read and understand Norwegian.
5. Able to complete an exercise training intervention.
6. WHO status ≤ 2.
7. No serious comorbidity that contraindicates physical activity.
8. Able to give informed consent.
9. Not been treated for other cancer types the last 5 years before inclusion (except skin basaliomia and carcinoma in situ cervix)

3.3 Variables and procedures

Primary outcome was the association between EORTC QLQ-CIPN20 and CTCAE.
Secondary outcome is the association between EORTC QLQ-CIPN20 score and self-reported physical activity.

Independent variables: Age, gender, education, treatment type.
Dependent variables: patient-reported physical activity, EORTC QLQ-CIPN20 score, CTCAE score.

EORTC QLQ-CIPN20 is measured at five time points; at baseline (before chemotherapy start-up), 3 months (halfway in the treatment plan), 6 months after inclusion (last cure), 9 months and 1 year after inclusion. CTCAE was measured at baseline, 3 months and 6 months. The patients were given assistance in completing the EORTC QLQ-CIPN20 if needed. Demographic characteristics were reported in questionnaires, and medical history, type of cancer surgery and adjuvant chemotherapy treatment were collected from the patients' medical journal.

The exercise intervention started as soon as possible after the baseline testing and adjuvant chemotherapy had started, preferable the same week. Supervised exercise was offered twice a week through the whole treatment period, estimated 6 months or 24 weeks. In addition, the participant were encouraged to complete an exercise session on their own once a week. The physical therapist supervising the exercise filled out an exercise-log for the patient at every visit.

Details about primary and secondary outcomes are described below.

3.3.1 Peripheral neuropathy
Patient-reported neuropathy: EORTC QLQ-CIPN20 (Appendix 1) is a questionnaire with 20 questions developed to highlight the patients' experience from symptoms and functional limitations related to CIPN (24). The EORTC QLQ-CIPN20 is divided into three subscales. The sensory subscale consists of items 1-6, 9-10 and 18, motor items 7-8, 11-15 and 19, and autonomic items 16-17. The grading is from 1 to 4; no symptom at all, little symptoms, moderate symptoms and a lot of symptoms. In this study only question 1 to 19 are included, since question 20 is grading male impotence which is not relevant for the research question and excludes the females. Total score ranges from 19-76, whereas higher scores indicate more symptoms. The user manual of EORTC QLQ-CIPN20 (59) recommend to linearly convert items and scales to 0-100 scales. For this analysis the EORTC QLQ-CIPN20 are converted to a Likert-scale (1,2,3,4) and a Raw Score. $Raw\ Score = (I_1 + I_2 + \ldots + In)/n.$ The scores for each subscale are done by the formula $score = ((Raw\ Score - 1)/range) \times 100)$, where range is the difference between minimum and maximum alternative for each question. This gives a

sumscore from 0 to 100. The questionnaire is validated for cancer patients with different chemotherapy-treatments (38).

For the analysis of the second hypothesis the EORTC QLQ-CIPN20 are also analysed by each subscale (sensory, motor and autonomic symptoms) in addition to the sumscore.

Physician-reported neuropathy: Common Terminology Criteria for Adverse Events (CTCAE) (21) (Appendix 2) is reported by the physician. The assessment divides symptoms in paraesthesia, peripheral motor neuropathy and peripheral sensory neuropathy. Paraesthesia is graded from 0-3, while peripheral motor neuropathy and sensory neuropathy are graded from 0-4. Total score ranges from 0-11, where higher score indicates more symptoms. In the analysis the sumscore 0-11 will be used.

3.3.2 Physical activity

Patient-reported physical activity is assessed by three questions from the Helseundersøkelsen i Nord-Trøndelag (HUNT-study) (Appendix 3) which includes frequency, duration and intensity of the physical activity. The three questions with possible answers are:

1. How often have you been physically active the last seven days?
   - Never, rarer than once a week, once a week, two to three times a week, approximately every day
2. What was the duration of the activity each time?
   - Less than 15 minutes, 15-29 minutes, 30 minutes up to one hour, more than one hour
3. On a scale from 6 (no exertion) to 20 (maximal exertion), how intense was the activity?

In the analysis the variable of self-reported physical activity is implemented as meeting the national and international guidelines for physical activity (yes or no). They must either have minimum 150 minutes of moderate activity or 75 minutes of high intensity activity a week. The intensity of the activity is measured by Borg's rating scale, were item $\leq$14 is defined as moderate intensity, and $\geq$15 is high intensity (60). The rating assesses the subjective perception of effort. Self-reported physical activity was collected at baseline, 3 months, 6 months, 9 months and 12 months after inclusion.

3.4 Data Analysis

All data preparation and analysis were conducted in IBM SPSS Statistic version 25 for Windows. Each statistical test used in this study will be individually elaborated on and the process of analyses will be described in the following sections.

3.4.1 Internal consistency

The scoring manual for EORTC QLQ-CIPN20 (59) recommends testing for internal consistency of the scales. In this study we calculate the Cronbach's alpha coefficient, which should preferably be above 0.70 for any given multi-item scale.

3.4.2 Descriptive statistics

Descriptive statistics is used for describing demographic data for the study population, and describing central tendency and variation for CTCAE, EORTC QLQ-CIPN and physical activity at the different time points.

3.4.3 Association between physician-reported and patient-reported symptoms

To analyse the association between physician-reported and patient-reported CIPN the bivariate analysis Kendall rank tau b correlation analysis is used. The null hypothesis is that there is no difference between the burden of symptoms between physician-reported and patient-reported CIPN: H0: $\tau = 0$. Significance level is set to 0.05.

3.4.4 The burden of symptoms and physical activity

The Mann Whitney U-test is used to assess whether the burden of symptoms from CIPN differ for those who meet the national recommendation for physical activity and for those who do not. In this analysis the variable of patient-reported CIPN will be used against the variable of self-reported physical activity. The null hypothesis is H0: the probability is 50% that a randomly drawn patient of the first group (those who meet the national guidelines for physical activity) will exceed a member of the second group (those who do not meet the national guidelines for physical activity). Significance level is set to 0.05.

3.4.5 Missing data

Simple imputation is used when missing data in the EORTC QLQ-CIPN20, according to the scoring manual (32). The following procedure is used in this study; assuming that the missing items have values equal to the average of those items which are present for the respondent.

The missing data from CTCAE and self-reported physical activity are reported as missing.

3.5 Schedule

The study is based on already collected data material. Literature search for background information started January 2019. Data processing at St.Olav Hospital, Trondheim University Hospital started March 2019. Statistical analysis, literature search and writing were done consecutively summer/autumn 2019. Finalizing the thesis was planned to be done early in 2020, but because of personal events it is finished earlier.

3.6 Ethical considerations

This study is a secondary analysis using data from an intervention study. The original study followed high ethical standards according to The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice (ICH GCP) and as described in the Helsinki-declaration. REK approval is present (2015/1050) (Appendix 4). Independent of the participation of the original study, the patients received standard oncological treatment.

3.6.1 Possible benefits and disadvantages for the participant

Several positive effects of physical activity during adjuvant chemotherapy are documented and include; improved health-related quality of life, less psychosocial challenges, lower fatigue, lower pain, and prevention of colorectal recurrence and mortality (34, 46-50). No life-threatening adverse effects have been reported (61-63). The positive effects outweigh potential adverse effects of exercise, and that is why exercise is recommended under treatment as well as before and after.

4.Results

4.1 Baseline characteristics

In the original intervention study a total of 19 patients were included. Of these there were six dropouts during the six months intervention period (Figure 1). Then they were left with 13 patients with complete data throughout the intervention period. Baseline characteristics are presented in Table 1.

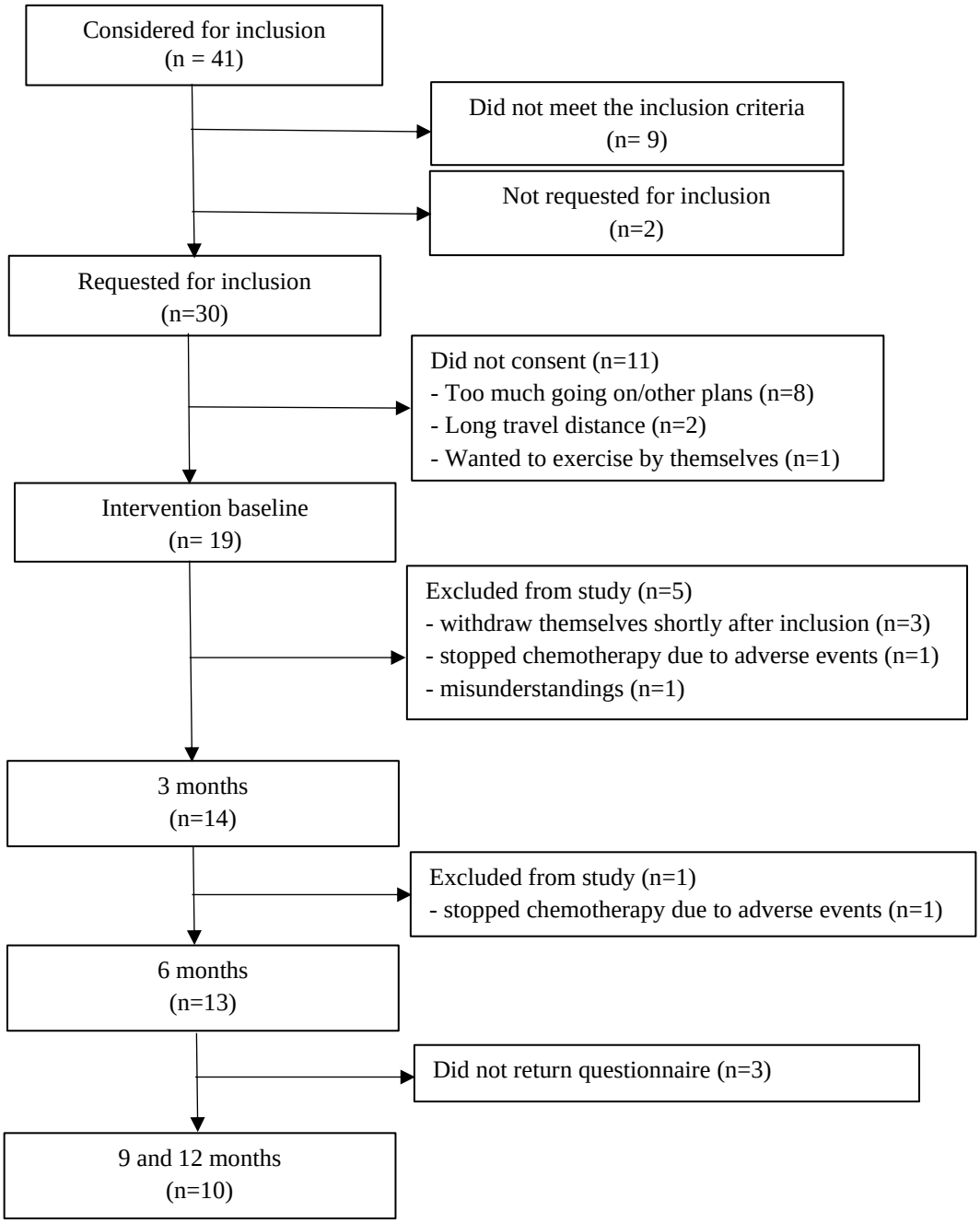

Figure 1: Flowchart of the study

Table 1. Baseline characteristics of study population (N=13).

	Median	SD [Range]
Age	58	12 [33,78]
	N	**%**
Gender		
Male	8	61.5
Female	5	38.5
Education		
≤ 13 years school attendance	1	7.7
< 4 years university	6	46.2
≥ 4 years university	4	30.8
Missing	1	7.7
Occupation		
In paid work	9	69.2
Retired	3	23.1
Missing	1	7.7
WHO status		
0	5	38.5
1	4	30.8
Missing	4	30.8
Type of surgery		
Laparoskopy	9	69.3
Laparotomy	4	30.4
Adjuvant chemotherapy		
Combination treatment		
Capox	6	46.2
Flox	6	46.2
Monotherapy		
Capecitabin	1	7.7

4.2 Association between physician reported and patient-reported symptoms

4.2.1 Internal consistency

The Cronbach's Alpha for all the items is 0.883 and forming a scale appears to be justified.

4.2.2 Patient-reported (EORTC QLQ-CIPN20) and physician-reported (CTCAE) peripheral neuropathy at 3 and 6 months.

The median EORTC sumscore increased from 3 to 6 months, while the median CTCAE remained the same at both points (Table 2).

Table 2. Median, QR1, QR3 and range for self-reported (EORTC QLQ-CIPN20) and physician-reported (CTCAE) chemotherapy-induced peripheral neuropathy during study period.

	EORTC[1]			CTCAE[2]		
	Median	**(QR1, QR3)**	**[Range]**	**Median**	**(QR1, QR3)**	**[Range]**
Baseline	1.9	(0, 15.7) N=13	[0, 40.7]	0	(0, 0) N=13	[0, 2]
3 months	14.8	(9.3, 14.8) N=13	[3.7, 38.9]	2	(1.5, 2) N=13	[0, 6]
6 months	24.8	(11.1, 42.6) N=13	[0, 59.3]	2	(1, 5.5) N=9[3]	[0, 6]
9 months	21.3	(6.9, 31.9) N=10	[0, 50]			
12 months	19.4	(5.6, 30.1) N=10	[3.7, 44.4]			

[1] European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN (sumscore 0-100)
[2] NCI Common Terminology Criteria for Adverse Events (sumscore 0-11)
[3] There were 4 missing data from the CTCAE sumscore at 6 months

The linear relationship between patient-reported and physician reported CIPN is illustrated in Figure 2. At 3 months there are some outliers at CTCAE sumscore grade 2.

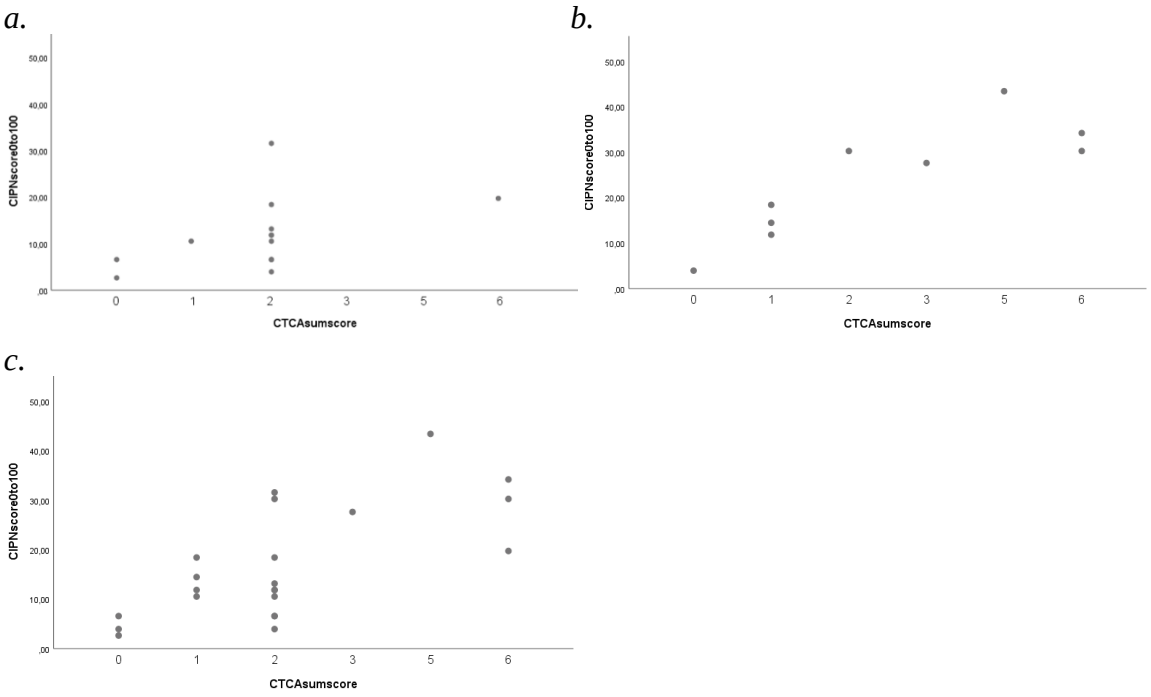

Figure 2: Simple scatter plot of EORTCsumscore by CTCAEsumscore a.: 3 months, b: 6 months, c: 3 and 6 months.

4.2.3 Correlation between patient-reported (EORTC QLQ-CIPN20) and physician-reported (CTCAE) peripheral neuropathy

Bivariate correlation was conducted for the variables EORTC QLQ-CIPN20 and CTCAE. As can be read in Table 3, the data from both 3 and 6 months together show a moderate positive correlation with correlation coefficient of r = .530 (p=0.002). The correlation coefficient at 3 months and 6 months separately is r = .512 (p=0.03) and r = .747 (p=0.007).

Table 3: Correlation between patient-reported (EORTC QLQ-CIPN20) sumscore and physician-reported (CTCAE) sumscore.

CTCAE sumscore	EORTC sumscore correlation coefficient[1]	p-value
3 months	0.512	0.033
6 months	0.747	0.007
3 and 6 months	0.530	0.002

[1]*Correlation coefficient analysed by Kendall tau b correlation.*

4.3 The burden of symptoms and physical activity

Most patients reported minor symptoms at baseline except three patients presenting outliers. Two of them completed the self-reported questionnaire days after the start of adjuvant chemotherapy instead of before. This is illustrated in Figure 3 with the large range in the total score and for the subscales. The symptoms gradually increased up to 6 months after inclusion, and then gradually decreased from 6 months to 12 months. The symptoms from sensory peripheral neuropathy was the highest through the treatment period.

The median [range] EORTC QLQ-CIPN20 sumscore for subjects who met the national guidelines for physical activity and for those who did not are 16.7 [0, 59.3] respective 14.8 [0, 50] for the data from baseline, 3, 6, 9 and 12 months together (p=0.987). The subscale of motor neuropathy at 3 months is the only significant difference for those who met the national guidelines (4.8 [4.8, 4.8]), and for those who did not (19 [4.8, 23.8]), p = 0.048. Those who did not meet the national guidelines for physical activity had a significant higher burden of symptoms from CIPN.

Table 4: Adherence to physical activity national guidelines, and patient-reported neuropathy measured with EORTC QLQ-CIPN20 by sumscore and subscales through study period.

Physically active[1]	**N (%)**	**EORTC sum**	**EORTC sensory**	**EORTC motor**	**EORTC autonomic**
		Median (QR1, QR3) [range]	Median (QR1, QR3) [range]	Median (QR1, QR3) [range]	Median (QR1, QR3) [range]
Baseline	13	p=0.940	p=0.940	p=0.825	p=0.825
Yes	4 (31)	2.8 (0, 25) [0, 31]	1,9 (0,25.9) [0,48.1]	2.4 (2.4,19) [0,23.8]	8.3 (0.41.7) [0,50]
No	9 (69)	1.9 (0, 15.7) [0, 41]	0 (0,11.1) [0,33.3]	0 (0,21.4) [0,38.1]	0 (0,16.7) [0,50]
3 months	12[2]	p=0.343	p=0.755	p=0.048	p=0.149
Yes	5 (42)	9.3 (4.6,18.5) [3.7,18.5]	14.8 (3.7,29.6) [0,33.3]	4.8 (4.8,4.8) [4.8,4.8]	0 (0,25) [0,33.3]
No	7 (58)	14.8 (9.3,27.8) [9.3, 38.9]	14.8 (11.1,25.9) [7.4,44.4]	19 (4.8,23.8) [4.8,23.8]	16.7 (16.7,50) [0,66.7]
6 months	13	p=0.371	p=0.371	p=0.371	p=0.937
Yes	10 (77)	23.1 (5,42.6) [0,59.3]	33.3 (2.8,57.4) [0,70.3]	11.9 (8.3,26.2) [0,57.1]	16.7 (0,33.3) [0,83.3]
No	3 (23)	42.6 (18.5, 42.6) [18.5,50]	59.3 (22.2,29.3) [22.2,66.7]	19 (14.3,19) [14.3,47.6]	16.7 (0, 16.7) [0,33.3]
9 months	10[2]	p=0.711	p=0.711	p=0.889	p=0.400
Yes	8 (80)	21.3 (8.3,30) [0, 33.3]	27.8 (10.2,42.6) [0,59.3]	11.9 (1.2,17.9) [0,19]	16.6 (4.2,16.7) [0,33.3]
No	2 (20)	28.7 (7.4,28.7) [7.4,50]	40.7 (7.4,40.7) [7.4,74.1]	14.3 (0,14.3) [0,28.6]	25 (16.7,25(QR2)) [16.7,33.3]
12 months	10[2]	p=0.352	p=0.914	p=0.257	p=0.610
Yes	6 (60)	13 (5,27.8) [3.7,44.4]	16.7 (2.8,41.7) [0,51.9]	4.8 (3.6,20.2) [0,38.1]	16.7 (0,33.3) [0,33.3]
No	4 (40)	26.9 (10.2,31) [5.6,31.5]	25.9 (5.6,46.3) [0,55.6]	14.3 (9.5,29.8) [9.5,33.3]	16.7 (16.7,41.7) [16.7,50]
Merged	58	p=0.987			
Yes	33 (57)	16.7 (5.6,28.7) [0,59.3]			
No	25 (43)	14.8 (4.8,30.6) [0,50]			

[1] *National guideline for physical activity: minimum 150 mins of moderate activity or 75 mins of high intensity activity a week.*
[2] *Missing data from 3, 6 and 9 months (n=1 and 3)*
**P-value calculated with Mann-Whitney U test.*

Only one patient had minimum 150 minutes of moderate activity or 75 minutes of high intensity activity a week at both 3, 6, 9 and 12 months. This was a female over 70 years old, highly educated (> 4 years at university), retired and had undergone laparotomy. Her EORTC QLQ-CIPN20 sumscore was at 1.85 baseline, 3.70 at 3 months, 5.56 at 6 months, 5.56 at 9 months and 3.70 at 12 months, which are all below the median sumscores for each time point for the study population.

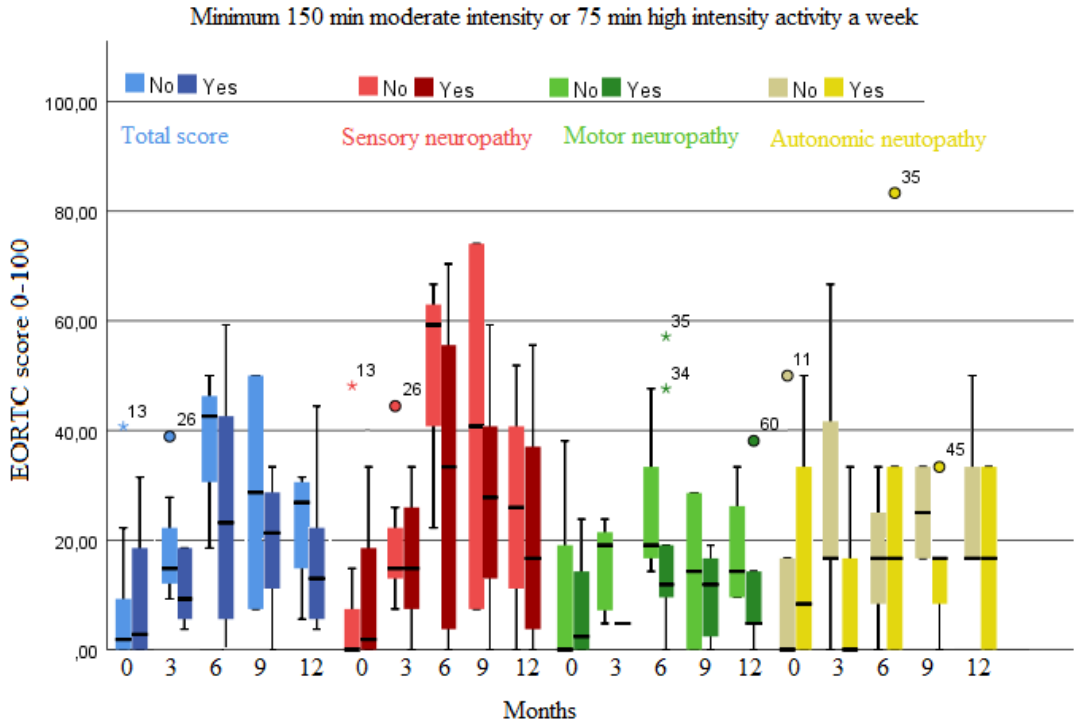

Figure 3: Illustration of self-reported adherence to physical activity national guidelines and self-reported neuropathy measured sorted by months.

4.4 Missing data

Simple imputation was performed in four cases. See Table 5 below for details.

Table 5: Simple imputation of missing data from EORTC QLQ-CIPN20

Variable	Time point	Value
EORTC question 35	6	1
EORTC question 35	6	1
EORTC question 43	3	1
EORTC question 33	12	1

5. Discussion

5.1 Findings and hypotheses

In the present study there was a moderate positive correlation between patient-reported and physician-reported CIPN. Further, there was no difference in burden of symptoms between patients who met the national guidelines for physical activity and those who did not.

5.2 The association between patient-reported and physician-reported CIPN

The moderate positive correlation between patient-reported and physician-reported CIPN supports the null-hypothesis that there is no significant difference in the burden of symptoms reported by physicians and patients themselves. Other studies have also shown positive correlation between physician-reported and self-reported chemotherapy-induced peripheral neuropathy (7, 29, 30). However, the present study stands out from the other three in the characteristics of the patients, where all participants had the same type of cancer, and just a small variation in type of surgery and chemotherapy. The type of cancer, as well as treatment regime, will naturally influence the symptoms. Although there is a significant positive correlation the correlation is strongest at 6 months and when merging data from 3 and 6 months together.

In EORTC QLQ-CIPN20 sumscore there is a change in the burden of symptoms from 3 to 6 months, but in CTCAE sumscore the symptoms are the same for the two timepoints. This may implicate that the EORTC QLQ-CIPN20 is more sensitive for small changes than CTCAE, but results cannot be generalised due to low sample size. At 6 months there was CTCAE-assessments from only nine patients due to missing reports from the physicians. A study that compared patient-reported and physician-reported CIPN in women with breast cancer (64) found that the agreement between the assessment method was highest at the CTCAE grade 0, and lower for the grades 1 and 2. The results is opposite to the present study, where the difference in the grading of severity between EORTC QLQ-CIPN20 and CTCAE were more pronounced when the burden of symptoms was lower. However, patient-reported CIPN was assessed with the Patient-Reported Symptom Monitoring (41) and results are thus not comparable. Correlation analysis was not done at baseline due to the two participants answering the questionnaire after start of chemotherapy, resulting in different timepoints collecting data from patient-reported and physician-reported CIPN. It is important that the data is collected at the same timepoint in correlation analysis. When assessing the linear relationship between EORTC QLQ-CIPN20 and CTCAE at three months there was a large range in patient-reported sumscores at CTCAE grade 2. This finding in addition to the change

in EORTC QLQ-CIPN20 from 3 to 6 months, is supported by three other studies finding that even though there is an association between physician-reported and patient-reported CIPN, the EORTC is more sensitive for change over time (7, 24, 29). Thus, adding another aspect compared to the physician-reported CIPN.

The symptoms of CIPN at baseline were low, except in three participants in which two of them answered the questionnaire after started adjuvant chemotherapy. According to the protocol baseline reporting was planned to be done before start of adjuvant chemotherapy at the same time as physician-reports. Unfortunately, this was missed due to practical reasons in two patients and these patients reported after start of chemotherapy. Therefore, the range in the total score as well as subscales in EORTC QLQ-CIPN20 at baseline (0 months) are larger than expected. This may be explained by the acute neurotoxicity of oxaliplatin in two patients. The acute neurotoxicity results in higher burden of symptoms for the two participants at baseline and will affect the median and range for the study population.

The symptoms of acute neurotoxicity are distal/peripheral paraesthesia and/or dysesthesia, as well as peripheral motor neuropathy symptoms such as muscular contractions, stiffness of muscles in the hands or feet and inability to release grip is presented (11, 12). The damage of the peripheral nerves from oxaliplatin leads to a disturbed somatosensory processing in peripheral/and or central nervous system (65, 66). Pain is one of the symptoms that patients with CIPN may experience (4-6, 15-17). The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” (67). The definition explains pain as a subjective experience that exists only in the person that feels it. Patient-reported assessment will bring up the patients’ perspective and perception of symptoms and may be superior to the physician-reported symptoms.

The toxicity of chemotherapy can develop several weeks after started treatment, and the symptoms are often subjective, like neuropathy and pain, and thus best captured by patient-report (41, 68). The toxicity of chemotherapy with oxaliplatin and symptoms from CIPN is dose-limiting and can in worst case stop the treatment (3, 25). That is a serious adverse effect event, and it is crucial that CIPN (and other toxicity symptoms) is measured and evaluated in a good and structured way. It is recommended to include assessment of patient-reported symptoms in clinical studies in adult oncology, and the EORTC QLQ-CIPN20 is a valid, reliable and sensitive measure in a comparable population (69).

5.3 Physical activity and the burden of symptoms from CIPN

There was no significant difference in the burden of symptoms from CIPN between patients who met the physical activity guidelines and not. This may indicate that a higher burden of symptoms from CIPN in this study population does not limit the ability to be physically active. However, there are some factors that should be considered. In this study population the median age is 58 years of age, while median age at diagnosis for colon cancer in Norway is 73 years of age (1). Therefore, the results may be biased by a relatively younger study population. A higher age is associated with reduced balance (70). Balance is a motor skill that derives from interaction of multiple sensorimotor processes (71). The sensorimotor system is affected by the damage of the peripheral nerves from chemotherapy and represents an additional factor challenging the balance for the elderly patients. A Dutch study of colorectal cancer patients treated with chemotherapy and mean age of 66.7 years old, found that not meeting the recommendations of 150 minutes of moderate to vigorous physical activity a week was associated with more CIPN (34). Other studies have shown that the patients report higher degree of CIPN when they are not meeting the physical activity recommendations (34, 72). This is a question of "the hen and the egg", whether the degree of CIPN affects physical activity and/or the opposite. The causality of the burden of symptoms from CIPN and physical activity must be explored in an RCT.

The median score of patient-reported CIPN in the current study is moderate, with median 14.8 (not meeting physical activity guidelines) and 16.7 (meeting physical activity guideline) for all months. The highest score reported was 66.7. The relatively low burden of symptoms may influence the results. The participants from the Dutch study (34) had a mean sensory score of 10.9 (meeting the national physical activity guidelines) and 14.0 (not meeting the national physical activity guidelines), and motor score 9.0 (meeting physical activity guideline) and 17.6 (not meeting physical activity guideline). These scores are also moderate and comparable with the current study. Other studies in colorectal cancer patients have a higher degree of CIPN symptoms from treatment with oxaliplatin (73-75). Because of the different characteristics of the study population the results are not entirely comparable. In the present study participants got guidance and pushed by a physical therapist during the treatment period. Younger age and guidance from a physical therapist may have a positive impact on level of physical activity during treatment with adjuvant chemotherapy in colorectal patients.

In addition, the prior cancer-surgery and that the exercise intervention had not started will most likely influence whether they meet the physical activity guidelines or not at baseline. Because of the low sample size, the two-three outliers at baseline were included, even though it can be discussed if they should be excluded. One should bear in mind that the higher burden of symptoms in the participants that already had started chemotherapy when answering baseline questionnaire might affect the self-reports of physical activity.

The Dutch study (34) included 506 patients with CIPN, while the study from Tofthagen (16) included 14 patients with CIPN, which is more similar to the current study. The small sample size leads to a higher variability and may lead to bias and affects the reliability of the results. Due to low sample size, low median age and a highly educated study population the results of this study cannot be generalised to the whole colorectal cancer population. However, the trend is that the burden of symptoms does not affect the ability to be physically active. The data from this study is from an intervention study where participants have consented to a 12-week exercise program, and there may be a population that initially wishes to be physically active. They also had professional guidance and follow-up, and therefore were pushed more than if they were to be active completely on their own.

5.3.1 The impact of guidance from physical therapist

A qualitative study from the same population included eight of the patients and did repetitive semi-structured interviews at baseline, three months and six months after inclusion (76). A perspective from the participants was that walking with moderate intensity made a positive impact on the paraesthesia (reduced symptoms) in peripheral upper and lower limb when the body temperature increased under activity. They also reported that the sense of achievement, to be seen and heard by the physical therapist, and good experience from the exercise contributed to the priority of physical activity as a weekly “to do”. The exercise gave a good feeling afterwards. The participants that exercised regularly before inclusion had thoughts about doing exercise after the study. Those who did not exercise before inclusion had plans of continuing exercising after ended treatment (76). Fatigue was a limiting factor for activity in everyday living, and it became harder to complete exercise. Despite all the limiting factors, the data from nine and twelve months after inclusion in the current study show that respectively 8/10 (80%) (nine months) and 6/10 (60%) (twelve months) participants met the guidelines for physical activity, compared to 4/13 (31%) participants at baseline.

In the pilot study the intervention was individually tailored and supervised exercise training. The aim of the current study is to look at physical activity, not the adherence to the intervention in the original study. Even though, there are some interesting aspects to look at from the intervention. The fact that the participants had a place to go for exercise two-three times a week may impact the feasibility, motivation, duration and intensity of exercise. The participants reported that the commitment and the fact that someone is waiting for you was an important contribution to the feasibility to the planned exercise program (76). They also highlighted the physical therapist's role for structuring and making progress as well as customizing the exercise program individually by adverse events and general condition of the day. Also, the knowledge of cancer disease, treatment, adverse events and earlier experience with cancer patients were appreciated and made the participants feel safe during exercise (76).

The research in the area of exercise and cancer has developed in the course of the last decade. There are now some studies including patients undergoing exercise training before, under and after cancer treatment including chemotherapy, radiation and immunotherapy (77, 78). These studies confirm that patients with colorectal cancer undergoing adjuvant chemotherapy are able to be physically active despite moderate CIPN.

5.3.2 Feasibility to physical activity

American College of Sports Medicine recommends cancer patients and survivors a minimum of 150 minutes of moderate-to-strenuous or 75 minutes of strenuous physical activity per week (79). A study of 431 patients with colorectal cancer studied levels of physical activity before diagnosis, during chemotherapy treatment and after completion of treatment. They found that the percentage of patients meeting the American College of Sports Medicine guidelines was reduced from 27% before diagnoses to 10% during treatment (80). In the present study, 31% met the recommended physical activity level at study entry approximately four weeks after cancer surgery. While, at 6 and 9 months the percentage increased (77% and 80%, respectively). The two studies are comparable in percentage of patients meeting the physical activity guidelines before treatment, but in the current study the patients increased the adherence to physical activity under treatment considerably (from 31% to 77%), while the opposite was found in the other study. Six months after the cancer treatment and exercise intervention were completed (at 12 months after inclusion) the percentage decreased to 60%, but still higher than before the intervention. The decrease in physical activity after 12 months may be explained by the lack of follow-up from the physical therapist, since many of the patients reported the presence of a professional as a motivational factor (76). Studies find that

only 29.6-47.3% of cancer survivors fulfil the recommendations regarding physical activity (47, 51-54, 80). In comparison, among Norwegian adults in general 32% meets the national guidelines for physical activity (81). The median symptoms of CIPN were decreased from six to twelve months, and do not explain the decrease in physical activity. Although the participants had moderate burden of symptoms from CIPN they were still able to complete physical activity.

5.4 Exercise as adjunct therapy

In recent years, researchers have investigated the relationship between physical activity and cancer. In the present study the term physical activity is used, while in other studies exercise is the variable they look at. While exercise is planned, structured and has a clear physical fitness goal, physical activity is referred to as all body movement by muscle work that leads to increased energy use (45). The effects of exercise on health-related quality of life among colorectal cancer patients are promising (51,52). However, the effect of physical activity or exercise on CIPN symptoms is poorly investigated. A systematic review summarizing the current body of evidence of specific exercise protocols included 5 studies and found significant improvement on postural control for patients with CIPN symptoms following cancer treatment with chemotherapy (78). Postural control is challenged by the peripheral sensory and motor neuropathy, so the finding may indicate that exercise can prevent or relieve CIPN symptoms. The positive effects were associated with a combined exercise protocol including aerobic exercise, body strength exercise and sensorimotor training (78). We need high quality randomized controlled trials to study the effect of different exercise regimens and whether exercise is preventive, relieving or cures CIPN. The aim of the current study was not to assess effect of physical activity or exercise, but rather assess the association between burden of CIPN symptoms and level of physical activity. However, relevant for further research is to assess whether physical activity in general or specific exercise training can prevent or reduce CIPN during cancer treatment.

The number of studies looking at the effect of exercise as an adjunct treatment of cancer is increasing. As illustrated in the figure below, exercise has broad-reaching systemic implications that affect the overall health of the patient, not just the physiologic adaptations to the skeletal muscle.

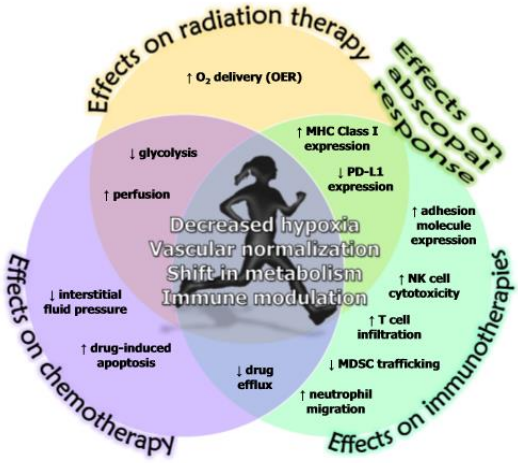

Figure 4: The effects of exercise on different cancer treatments. Printed with permission from the author Mark Dewhirst (77).

Tumor hypoxia and oxidative stress contribute to tumor aggressiveness (77). Ashcraft et al. (2019) describes exercise as a nonpharmacological therapy regulating oxidative stress, alternating of hypoxia, vascular normalization, metabolic reprogramming and immune cell mobilization.

Exercise has also been shown to have a role in maintaining a healthy immune system, controlling infections and inflammation in cancer (82-84). The literature supports that a healthy immune system will promote antitumor activity (85). Thus, to investigate if exercise and/or physical activity have an impact on the cancer treatment or the late effects from chemotherapy, we need to know if the patients are able to be physical active under and after treatment. This study is showing that most of the participants were able meet the national guidelines for physical activity during chemotherapy treatment.

5.5 Patient pathway

There is no standardised assessment for CIPN. Nor are there guidelines regarding physical activity for patients under treatment for colorectal cancer, other than the standard national guidelines for adults in general. Standardised assessment for symptoms is needed for evaluation of the treatment, comparison between groups and comparisons between different treatments. The toxicity of chemotherapy and symptoms from CIPN is dose-limiting when treatment with oxaliplatin, and in worst case the treatment must be stopped (3, 25). Evaluation of toxicity from treatment with chemotherapy will be comparable if agreeing upon a gold standard for measuring CIPN. The lack of a gold standard measure is also a challenge in the study of CIPN (27). Patient pathway is described as «A complex intervention for the mutual decision making and organization of predictable care for a well-defined group of patients

during a well-defined period» (86). This study presents the association between two assessment methods, one physician-reported and one patient-reported. The challenge with missing data and report of CIPN from physicians may be an illustration of the lack of standardised pathway. This may be an important area to study for the future to ensure a good measure and evaluation of CIPN during and after treatment.

5.6 Strengths and limitations

5.6.1 Strengths

A strength of the present study is the inclusion of a homogenous study population regarding type of cancer and little variation in the type of treatment. The prospective study design gives the opportunity to follow the participants before the symptoms of CIPN (in this case) occur and study the characteristics. The length of the follow up as well as the frequent data point is also a strength. The follow up period is 12 months and includes the whole duration of the adjuvant chemotherapy and exercise intervention, as well as three and six months after completed treatment and intervention. This gives the opportunity to study the participant over a long period of time with various challenges.

The use of the analysis method Kendall rank tau b is a strength since the two outcome measures have different characteristics, where EORTC QLQ-CIPN20 is continuous and CTCAE is graded and categorical. It does not rely on any assumptions on the distribution of the variables and is suited for analysis were there are a small sample size and many tied ranks. It also adjusts for ties. Other correlation methods like Pearson's correlation coefficient relies on the assumption that the variables are continuous, and Spearman correlation that relies on the assumption that the two variables are either continuous or ordinal. The same challenge is present in the use of Cohen's kappa that measures the inter-rater agreement for categorical scales.

5.6.2 Limitations

A major limitation in this study is the small sample size thus affecting the external validity. Few participants result in greater spread in the data and vulnerability to extreme variables. Further, the study sample with low median age and high education also limits the generalisability to the whole colorectal cancer population. Since the patients were younger than the mean age for colorectal cancer patients the results may not be generalised to elderly deconditioned patients.

The CTCAE was conducted from multiple physicians. The physicians may have different experience and expertise in the field, that affect the perception of the different grades of CIPN in the CTCAE although it is described in the manual (43). Although physicians were instructed to assess CTCAE in study participants there were several missing data at six months. The physicians may have forgotten to document the CIPN or there was too little time. For further research it should be more implemented in the standard pathway for cancer treatment and the physicians may benefit from training in the use of the assessment method. The CTCAE is just a small part of the consultation. This is a weakness that reduced the internal validity. The patient-reported CIPN (EORTC QLQ-CIPN20) is always reported by the patients themselves, and they have more time to fill it out. Patient-reported physical activity and patient-reported CIPN were documented at nine and twelve months, but CTCAE was unfortunately not.

Self-reported physical activity may be inferior to objective measures of activity. An objective measure with SenseWear Armband was planned. SenseWear Armband is an activity bracelet which measures the amount of physical activity, total energy use and intensity of the activity. Unfortunately, the data from SenseWear were not collected in the study. The external validity is also affected since the participants are included in an exercise intervention. They may be more willing to be active than the rest of the colorectal cancer population, and they may be more active than they would be without the intervention and close follow-up. Guidance from a professional was an important factor in the feasibility of the physical activity.

5.7 Suggestions for further research

Although this study has some methodological limitations, the findings have generated some new research questions. In future studies elderly and deconditioned patients should be included to better represent the colorectal cancer population. Agreeing upon a gold standard measurement of CIPN and assessing the prevalence of CIPN in colorectal cancer patients receiving adjuvant chemotherapy is also an important research area.

Further, studying the possible preventive or treating effects of physical activity and exercise on CIPN for patients under adjuvant chemotherapy should be done in an RCT. Such a study should include an objective measure for physical activity. Although both aerobic and strength exercise has shown promising results, further research is needed to give qualified advice about the dose-response of physical activity and types of exercise. We need to have more knowledge about what specific exercise training that the colorectal cancer patients (and other

cancer types) undergoing chemotherapy should be recommended as a standard exercise prescription. To my knowledge, no previous studies have assessed whether there is causality between CIPN-symptoms and level of physical activity. Especially there is a need for RCT's on the effect of physical activity and/or exercise training to prevent and relieve CIPN, since CIPN is an important dose-limiting factor.

6. Conclusion

Results from this prospective cohort study show a significant moderate positive correlation between -reported and physician-reported CIPN. The participants had an increase in patient-reported CIPN symptoms from baseline to six months after inclusion, and then a decrease in symptoms after ended chemotherapy. Further, there was no difference in the burden of symptoms from patient-reported CIPN between those who met the national guideline for physical activity and for those who did not. The participants were able to be physically active despite moderate symptoms from CIPN. Due to the limitations of this study safe conclusions cannot be drawn regarding the correlation between patient-reported and physician-reported CIPN, as well as the severity of CIPN-symptoms and adherence to physical activity guidelines. Future research should be focusing on standardizing CIPN-assessment in the colorectal cancer population and explore the dose-response relationship of different types of exercise protocols for patients undergoing chemotherapy treatment with CIPN symptoms.

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7ff8ee07cf06:eff5c93b46b28a3b1a4d2b548fc53b9f51498748/Fysisk%20aktivitet%20og%20sedat%20tid%20blant%20voksne%20og%20eldre%20i%20Norge.pdf
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Appendix 1: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN.

Mnd: ☐☐ **EORTC QLQ-CIPN20** PID: ☐☐☐☐

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**
1. Har du hatt kribling i fingre eller hender?	☐	☐	☐	☐
2. Har du hatt kribling i tær eller føtter?	☐	☐	☐	☐
3. Har du hatt nummenhet i fingre eller hender?	☐	☐	☐	☐
4. Har du hatt nummenhet i tær eller føtter?	☐	☐	☐	☐
5. Har du hatt ilende eller brennende smerte i dine fingre eller hender?	☐	☐	☐	☐
6. Har du hatt ilende eller brennende smerte i dine tær eller føtter?	☐	☐	☐	☐
7. Har du hatt kramper i dine hender?	☐	☐	☐	☐
8. Har du hatt kramper i dine føtter?	☐	☐	☐	☐
9. Har du hatt problemer med å stå eller gå p.g.a. vanskeligheter med å føle bakken under dine føtter?	☐	☐	☐	☐
10. Har du hatt vanskelig for å skille mellom varmt og kaldt vann?	☐	☐	☐	☐
11. Har du hatt vanskeligheter med å skrive p.g.a.at du har hatt problemer med å holde en penn?	☐	☐	☐	☐
12. Har du hatt vanskeligheter med å håndtere små gjenstander med fingrene (f. eks. kneppe små knapper)?	☐	☐	☐	☐
13. Har du hatt vanskeligheter med å åpne et glass med skrukork eller en flaske p.g.a. kraftløshet i hendene?	☐	☐	☐	☐
14. Har du hatt vanskeligheter med å gå p.g.a. at føttene dine falt nedover (droppfot)?	☐	☐	☐	☐
15. Har du hatt vanskeligheter med å gå i trapper eller reise deg fra en stol p.g.a. kraftløshet i bena?	☐	☐	☐	☐
16. Har du blitt svimmel når du har reist deg fra en sittende eller liggende stilling?	☐	☐	☐	☐
17. Har du hatt uklart syn?	☐	☐	☐	☐
18. Har du hatt vanskelig for å høre?	☐	☐	☐	☐

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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
19.	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
20.	Har du hatt vanskeligheter med å få eller opprettholde en ereksjon?	☐	☐	☐	☐

Appendix 2: The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE). Partly translated to Norwegian.

Midlertidig utfylling. Skal føres over i webCRF Navn: Født: Etter hvilken kur:		
Dato for utfylling	Dato	dd.mm.åå
Adverse event	Alternativ	Utfyllingsboks
Høyeste grad på hvilket som helst tidspunkt etter forrige kur skal noteres.		
Paresthesia	0 Ingen	Et X
Definition: A disorder characterized by functional disturbances of sensory neurons resulting in abnormal cutaneous sensations of tingling, numbness, pressure, cold, and warmth that are experienced in the absence of a stimulus.	1. Mild symptoms	
	2. Moderate symptoms; limiting instrumental ADL	
	3. Severe symptoms; limiting self-care ADL	
Peripheral motor neuropathy	0 Ingen	Et X
Definition: A disorder characterized by inflammation or degeneration of the peripheral motor nerves.	1. Asymptomatic; clinical or diagnostic observations only; intervention not indicated	
	2. Moderate symptoms; limiting instrumental ADL	
	3. Severe symptoms; limiting self care ADL; assistive device indicated	
	4. Life-threatening consequences; urgent intervention indicated	
Peripheral sensory neuropathy	0 Ingen	Et X
Definition: A disorder characterized by inflammation or degeneration of the peripheral sensory nerves.	1. Asymptomatic; loss of deep tendon reflexes or paresthesia	
	2. Moderate symptoms; limiting instrumental ADL	
	3. Severe symptoms; limiting self care ADL	
	4. Life-threatening consequences; urgent intervention indicated	

Appendix 3: Self-reported physical activity. Question 2-4 are used in the study.

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

Appendix 4: REK approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord	Lill Martinsen	77646140	20.12.2016	2015/1050/REK nord
			Deres dato:	Deres referanse:
			14.12.2016	

Vår referanse må oppgis ved alle henvendelser

Eva Hofsli
Kreftavd.

2015/1050 Fysisk trening under adjuvant kjemoterapi ved tykktarmskreft (FAKT-studien)

Forskningsansvarlig: St. Olavs Hospital
Prosjektleder: Eva Hofsli

Vi viser til søknad om prosjektendring datert 14.12.2016 for ovennevnte forskningsprosjekt. Søknaden er behandlet av REK nord på fullmakt, med hjemmel i helseforskningsloven § 11.

Vurdering
De omsøkte prosjektendringene gjelder ny kontaktperson ved forskningsansvarlig institusjon, St. Olavs Hospital HF, fra Jo-Åsmund Lund til Arne Solberg, to nye prosjektmedarbeidere, samt endring av prosjektets sluttdato fra 31.08.2020 til 13.12.2022.

Under punktet *«annen prosjektendring»* søkes det om å endre inklusjon- og eksklusjonskriterier hvor det inkluderes pasienter med diagnose cancer recti i tillegg til pasienter med diagnose cancer coli.

Prosjektet vil også endre navn fra «Fysisk trening under adjuvant kjemoterapi ved tykktarmskreft (FAKT-studien)» til «Fysisk aktiv under kreftbehandling (FAKT-studien)». Og det skal også legges til fysiske tester i intervensjonen, hvor testene er beskrevet i vedlagte protokoll.

Det opplyses om at studien ennå ikke er oppstartet, og at det ønskes å kjøre pilot, jf. opprinnelig protokoll på 10 deltakere, samt 10 deltakere i tillegg, jf. inneværende søknad, så snart alle omsøkte endringer har mottatt godkjenning.

Rek har ingen innvendinger til de omsøkte prosjektendringene.

Etter fullmakt er det fattet slikt

Vedtak

Med hjemmel i helseforskningsloven § 11 og forskningsetikkloven § 4 godkjennes prosjektendringene.

Endringen godkjennes under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden, endringssøknaden, oppdatert protokoll og de bestemmelser som følger av helseforskningsloven med forskrifter. For øvrig gjelder de vilkår som er satt i forbindelse med tidligere godkjenning av prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest (et halvt år etter prosjektslutt), jf.

Besøksadresse:
MH-bygget UiT Norges arktiske universitet 9037 Tromsø
Telefon: 77646140
E-post: rek-nord@asp.uit.no
Web: http://helseforskning.etikkom.no/

hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Prosjektleder kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra mottak av dette brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
Sekretariatsleder

Lill Martinsen
Rådgiver

Kopi til: *jo-asmund.lund@stolav.no*

Appendix 5: Information sheet and declaration of consent

FAKT-studien. Desember 2016

Forespørsel om deltakelse i forskningsprosjekt

Fysisk aktiv under kreftbehandling

- *En pilotstudie*

Bakgrunn og hensikt
Dette er et spørsmål til deg om å delta i en forskningsstudie for å undersøke gjennomførbarhet og effekter av et tilrettelagt treningsprogram under behandling med cellegift. De som kan delta i studien er pasienter som er operert for tykk- eller endetarmskreft og som skal få etterbehandling med cellegift, og det er derfor du blir spurt om å delta i studien. Det er St. Olavs Hospital i samarbeid med NTNU som er ansvarlig for studien.

Hva innebærer studien?
Dersom du takker ja til å delta i studien vil du i perioden med etterbehandling med cellegift i tillegg få egen oppfølging og veiledning med fysisk trening. Du vil få et tilrettelagt treningsprogram som skal følges gjennom hele behandlingsperioden. Det legges opp til 3 treninger i uka hvorav to økter er med fysioterapeut ved Pusterommet enten alene eller i gruppe, og en økt er egentrening.

For å undersøke hvilke effekter et tilrettelagt treningsprogram under behandling med cellegift har, vil det bli foretatt målinger og kartlegginger av deg i form av enkle fysiske tester, blodprøver, utfylling av spørreskjema og individuelle samtaler. For å få et objektivt mål på fysisk aktivitet vil du bære en aktivitetsmåler på armen i 14 dager ved tre anledninger. Denne er utformet som et armbånd og medfører ikke ubehag. Målingene gjennomføres før, under og etter behandlingsperioden med cellegift.

Dersom du ikke ønsker å delta i studien vil du motta vanlig oppfølging underveis i behandlingen. På samme vis som de som takker ja til å delta i studien blir du deretter henvist til lokal oppfølging i din hjemkommune etter at behandlingen er ferdig.

Mulige fordeler og ulemper
Ut ifra den kunnskapen vi har i dag, kan det se ut som at fysisk aktivitet under behandling med cellegift kan bidra til å redusere bivirkninger. Vi har heller ingen grunn til å tro at tilrettelagt trening under cellegift innebærer en risiko. Ekstra blodprøver som tas vil i størst mulig grad tilpasses tidspunkt da du uansett skal ta blodprøve som ledd i ordinær behandling.

Hva skjer med prøvene og informasjonen om deg?
Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres. Datainnsamlingen vil bli avsluttet innen 2022. Alle data blir anonymisert 5 år etter prosjektslutt i henhold til offentlige retningslinjer.

Frivillig deltakelse
Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte studiekoordinator Ingunn Hatlevoll på telefon 90866361 eller e-post ingunn.hatlevoll@stolav.no

Ytterligere informasjon om studien finnes i kapittel *A* – *utdypende forklaring av hva studien innebærer.*
Ytterligere informasjon om personvern og forsikring finnes i kapittel B – *Personvern, økonomi og forsikring.*

Samtykkeerklæring følger etter kapittel B.

Kapittel A- utdypende forklaring av hva studien innebærer

Bakgrunnsinformasjon om studien
Pasienter med tykktarmskreft som får cellegift sliter med flere bivirkninger som følge av behandling. Uttalt trøtthet (fatigue) og såkalt perifer sensorisk nevropati (kriblinger, nummenhet og eventuelt smerter i hender og føtter) er to bivirkninger som ses hyppig og som kan gi betydelig nedsatt livskvalitet. Andre bivirkninger kan være påvirkning av immunforsvaret og blodplater som kan medføre både infeksjon og utsettelse av behandling. Formålet med prosjektet er å finne ut om et tilrettelagt treningsprogram kan bidra til å redusere bivirkninger av kreftbehandling, bedre livskvalitet på kort og lang sikt, komme raskere tilbake i jobb (for de det gjelder) og på sikt bedre resultatet av selve kreftbehandlingen. I pilotstudien ønsker vi spesielt å se på gjennomførbarhet av et tilrettelagt treningsprogram.

Kriterier for deltakelse
Følgende kriterier ligger til grunn for å kunne delta i studien: Alder mellom 18 og 80 år, gjennomgått operasjon for tykktarmskreft siste 3 måneder og planlagt for etterbehandling med cellegift, i stand til å gjennomføre tilrettelagt trening, ingen annen alvorlig sykdom som medfører at man ikke bør trene og underskrevet skriftlig informert samtykke.

Tidsskjema – hva skjer og når skjer det?
- Før oppstart behandling med cellegift: Fysiske tester, blodprøver, utfylling av spørreskjema, og individuell samtale. Det vil være spørsmål som handler om din livskvalitet, fysisk og psykisk form, fysisk aktivitet, bivirkninger av cellegift, mage- tarmfunksjon, osv.
- Standard varighet av etterbehandling med cellegift etter operasjon for tykktarmskreft er i underkant av 6 måneder.
- Halvveis i cellegiftbehandlingen (ca. 3 måneder): Fysiske tester, blodprøver, utfylling av spørreskjema og individuell samtale.
- Umiddelbart etter avsluttet cellegift: Fysiske tester, blodprøver, utfylling av spørreskjema og individuell samtale.
- 12 måneder etter start av cellegift: Utfylling av spørreskjema.
- I inntil 5 år etter at du ble med i studien vil vi følge med på hvordan det går med deg, spesielt med tanke på eventuelt tilbakefall av kreftsykdommen.
- I hele behandlingsperioden med cellegift følger du ditt tilrettelagte treningsprogram.

Kompensasjon for eventuelle utgifter

Du vil få dekket utgifter på lik linje med andre pasienter gjennom de ordninger som allerede eksisterer. Eventuelle ekstra utgifter i forbindelse med veiledet trening blir dekt av studien.

Alternative prosedyrer eller behandling pasienten får dersom personen ikke velger å delta i studien
Alle som takker nei til deltakelse i studien vil motta standard kurativ cellegiftbehandling som planlagt og etter vanlige rutiner, og det får dermed ingen behandlingsmessige konsekvenser.

Kapittel B - Personvern, økonomi og forsikring

Personvern
Opplysninger som registreres om deg er informasjon som vi anser som relevant for forskningsprosjektet. Dette er for eksempel opplysninger om din helsetilstand, sivil status, utdannings- og arbeidsforhold, tobakk- og alkoholvaner, hvilke symptomer du har, gjennomgått behandling og behandling du mottar. Opplysningene vil bli innhentet fra deg, din sykehusjournal, fra fastlege eller annet helsepersonell. Det kan også være aktuelt å innhente relevant informasjon fra offentlige registre (for eksempel Folkeregisteret, Kreftregisteret, FD trygd, Dødsårsaksregisteret og Norsk pasientregister) eller fra andre studiedatabaser dersom du deltar i andre forskningsprosjekter.

Kreftklinikken, St. Olavs Hospital ved administrerende direktør er databehandlingsansvarlig.

Utlevering av opplysninger til andre
Hvis du sier ja til å delta i studien, gir du også ditt samtykke til at avidentifiserte opplysninger utleveres til EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Group i Belgia.

Rett til innsyn og sletting av opplysninger om deg og sletting av prøver
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Forsikring
Alle pasienter som deltar i studien er forsikret under Pasientskadeerstatningsordningen.

Informasjon om utfallet av studien
Du som velger å delta i studien har rett til å få informasjon om utfallet/resultat av studien.

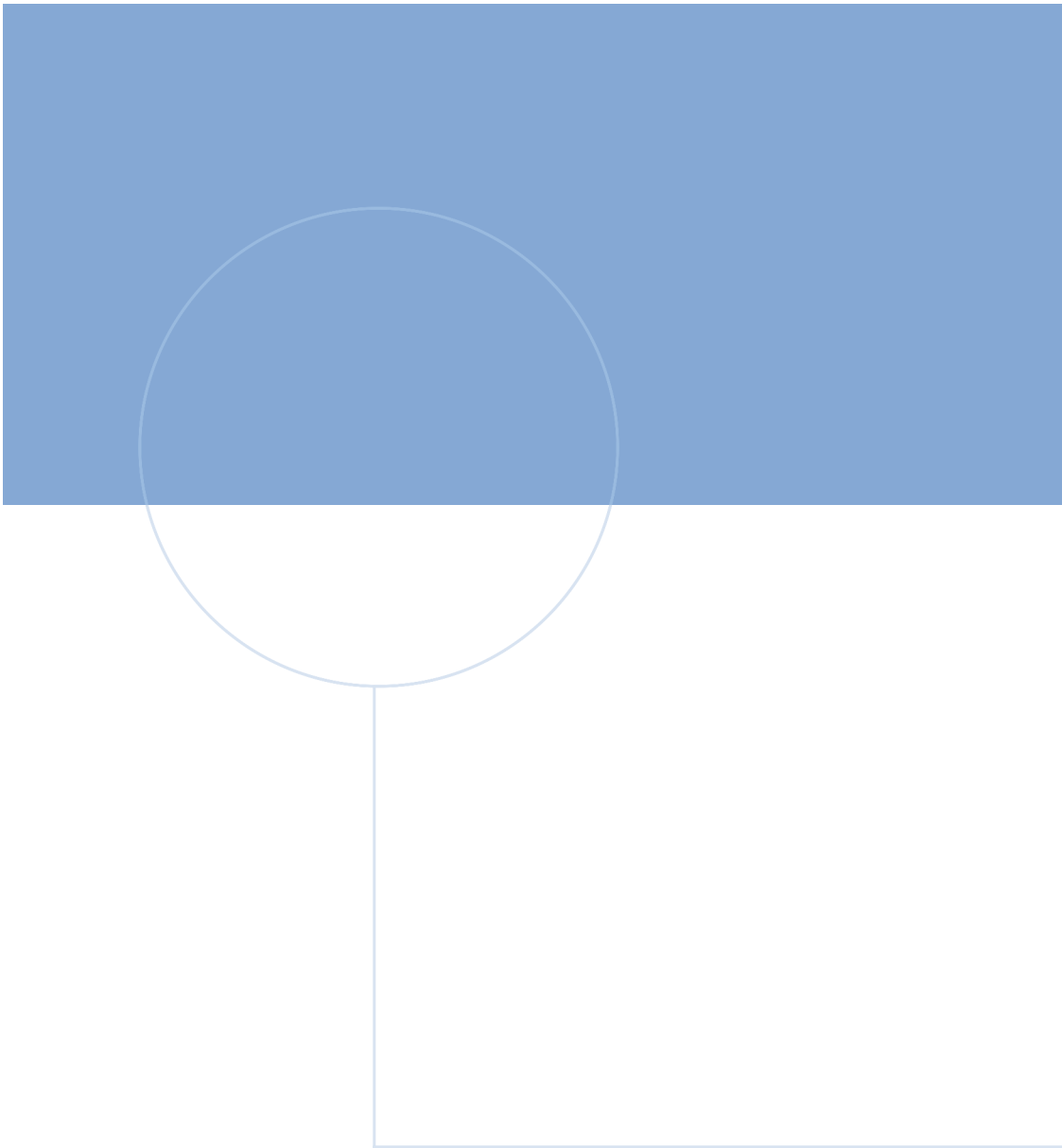
Samtykke til deltakelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)



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