PhD Thesis

Perioperative Rehabilitation in Operable Lung Cancer Patients (PROLUCA)

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Submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen December 30, 2017
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Preface and Acknowledgements

This thesis was initiated because Copenhagen Centre for Cancer and Health has a profound ongoing interest in investigating and developing the best rehabilitation for cancer patients. This interest in improving standard practice has led to national and international collaboration with various research departments. The present research project, PROLUCA, received grants from the Center for Integrated Rehabilitation of Cancer Patients (CIRE), which was established and is supported by the Danish Cancer Society and the Novo Nordisk Foundation. Financial support has also been provided by the City of Copenhagen, Rigshospitalet and the Faculty of Health and Medical Sciences, University of Copenhagen.

First, I would particularly like to thank the patients who participated in the PROLUCA feasibility study for their bravery and willingness to be the first group to begin exercising two weeks after lung cancer surgery. I would also like to express my most sincere gratitude to everyone who contributed to this thesis because clinical research requires an immense amount of effort and I could not have gotten this far on my own. I also owe a debt of appreciation to the staff at Copenhagen Centre for Cancer and Health for their superb help, huge flexibility and excellent cooperation in collecting data, but also to the outstanding staff at the collaborating hospitals for their contribution to the data collection.

This thesis would not have been possible without the tremendous support of my boss and head of Copenhagen Centre for Cancer and Health, Jette Vibe-Petersen, and research coordinator and nurse Karen Trier. A heartfelt thank you to both of you for the time and effort you invested in this thesis. I also wish to give a special thanks to my supervisors Jesper Holst Pedersen, Klaus Richter Larsen and Henning Langberg for providing me with competent academic feedback. I also want to thank my colleagues at Copenhagen Centre for Cancer and Health, CopenRehab and CIRE research group for their great support and invaluable help.

Finally, my deepest gratitude goes to my family and friends for their incredible support.

Maja Schick Sommer
Copenhagen, December 2017
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Abbreviations

ACSM  American College of Sports Medicine
ATS   American Thoracic Society
BP    Blood Pressure
CI    Confidence Interval
CONSORT Consolidated Standards of Reporting Trials
COPD  Chronic Obstructive Pulmonary Disease
DHA   Danish Health Authority
DM    Diabetes Mellitus
EORTC QLQ-C30 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer 30
EORTC QLQ-LC13 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 15
FACT-L Functional Assessment of Cancer Therapy-Lung
FEV₁  Forced Expiratory Volume in the first second
FVC   Forced Vital Capacity
GRADE Grading of Recommendations, Assessment, Development and Evaluation
HADS  Hospital Anxiety and Depression Scale
HR    Heart Rate
HRmax Maximal Heart Rate
HRQoL Health-Related Quality of Life
LCS   Lung Cancer Subscale
MID   Minimal Important Difference
MSPSS Multidimensional Scale of Perceived Social Support
n     Number
NCCN  National Comprehensive Cancer Network
NSCLC Non-small Cell Lung Cancer
PROLUCA Perioperative Rehabilitation in Operable LUng CAncer patients
QoL   Quality of Life
r     Correlation coefficients
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<td>Short Form Health Survey</td>
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<td>SMD</td>
<td>Standardised Mean Differences</td>
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<td>TNM</td>
<td>Tumor Node Metastasis</td>
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<td>VATS</td>
<td>Video-Assisted Thoracoscopic Surgery</td>
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<tr>
<td>VO$_2^{\text{max}}$</td>
<td>Volume of maximal oxygen consumption</td>
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<tr>
<td>VO$_2^{\text{peak}}$</td>
<td>Volume of peak oxygen consumption</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>1RM</td>
<td>1 Repetition Maximum</td>
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<td>6MWD</td>
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**Dansk resumé**

**Titel:** Perioperativ Rehabilitering ved Operation for LUngeCAncer (PROLUCA)

**Baggrund:** En forbedret overlevelse for patienter med operable lungekræft har betydet, at flere lever længere med fysiske og psykosociale følger til sygdom og behandling. Følger som nedsat fysisk kapacitet, træthed og depression kan nedsætte patientens funktionsevne og livskvalitet. Forskning tyder på, at fysisk træning i forbindelse med behandling af en række kræftsygdomme, herunder operabel lungekræft, har en positiv effekt på såvel fysiske som psykologiske parametre. Få undersøgelser beskæftiger sig med en tidlig indsats. Forskning har ikke tidligere belyst sikkerheden og gennemførbarheden af en perioperativ rehabiliteringsindsats, i kommunale omgivelser, hvor den postoperative træning består af høj intensivt interval træning, der initieres 2 uger efter en operation for lungekræft.

**Formål:** Det overordnede mål med denne ph.d. afhandling var at evaluere sikkerheden og gennemførbarheden af en perioperativ rehabiliterings indsats i kommunale omgivelser, bestående af præoperativ fysisk træning og tidlig postoperativ rehabilitering, med fokus på træning, i forbindelse med helbredende operation for lungekræft. I tillæg undersøger denne afhandling effekten af tidlig postoperativ træning sammenlignet med sen iværksat træning til samme patient population.

**Metode:** Afhandlingen består af en undersøgelse af sikkerhed og gennemførbarhed i et klinisk lodtrækningsforsøg, hvor 40 deltagerne afprøvede en af fire interventioner, heraf tre eksperimentelle og én kontrol (artikel I-III). I tillæg blev en systematisk gennemgang af litteraturen og en metaanalyse anvendt til at belyse effekten af tidlig postoperativtræning til patienter med ikke småcellet lungekræft (artikel IV).

**Resultater:**
Ingen utilsigtede hændelser opstod under den tidlige postoperative træning og gennemsnitligt startede patienterne randomiseret til den tidlige iværksatte træningsgruppe 18 dage efter operation (range 13-29) og 47 dage (range 22-80) efter operation i den sent iværksatte træningsgruppe. Ingen patienter havde spontane eller uventede reaktioner til at træne høj intensivt interval træning to uger efter operationen. Den postoperative træning blev gennemført af 73% af de patienter der var randomiseret til denne intervention. Da kun tre patienter ud af tolv trænede dagligt før operationen i
et accelereret patient forløb blev den præoperative hjemmetræning vurderet ikke gennemførbar, da der ofte er diagnostiske tiltag som tager tid og kræfter hos patienterne kombineret med det accelererede patient forløb som maksimalt efterlader 2 uger fra diagnose til operation.
I det systematiske review blev fire randomiserede kontrollerede forsøg identificeret, omhandlende 262 deltagere. Resultater ved kort opfølgning (12–20 uger) viste signifikant højere fysisk kapacitet og den fysiske komponent af den helbredsrelaterede livskvalitet i interventionsgruppen sammenlignet med kontrol gruppen; henholdsvis standardiseret gennemsnits forskel på 0.47 (95% konfidens interval 0.07 til 0.88) og standardiseret gennemsnits forskel på 0.51 (95% CI 0.22 til 0.80). Ingen effekter var at se på den fysiske kapacitet eller den helbredsrelaterede livskvalitet i en sensitivitets analyse af det studie som initierede træning tidligt, indenfor to uger postoperativt.

**Konklusion:**
Denne afhandling fandt at højt intensivt interval træning, der er iværksat 2 uger efter operation for ikke små-cellet lungekræft er sikkert og gennemførbart i en kommunal setting. Rekrutteringen af patienter med ikke små-cellet lungekræft til perioperativ rehabilitering med fokus på træning var udfordrende i et accelereret patient forløb. Den præoperative hjemmetræning var inkonsekvent og ikke gennemførbart i et set-up, hvor der maksimalt er 14 dage mellem diagnose og operation (artikel II-III). Det systematiske review fandt, at træning kan have gavnlige effekter på trænings kapacitet samt den fysiske og mentale komponent af HRQoL for operable lungekræft patienter. Grundet lav kvalitet af evidensen må disse resultater tolkes med forsigtighed. Det var ikke muligt at konkludere på effekten af tidlig postoperativ træning sammenlignet med en sent iværksat træning på grund af mangel på veludførte randomiserede kontrollerede forsøg (artikel IV).
English Summary

Background: Lung cancer is the leading cause of cancer-related death worldwide. The most effective treatment in early stages of non-small cell lung cancer (NSCLC) is present lung resection. Despite improvements in medical and surgical treatment of NSCLC, surgery is associated with a potentially substantial morbidity, functional limitations and decreased health-related quality of life (HRQoL). Patients with NSCLC are typically older and are current or former smokers, and they commonly have other concomitant smoking related chronic diseases (e.g., COPD, ischemic heart disease) that may affect the cardiorespiratory system. Literature on NSCLC patients indicates that exercise is beneficial, but research is limited, highlighting that supporting evidence is needed to determine the optimal type, timing and amount of exercise when diagnosed with lung cancer.

Aim: The overall aim of this thesis was to evaluate the safety and feasibility of preoperative and early postoperative non-hospital rehabilitation, with a focus on exercise, in patients with NSCLC. Subsequently, it was also to evaluate, in a systematic review, the effect of early-initiated postoperative exercise compared to late-initiated exercise in the same population.

Methods: Different research designs were applied in this PhD thesis. Paper I describes the setup of the PROLUCA RCT I. Papers II-III examine a single-centre four-arm prospective randomized controlled feasibility study in 40 patients with operable lung cancer. Paper IV is a comprehensive systematic review and meta-analysis of the available evidence from randomized controlled trial (RCT) comparable studies.

Results: No adverse events were reported or observed during the postoperative exercise program, and the average onset of exercise was 18 days (range 13-29) post surgery in the early intervention group and 47 days (range 22-80) in the late intervention group. No patients had spontaneous or unexpected reactions to performing high intensity interval exercises two weeks after surgery and the postoperative exercise was completed by 73% of the patients randomized to this intervention. Three out of 12 patients managed to exercise daily prior to surgery in a fast-track setting, which is why the preoperative home-based exercise program was interpreted as not feasible due to interfering diagnostic procedures and the fast-track surgery, which only left one to two weeks between diagnosis and surgery. Four RCTs were identified involving 262
participants. Results on short-term follow-up (12-20 weeks) showed a significantly higher exercise capacity and physical component of HRQoL in the intervention group compared to the control group, standardised mean difference (SMD) 0.47 (95% confidence interval (CI) 0.07 to 0.88) and SMD 0.51 (95% CI 0.22 to 0.80), respectively. No short-term effects were seen on any of these outcomes in a sensitivity analysis of studies initiating exercise training early, i.e., within two weeks post surgery.

**Conclusion:** This thesis showed that a high intensity interval exercise program starting two weeks after surgery in patients with NSCLC was safe and feasible. Recruitment of NSCLC patients to the perioperative rehabilitation intervention, with a focus on exercise, was challenging in a fast-track surgical program. The preoperative home-based exercise was found to be inconsistent and not feasible in a set-up where the time interval between referral and surgery (fast-track surgical program) was restricted to 14 days (Paper II-III). This thesis also showed, in a systematic review, that exercise improved exercise capacity and the physical component of HRQoL in the short-term, but no beneficial effect was found in the mental component of HRQoL. In the systematic review, it was not possible to draw conclusions about the effect of early-initiated postoperative exercise compared to late-initiated exercise due to the lack of well-conducted RCTs.
Background

Lung Cancer

Incidence and Prognosis
Lung cancer is a leading cause of cancer-related death worldwide and the most common cancer (1). Global lung cancer incidence rates continue to decline, but gender differences exist nationally and internationally, with women facing a growing risk and men a falling risk (1,2). In Denmark, more than 4500 patients are diagnosed with lung cancer every year (3,4). Due to its high mortality, the disease accounts for 24% of all cancer-related deaths, which is comparable to the estimated 26% of all cancer-related deaths in the United States of America (2,5).

At the close of 2015, the number of people living with or after lung cancer in the Nordic countries was 33236, of whom 10435 were Danes (5). At present, the international median age at diagnosis is more than 70 years, which is comparable to the situation in Denmark (4,6).

Although lung cancer does occur in people under the age of 55, it is uncommon (6). The gender differences mentioned above are caused by historical differences in tobacco use, which is why slightly more men (54%) than women (46%) are diagnosed with lung cancer. Women took up smoking in large numbers later, at an older age than men and women are slower to quit smoking (2,4).

Cigarette smoking, the greatest risk factor for lung cancer, is estimated to be responsible for 90% of all cases. Another known risk factor for lung cancer includes exposure to various occupational and environmental carcinogens (7). Consequently, tobacco-related diseases are particularly frequent in patients with lung cancer (8,9). Comorbidity affects the outcome of patients with lung cancer in several ways, such as decreased performance status, reducing the efficacy of the treatment and increasing the side effects (10). As a prognostic factor, comorbidity is a part of the risk stratification in patients who are candidates for the treatment of lung cancer. Out of the four most common cancer diagnoses, patients with lung cancer have the highest prevalence of comorbidities, with the most prevalent comorbidity being chronic obstructive pulmonary disease (COPD). In an American population-based study with 6000 patients diagnosed with lung cancer, COPD was present in around 53% of them, diabetes mellitus (DM) in 16% and congestive heart failure in 13% (11,12). Other comorbidities, such as, hypertension, ischemic heart disease and
cerebrovascular disease are also present in patients diagnosed with lung cancer (9). These comorbid diseases are considered to have a significant influence on the survival rate of lung cancer patients (13). Furthermore, previous studies have demonstrated that less aggressive treatment is given to patients with lung cancer with specific existing comorbidities (14). In Denmark, half of the patients diagnosed with lung cancer have one or more comorbidities at the time of diagnosis (4), which is comparable to studies from other European countries (9,15). Besides comorbidity, age and performance status, the prognosis of patients with lung cancer is affected by the anatomic extent of the lung cancer disease (16). In Denmark, the five-year survival rate is around 50% in patients with lung cancer stage IA, whereas a very poor prognosis is found in patients with lung cancer classified as stage IV, 2% of whom are alive five years after time of diagnosis (17). These numbers are comparable to international prognoses (18). In general, the prognosis of lung cancer patients is also affected by environment-related factors, such as access and quality of care, and treatment-related factors, e.g., the type of treatment selected and the initiation of treatment (16).

**Staging and Treatment Modalities**

Lung cancer is classified into two major histologic types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) (19). NSCLC, the most common type worldwide, accounts for approximately 85% of all new lung cancer diagnoses (4,20). Adenocarcinoma, squamous cell carcinoma and large cell carcinoma are the three main NSCLC subtypes (21). The extent of the disease is classified by the Tumor Node Metastasis (TNM) system, version seven (22), which is used to select candidates for surgical resection (22,23). Patients classified as stage one, two and partly three (stage I, II, IIIA), are candidates for lung resection (22,23). In Europe, the proportion of patients who undergo surgery for lung cancer is around 10-20% (24). In Denmark, approximately 30% of patients diagnosed with lung cancer are suitable for treatment with curative intention (4), with around 20% receiving surgical treatment and 10% undergoing radiotherapy treatment (4). Adjuvant chemotherapy is offered in approximately one third of the patients following lung resection, whereas radiotherapy is rarely used as an adjuvant to surgery (4,25). The selection of patients who are offered adjuvant chemotherapy is based on TNM staging, histology, comorbidity and general condition. Treatment of patients with inoperable lung cancer, stage IIIb and IV, is life-prolonging and symptom relieving (22).
Operable Lung Cancer

Earlier detection of lung cancer and improvements in surgical techniques, combined with more effective adjuvant treatments, has led to improved survival for patients with operable lung cancer (25). Today, the two and five-year survival rate in Denmark is 79% and 56%, respectively, following surgery for lung cancer (17). In Denmark, the overall risk of mortality 30 days after surgery is 1%, which is in accordance with the findings in a survey from the U.S. conducted in 2002-2008 (4,26), but lower than the 2.6 % reported from the UK (27).

Surgical Procedure and Postoperative Complications

The surgical procedure consists of removal of the affected lung tissue, combined with removal of the regional (mediastinal or peribronchial) lymph nodes (28). The degree of resection ranges from wedge resection or segmentectomy to major resections with removal of one or two lobes (lobectomy or bilobectomy) or pneumonectomy (29). The surgical approach is either by thoracotomy (open method) or minimal invasive video-assisted thoracoscopic surgery (VATS) (19,25). The proportion of NSCLC patients treated with VATS nationally is 66% but has regional variations, with the highest number (86%) at Copenhagen University Hospital, Rigshospitalet (17). The VATS approach allows earlier recovery, with fewer postoperative complications (30) and shorter hospital stays (31,32). Postoperative complications are defined as complications occurring within 30 days after surgery (33). The rate of complications after thoracic surgery varies between 19 to 59% (34) and, in Denmark, 25% of patients treated for NSCLC experience one or more postoperative complications (17). The most common postoperative complication is prolonged air leakage (9%), pneumonia (5%) and cardiac arrhythmias (3%) (17,35).

Physical and Mental Impact of Surgery

Despite improvements in the treatment modalities of NSCLC, surgery, in addition to postoperative complications, is also associated with long-term and late effects of the surgery. Long-term effects are defined as side effects or complications that begin during or very shortly after treatment and persist afterward, causing compensatory behavior in patients with cancer. Late effects distinguish themselves from long-term effects in that they appear months or years after treatment completion (e.g., arrhythmias or cardiomyopathies after exposure to cardiotoxic agents) (36). Long-term and late side effects following surgery for NSCLC are a reduction of pulmonary capacity, cardiorespiratory capacity and decreased quality of life (QoL) (31,32).
Depending on the extent of the resection, both pulmonary and exercise capacity are decreased just after surgery and followed by an increase during the first 12 months, leading to a permanent loss in pulmonary capacity of around 10-15% (32,33,37) and a 16% loss in exercise capacity six month after surgery (38). A decrease in post-surgical pulmonary capacity measured by forced expiratory volume in the first second (FEV₁) and health-related quality of life (HRQoL) compared to pre-surgical status has been demonstrated in individuals with NSCLC, up to two years after surgery (39,40). Compared to healthy individuals, the levels of exercise capacity and HRQoL are significantly impaired after lung resection in patients with NSCLC (41).

**Exercise and Surgery in Lung Cancer**

Exercise is defined as physical activity that is planned, structured and repetitive, with the goal to obtain or maintain physical fitness (42). Several systematic reviews and meta-analyses have extensively evaluated the literature investigating the effect of exercise following a cancer diagnosis. All of them come to the same conclusion, that exercise training is beneficial both during and following the completion of adjuvant therapy in adult cancer patients (43–48). Evidence on the beneficial effect of exercise has been established for relatively few cancer diagnoses and research in this area is primarily conducted in patients with breast and colon cancer (43–48). Research on exercise in lung cancer has previously been given low priority, partly due to the low survival rate. In the last 10-15 years, the amount of research evaluating exercise interventions for patients with lung cancer has grown (49,50).

**Preoperative Evaluation and Exercise**

Danish and international clinical practice guidelines recommend that all patients undergo preoperative assessment of the risks of surgery (17,25). In Denmark, this risk assessment includes the following: 1) assessment of lung function, which entails: spirometry and measuring the lung carbon monoxide transfer factor, regardless of spirometric values; 2) calculation of the predicted postoperative lung function (using ventilation scintigraphy, perfusion scintigraphy or quantitative computed tomography (CT) scan; and 3) general functional assessment using either a six-minute walk distance (6MWD) test (a distance of >400 meter is a cut-off for good function) or a cardiorespiratory exercise test to measure volume of peak oxygen consumption (VO₂peak) (using >15 mlO₂/kg/min as a cut-off for good function) (25). The guidelines use the term “consider” for the assessment of functional capacity (25), and due to restricted availability, these tests are not used routinely in assessing the risk of surgery. When maximal oxygen consumption
(VO₂max) is <10mL/kg/min, patients are potentially at high risk of serious postoperative complications, which is why lobectomy and pneumonectomy are usually not recommended (51). In addition, international guidelines also recommend: assessment for operative mortality using a global risk score, such as a thoracoscore to estimate the risk of death and a risk assessment for cardiovascular morbidity using the American College of Cardiology guidelines as a basis for assessing perioperative cardiovascular risk (25).

For patients assessed as unfit for surgery, the prognosis changes dramatically since the treatment for lung cancer is no longer curative but palliative (52). Preoperative exercise offered to NSCLC patients attracts attention because it may move patients from being unfit for surgery to being fit for surgery, consequently changing the prognosis of these patients dramatically (53). Preliminary evidence suggests that higher exercise capacity at the time of a diagnosis of NSCLC is related to prolonged survival (43,54). A recent Cochrane meta-analysis found that compared to no exercise training, preoperative exercise training showed a 67% reduction in the risk of developing postoperative pulmonary complications risk ratio (RR) 0.33, 95% confidence interval (CI) 0.17 to 0.61). This meta-analysis found that preoperative exercise decreased the duration of intercostal catheter use and postoperative length of hospital stay but also that exercise capacity and lung capacity, expressed as 6MWD and forced vital capacity (FVC), improved in people undergoing lung resection (53). Previous studies have demonstrated lower levels of exercise behavior among patients diagnosed with NSCLC compared to healthy individuals at the time of diagnosis, which supports the need for a preoperative exercise intervention (55).

**Postoperative Exercise**

Resection of the lung immediately affects cardiorespiratory capacity since lung tissue is removed, reducing the ventilatory and diffusion capacity (56). Furthermore, the cardiorespiratory capacity is affected negatively due to prolonged periods of bed rest, pain and inactivity (57). The level of physical activity is found to be lower from time of diagnosis and during the first six months following a diagnosis of NSCLC compared to healthy age-matched controls (55). Caspersen et al (1985) define physical activity as: “…a bodily movement by skeletal muscles that results in energy expenditure” (42). Additionally, there is an age-related limitation to exercise since cardiorespiratory capacity declines by around 10% per decade in healthy adults (58,59). Also, comorbidity adversely affects cardiorespiratory capacity and contributes to the aging effects (60). Evidence shows that postoperative exercise for NSCLC patients is both safe and associated with improvement in cardiorespiratory capacity and self-reported outcomes, such
as HRQoL and fatigue (49,61). Still, more research is required to understand the potential effect of exercise on NSCLC patients and to determine how individual components such as mode, intensity, frequency, duration and timing may contribute to the effect (49). In addition, patients who are offered adjuvant chemotherapy after surgery for lung cancer are even more exposed to deconditioning since chemotherapy is associated with an acute and long-term impact on the cardiovascular system (62). The direct effects of NSCLC chemotherapeutics on cardiopulmonary function in combination with lung surgery are not fully understood, although platinum-based regimens are found to reduce FEV₁ and cause anemia in patients with advanced lung cancer, affecting the physiologic adaptations to exercise (63). Research on the effect of exercise in patients with operable lung cancer receiving chemotherapeutics is diverse. One 2008 study indicated greater improvements in cardiopulmonary capacity and HRQoL endpoints among patients not receiving adjuvant chemotherapy (64). Another study showed an increase in median peak oxygen uptake of 2.6 mL/kg/min (range –0.9 to 3.9) in the exercise group compared to a decrease of 0.4 mL/kg/min (range –7.9 to 10.2) in the control group. The same study also found that none of the patients receiving chemotherapy were able to exercise during the last course of adjuvant chemotherapy, but seven out of nine patients successfully continued exercising subsequently (65). For an exercise intervention to be successful, it is important that the cancer patients adhere to the exercise program, but adherence during and after cancer treatment has previously been reported as challenging (66). Cyarto et al (2006) define adherence as: “… the degree of attendance or completion of prescribed exercise sessions” (67). A low adherence rate could also reflect the applicability of the exercise intervention in daily practice (68).

Theoretical Framework

The theoretical framework of the present thesis is inspired by the multiple-hit hypothesis and a concept called oxygen cascade, described by Lee Jones in 2007 and 2009 respectively (60,69). The multiple-hit hypothesis, a schematic presentation of cancer patients and their progress through the selected treatment regimens, highlights the fact that cancer and the treatment of cancer will have a negative impact on the patient’s cardiovascular system and increase the risk of cardiovascular disease dramatically (69). Oxygen cascade describes the negative reaction to the treatment of cancer that affects the functional capacity of cancer patients (50). Another theoretical framework is a concept called the teachable moment, a term used to describe the transition that takes place when patients are diagnosed with cancer (53). This transition can modify barriers and motivate the patient. Notably, the time of diagnosis has previously proven to
be an important health event that can also modify barriers and motivate patients to adopt a healthier lifestyle (70), possibly serving to improve participation in perioperative rehabilitation. The timing of initiating exercise may also influence outcomes in patients resected for NSCLC.

**Organizational Context**

Figure 1 presents the rehabilitation services at the municipal rehabilitation centre in Copenhagen. Of these interdisciplinary interventions available, exercise is to date the most well documented as being beneficial for a variety of cancer patients, including patients with lung cancer (48,49,71). However, there are still many unknown questions regarding the optimal exercise program for patients with different cancer diagnoses and the influence of comorbidity (61). The Danish Health Authority (DHA) has emphasized the need to clarify which exercise interventions should be offered to patients with different cancer diagnoses and the timing of the exercise interventions in the treatment trajectory (72,73).

<table>
<thead>
<tr>
<th>Cancer patients’ course of disease</th>
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</thead>
<tbody>
<tr>
<td>Diagnosis</td>
</tr>
<tr>
<td>Cancer treatment</td>
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<tr>
<td>Follow-up</td>
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</tbody>
</table>

![Diagram of rehabilitation process](image)

**MUNICIPAL REHABILITATION FOR PATIENTS WITH CANCER**

- **Assessment Interview**
  - An individualized rehabilitation program is planned jointly by the patient and contact person

- **Physical activity**
  - Strength and cardiovascular training, stability training, nature activities, running teams

- **Dietary guidance**
  - Individual and group counseling, cooking

- **Social counseling**
  - Individual counseling, rights, return to work

- **Patient education**
  - Disease/medication, life-style issues, coping skills, experience sharing

- **Other options**
  - Smoking cessation, meetings for relatives, counseling, yoga and mindfulness provided by the Danish Cancer Society

**Figure 1. Municipal rehabilitation for patients with cancer at the Copenhagen Centre for Cancer and Health**

In order to ensure that exercise and rehabilitation guidelines for cancer patients are applicable to daily practice, it is important that the research is carried out in close collaboration with the clinic
and, preferably, in the clinical setting (74). Research in a clinical setting can be challenging since it may include a great deal of coordination between various sectors (75). Figure 2, which presents a summary of the collaborating departments and their role in the treatment trajectory of NSCLC patients, illustrates the complexity of the PROLUCA research project.

Objectives

The overall aim of this thesis was to evaluate the safety and feasibility of preoperative and early postoperative non-hospital rehabilitation, with focus on exercise in patients with NSCLC. Subsequently, the aim was also to evaluate the effect of early-initiated postoperative exercise compared to late-initiated exercise in the same population.
Hypotheses

1. Preoperative home-based exercise is safe and feasible in patients with operable lung cancer (Paper II)
2. Early postoperative rehabilitation with focus on exercise is safe and feasible in patients with lung cancer, in a non-hospital setting (Paper II)
3. Improvement in physical capacity and HRQoL in patients following surgery for lung cancer is achievable in a rehabilitation program in a non-hospital setting (Paper II-III)
4. A systematic literature search and review of the evidence will reveal that early initiation of exercise, within two weeks following lung resection, will be more effective than exercise initiated later (Paper IV)

Methods and Materials

Structure of the PROLUCA Project

The project Perioperative Rehabilitation in Operable LUng CAnceR Patients (PROLUCA) was developed in 2011. The randomized clinical trial (RCT) named PROLUCA RCT I aimed at identifying the optimal timing of exercise to improve VO\textsubscript{2}peak in postoperative NSCLC patients. This RCT consisted of a preoperative home-based intervention combined with a postoperative rehabilitation program (Paper I). Due to an unexpected low recruitment rate, the study design in PROLUCA RCT I was adjusted to the PROLUCA feasibility study, which focused on recruitment to a pre and postoperative intervention, described in detail later in this section of the thesis and in Papers II-III. In addition, a comprehensive literature search and a systematic review were performed, as presented in Paper IV. Based on the results from the PROLUCA feasibility study and the systematic review, a new RCT comparing early versus late postoperative exercise interventions, was designed and conducted (PROLUCA II, not included in the present thesis). Figure 3 presents the overall structure of this thesis.
In order to reject or verify the four hypotheses, three different research designs were applied in this PhD thesis. Paper I describes the setup in the PROLUCA RCT I, while Papers II-III examine a single-centre four-arm prospective randomized controlled feasibility study in 40 patients with operable lung cancer. Finally, Paper IV is a comprehensive systematic review and meta-analysis of the available evidence from RCT comparable studies.

**Methods (Paper II-III)**

Recruitment and Eligibility

All patients were recruited from Department of Cardiothoracic Surgery, Copenhagen University Hospital, Rigshospitalet. Potential subjects were identified and screened for eligibility and informed by research coordinators at the involved hospitals (Bispebjerg University Hospital and Gentofte University Hospital). After referral to curative lung cancer surgery, the subjects were contacted by telephone and provided with a review of the study. If the subjects accepted to participate, the baseline assessment was performed at Copenhagen Centre for Cancer and Health. All patients had either histologically or cytologically confirmed NSCLC, stage I-IIIA (seventh TNM classification system) (22), or strong substantiated suspicion of NSCLC, were at least 18 years of age, had World Health Organization (WHO) performance status 0–2 (76), were a resident of the City of Copenhagen or a surrounding municipality, were able to read and understand Danish, and were approved by the primary surgeon. The exclusion criteria were: presence of metastatic disease or surgical inoperability, postoperative histologically verified cancer disease different from lung cancer or no malignant disease at all, severe cardiac disease,
and contraindications to maximal exercise testing as described by the American Thoracic Society (ATS) and by American College of Sports Medicine (ACSM) (77,78). From April 2012 to May 2013, forty patients age ≥18 years with NSCLC stages I to IIIa proven by biopsy and appointed for curative lung cancer surgery at the Department of Cardiothoracic Surgery were included in the feasibility study (Paper II-III).

**Group Allocation (randomization)**

In the feasibility study (Paper II-III), patients were individually randomized and allocated, after completion of baseline assessments, to one of four intervention groups. The random allocation sequences were executed externally by the Copenhagen Trial Unit, Centre for Clinical Intervention Research and concealed from all the employees in the study. A permuted block design with an allocation weight of 1:1:1:1 was used to create the group assignments.

**Interventions**

Figure 4 presents the timeline for the PROLUCA feasibility study. Group one did preoperative home-based exercise combined with postoperative rehabilitation initiated two weeks after surgery, while group two did preoperative home-based exercise combined with postoperative rehabilitation initiated six weeks after surgery. Group three had postoperative rehabilitation initiated two weeks after surgery and group four functioned as a control group with postoperative rehabilitation initiated six weeks after surgery, which is a widespread practice in Denmark. The intervention group assignment was not altered based on the participant’s adherence to the randomly allocated study arm. The intention-to-treat analysis included all randomized participants in their randomly assigned allocations, which included patients who were lost to follow-up. To make sure that the groups were similar at baseline, patient randomization was stratified based on type of surgery, i.e., VATS versus thoracotomy surgery.
Figure 4. Timeline for the PROLUCA feasibility study

Outcome Measures (Paper II-III)

The primary outcomes in the PROLUCA feasibility study (Paper II-III) were safety and adherence to the intervention. Secondary outcomes were cardiorespiratory capacity, muscular strength, walking distance, pulmonary capacity and patient-reported outcomes. All data were collected according to the data assessment schedule presented in Table 1.

Table 1. Data assessment schedule in the PROLUCA feasibility study
<table>
<thead>
<tr>
<th>Measurement</th>
<th>Baseline&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Follow-up&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Follow-up&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Follow-up&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Follow-up&lt;sup&gt;e&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthropometric data and cancer disease</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Physiological Measurements</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<tr>
<td>Six-minute walk distance (6MWD)</td>
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<td>X</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Patient-Reported Outcome</td>
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<tr>
<td>Health-related quality of life (FACT-L)</td>
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<td>X</td>
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<td>Symptoms and side effects (EORTC-LC13)</td>
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<td>Anxiety and depression (HADS)</td>
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<td>Well-being (SF-36)</td>
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<td>Distress thermometer</td>
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<td>Lifestyle</td>
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<td>Sickness absence and work status</td>
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<td>Other Measurements</td>
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<tr>
<td>Serious adverse events / adverse events</td>
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<td>Adherence to exercise</td>
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<td>Postoperative complications (30 days)</td>
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<tr>
<td>Duration of hospitalization</td>
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<td></td>
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<td></td>
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<tr>
<td>Survival, histological diagnosis and TNM stage</td>
<td></td>
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<td>X</td>
</tr>
</tbody>
</table>

<sup>a</sup> Baseline (0 week)  
<sup>b</sup> Pre-operation (the day before surgery)  
<sup>c</sup> Post-intervention (14/18 weeks after surgery)  
<sup>d</sup> Six months after surgery  
<sup>e</sup> One year after surgery

**Safety and Adherence**

Safety in the present feasibility study was defined as number of serious adverse events or adverse events and was registered by the staff in charge of the exercise sessions. Prior to every exercise session, a cancer nurse specialist measured blood pressure (BP) and asked patients if they had any symptoms consistent with side effects from the surgery, adjuvant treatment or the last exercise session. Exercise that same day was cancelled if the patient experienced any of the following symptoms/signs: fever (temperature >38°C Celsius); diastolic BP <45 or >110
(measured); resting HR >110 (measured) or dizziness. For patients in chemotherapy, training restrictions given to the patient from the hospital staff, based on levels of platelets <50×10⁹/l, leucocytes <1.0×10⁹/l (79,80) or low levels of hemoglobin, were asked for. Postoperative complications emerging within 30 days after surgery were registered based on medical records. Adherence to exercise in the present thesis was defined as number of attended exercise sessions. The attendance was registered by the patients at every exercise session in an exercise diary logbook kept at the rehabilitation centre. If the patients did not show up for an exercise session, they registered the reason for not attending. Adherence to the exercise intensity was monitored by HR monitor and software (Polar Team, Polar Electro Oy, Professorintie 5, 90440 Kempele, Finland) and an exercise diary logbook.

The following strategies were used to maximize adherence in all four intervention groups: telephone-based follow-up, free parking in front of the centre, and remuneration for transport expenses. A high degree of scheduling flexibility allowed patients to perform tests at a convenient time so that they were prepared for competing demands, such as medical appointments, work and family commitments.

**Cardiorespiratory Capacity**

The maximum oxygen uptake test is considered as a gold standard measurement of cardiorespiratory capacity and can be expressed as VO₂peak or VO₂max (81,82). VO₂peak is commonly used in patient populations and VO₂max is commonly used in healthy populations (82). In the feasibility study, cardiorespiratory capacity (VO₂peak) was evaluated by an incremental test using an electromagnetically braked cycle ergometer (Lode Corival Ergometer©) where inspired and expired gases were analyzed breath-by-breath by a metabolic cart (JAEGGER MasterScreen CPX©), patients began pedaling at seven watts and resistance increased 10 watts every minute according to a predefined ramp protocol until exhaustion or a symptom-limited VO₂peak was achieved (e.g. pain, dizziness and anxiety). Calibration of the equipment was performed prior to every test.

**Muscular Strength**

Muscular strength refers to the amount of force a muscle can produce with a single maximal effort. In the feasibility study, muscle strength was measured by one repetition maximum (1RM), defined as the greatest resistance that could be moved using the proper technique in a Technogym™ leg press and Technogym™ chest press (83). Prior to testing, every patient did a short warm-up, after which the resistance was increased so that the patients reached the
maximum in fewer than 10 attempts (to avoid fatigue). These procedures were standardized for both leg and chest presses and the 1RM method is found reliable for measuring muscular strength in upper and lower extremities in a healthy population (60-87 years) (84).

**Walking Distance**

Walking distance was measured by a test of 6MWD carried out over a pre-measured distance of 22 m and in accordance with the ATS statement (85). Participants were instructed to walk as far as possible for six minutes, with feedback given on how much time remained after each minute. 6MWD is one of the most commonly used measures of functional capacity in lung care and has demonstrated good reliability (test-retest reliability and consistency) and validity (criterion and construct validity) in patients with lung cancer and in chronic obstructive lung disease (41, 86–90). Participants were monitored prior to and as close to termination of the test as possible with portable pulse oximetry measuring arterial O\textsubscript{2} saturation (Nellcor, OxiMax N-65©), which provides the most accurate non-invasive assessment of blood arterial O\textsubscript{2} saturation levels.

**Pulmonary Capacity**

In the feasibility study, pulmonary capacity was specified by assessing FEV\textsubscript{1}, the ratio of FEV\textsubscript{1} compared with predicted values (FEV\textsubscript{1}%) and the FVC using a Triple V digital volume sensor© connected to JAEGGER MasterScreen CPX©. All pulmonary tests were carried out in accordance with ATS guidelines, recording the best of three attempts carried out in a standing position and performed with a nose clip, just as the patients were enthusiastically coached throughout the task to perform their best using appropriate body language and phrases such as “keep going” (91).

**Patient-Reported Outcome Measures**

**European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire**

**Cancer 30 (EORTC QLQ-C30) / Lung Cancer 15 (EORTC QLQ-LC15)**

The EORTC QLQ-C30 is a 30-item disease-specific multidimensional HRQoL questionnaire designed for use in cancer patient populations. It is composed of both multi-item scales and single-item measures that contain five independently functional subscales (physical, role, cognitive, emotional and social); three symptom subscales (fatigue, pain and nausea and vomiting); and a global health/QoL subscale. Furthermore, it also comprises six single items assessing symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation and diarrhea). All EORTC items are rated on a four-point Likert scale ranging from 1 = “Not at all” to 4 = “Very much” and the raw EORTC scores are translated into
scores ranging from 0 to 100. A high score for a functional subscale or for the global health status represents a high QoL, while a high score for a symptom scale represents a high level of symptomatology. Lung cancer symptoms and treatment-related side effects were further assessed using the EORTC QLQ–LC13, which is an additional page to the EORTC-QLQ specifically designed to cover a wide range of lung cancer patients varying in disease stage and treatment modality (92). The lung cancer-specific module, EORTC QLQ-LC13, comprises 13 questions assessing lung cancer associated symptoms (cough, hemoptysis, dyspnea and site-specific pain); treatment-related side effects (sore mouth, dysphagia, peripheral neuropathy and alopecia); pain; and medication. This questionnaire is designed for use in a wide range of lung cancer patients varying in disease stage and treatment modality, including chemotherapy and/or radiotherapy (93).

**Functional Assessment of Cancer Therapy–Lung (FACT-L) questionnaire**

HRQoL was also assessed using the FACT-L questionnaire, which is multidimensional and specifically addresses patients with lung cancer. It is a combination of the 27-item FACT-G and the nine-item lung cancer subscale (LCS). FACT-G contains four general subscales: physical well-being; social/family well-being; emotional well-being; and functional well-being, while LCS contains one lung cancer symptom-specific subscale that includes shortness of breath, loss of weight and chest tightness. A total FACT-L score is obtained by summing the FACT-G score with the LCS. This ranges from 0 to 136. All FACT-L items are rated on a five-point Likert scale ranging from 0 = “Not at all” to 4 = “Very much”, with scores ranging from 0-24 (emotional well-being), 0–28 (other four subscales), 0–84 (trial outcome index) and 0-136 (total score) (25,94). Higher scores represent better QoL or fewer symptoms (95).

**36-item Short Form Health Survey (SF-36)**

General well-being was assessed using the 36-item SF-36 version 1, standard recall (four weeks) questionnaire, which is a patient-reported survey of general health status consisting of eight domains clustered to form two higher-order component scores, one on physical health and the other on mental health. The former consists of four subscales: physical functioning; bodily pain; general health perception; and physical role functioning, while the four subscales in the latter comprise: emotional role functioning; social role functioning; mental health; and vitality. Items are scored primarily on a five-point Likert scale, with subscale scores from 0-100 score and component scores from 0-60. Higher the scores indicates better health (96,97).
**Hospital Anxiety and Depression Scale (HADS)**

Anxiety and depression were assessed using HADS, a 14-item questionnaire designed to measure general anxiety and depression in patients with physical illness (98). One half of the 14 items addresses anxiety and the other depression, forming two scores ranging from 0-21 (98). Scores are interpreted as: normal (0-7), mild (8-10), moderate (11-14) or severe (15-21) symptoms of anxiety and depression (98).

**The National Comprehensive Cancer Network (NCCN) Distress Thermometer**

The NCCN® Distress Thermometer was used to assess physical distress in general, combined with a ranking of physical problems, practical problems, family problems, emotional problems, and spiritual/religious concerns. The NCCN® Distress Thermometer is not yet tested for validity in patients with NSCLC; however, it is found to be valid in a population diagnosed with breast cancer. This questionnaire consists of a single item, with responses ranging from 0 to 10 (99).

**Multidimensional Scale of Perceived Social Support (MSPSS)**

The 12-item MSPSS was used to assess social support, with items scored on a seven-point Likert scale ranging from 1 = “Very strongly disagree” to 7 = “Very strongly agree”. The scale yields three subscale scores for: family, friends and significant others, and a total perceived social support score that has a summary score (100,101). In addition to the MSPSS questionnaire, responses to seven questions on the relationship with other cancer patients were collected that addressed support, network, social interactions and sharing hope for the future.

**Preoperative Exercise Training Protocol (Paper II-III)**

The preoperative exercise program contained a home-based exercise program that was individually designed according to functional status and comorbidity for each patient randomized to the preoperative intervention based on the physical activity guidelines for cancer patients recommend by the DHA and the ACSM (36,73). The program aimed at cardiovascular exercise of a moderate to vigorous intensity (~60-80% of maximal heart rate (HRmax)) for at least 30 minutes every day until surgery. To assure the exercise intensity, the patients were instructed to do exercises that made it impossible to talk because of breathlessness. Jointly with the patient, a suitable modality of exercise was chosen to be the program’s main activity, e.g., walking/running, stair climbing or bicycling. The exercise period varied in length based on the time available before surgery. The preoperative exercise was monitored by HR monitor and
Postoperative Exercise Training Protocol (Paper II-III)

Trained physiotherapists and cancer nurse specialists supervised the postoperative exercise program following principles recommended by ACSM (36,102). The ACSM guidelines were developed based on existing recommendations for exercise from ACSM, the American Heart Association (103) the American Cancer Society (104), and the physical activity guidelines for the American population described by the United States Department of Health and Human Services (105). It is recommended that exercise prescriptions are individualized according to treatment of the cancer patient and their general health condition (36). As a result, the postoperative exercise programs were individually tailored and consisted of supervised resistance exercise and group-based cardiorespiratory exercise twice a week (60 minutes/session) on non-consecutive days for 12 weeks, for a total of 24 sessions. The postoperative exercise included the following: warm-up (five minutes) and cardiorespiratory exercise (25 minutes) on an ergometer bike (BODY BIKE Classic Supreme©) and individually tailored resistance exercise (25 minutes) carried out using five machines (Technogym™): the leg press, chest press, leg extension, pull to chest and pull down (upper body).

The cardiorespiratory exercise consisted of high intensity interval exercise, including a warm-up period in which the participants aimed at reaching a level at 85% of their individually determined HRmax (5 minutes) followed by a short rest (1 minute). The duration of the high intensity interval exercises was 25 minutes. At each interval (1-2 minutes), the participants aimed at reaching a level of 85-100% of their individually determined HRmax in each interval, followed by a short rest (1 minute). The high intensity interval exercise was followed by a cool down period (2 minutes). After the cardiorespiratory exercise, supervised breathing exercises, stretching and tension-release techniques were performed for approximately five minutes (106). The first four weeks, of the intervention, the cardiorespiratory intensity of ~50-60% of individual determined HRmax and in the next eight weeks, the intensity increased to a moderate to high intensity at ~70-90%. The exercise protocol prescribed resistance exercise comprising three sets per exercise at an intensity of ~60-80% of 1RM two times a week for 12 weeks. Every other week, the resistance was progressively increased and the number of repetitions reduced, starting out at 12 repetitions in three sets, progressing to 10 repetitions in three sets, to a final eight
repetitions in three sets. The postoperative exercise intervention was combined with access to the other rehabilitation services available at the municipal rehabilitation centre in Copenhagen. Prior to the first postoperative exercise session, every patient was asked about rehabilitation needs according to a professional rehabilitation guide covering the following topics: disease specific, social, network, relatives, psychological, existential, diet, smoking, alcohol, physical activity, sexuality, sleep and stress. The theoretical framework by WHO on International Classification of Functioning (2001) (107), Bandura et al’s (1977) (108) self-efficacy theory and Miller et al’s (1996) (109) motivational interviewing formed the basis of this rehabilitation guide. The postoperative exercise intervention comprised 24 group-based exercise sessions, three individual counseling sessions and three group-based lessons in health-promoting behavior. If the patients had special needs in terms of smoking cessation, nutritional counseling or patient education, this was also offered as part of the rehabilitation. Figure 1 presents the rehabilitation services available at the municipal rehabilitation centre in Copenhagen.

Methods and Materials in the Systematic Review (Paper IV)

Carried out in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (2011) and reported in accordance with the PRISMA statement guidelines, Paper IV is a systematic review registered in the PROSPERO database under the registration number CRD42016027412 (110,111).

Search Strategy

A literature search matrix was used for MEDLINE and was adapted for use in the other databases: Embase, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL and PEDro (Table 2). The search strategy focused on two overall clusters: NSCLC and rehabilitation, with their associated synonyms and combined with AND, as shown in Table 2. No limitations were used in the electronic searches to avoid unintended exclusion of relevant trials. In order to identify additional trials, all reference lists of all primary studies and review articles were screened. Experts in the field of exercise and NSCLC were contacted in order to identify unpublished research. A search was also done of clinicaltrials.gov to identify ongoing, as yet unpublished trials.
### Table 2. Matrix of the search strategy for MEDLINE via PubMed

<table>
<thead>
<tr>
<th>‘NSCLC’</th>
<th>AND</th>
<th>‘Rehabilitation’</th>
</tr>
</thead>
</table>
exercise) initiated within one year after lung resection. Supervised and/or unsupervised exercise performed individually or in groups was also eligible intervention criteria. The type, intensity, frequency and duration of the exercise interventions were not a constraint but were recorded where possible. Control groups were considered eligible if they contained non-intervention control, usual care, waiting-list control or add-on treatments. Primary outcomes in the studies should be cardiorespiratory capacity measured by an maximum exercise capacity test (e.g. VO\textsubscript{2peak} or VO\textsubscript{2max}) or 6MWD measured as a primary or secondary outcome. Secondary outcomes in the studies were HRQoL measured by one of the following questionnaires: Generic SF-36 (97), cancer-specific EORTC QLQ-C30 (93) and the disease-specific patient-reported outcome FACT-L (95). All references identified were imported into the web-based software platform covidence.org. Selection of trials, risk of bias assessment and extraction of data were managed in this software. Two review authors (first and second author Paper IV) independently screened titles and abstracts, after which full-text screening was undertaken using the search strategy to determine eligibility for inclusion. Their decisions were recorded and disagreements were resolved by consensus. Two review authors (first and second author Paper IV) independently extracted data using a predefined form based on the Cochrane Collaboration’s checklist of items to consider in data extraction. Data comprised details of the trials, participant characteristics and results at postoperative time points. Disagreements on extraction of data were resolved by discussion. In cases of missing data, the authors of the trials were contacted and asked if they could provide the missing details. The review process continued without the information if the trial authors could not provide the requested information within one month. Results from intention-to-treat analyses were prioritized in the analysis of the present review and, if possible, results on missing individuals were recorded as well.

**Risk of Bias and Quality of Evidence Assessment**

Two review authors (first and second author Paper IV) independently assessed the risk of bias for all of the included trials, evaluated as either high, low or unclear risk of bias, using the Cochrane Collaboration’s tool for assessing risk of bias (111). Quality of evidence was assessed using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (2004) (112). The body of evidence identified for each outcome was rated as high, moderate, low or very low quality based on the following five factors: risk of bias, indirectness, inconsistency, imprecision and publication bias. Disagreements were resolved by discussion, or when
necessary, by a third reviewer (third author Paper IV), who was consulted and then agreement reached.

### Statistical Considerations

#### Data Analysis in the Feasibility Study (Paper II-III)

Descriptive statistics were used to assess the safety and adherence. Baseline values of the study populations were compared to values measured at post-intervention, which is 14 weeks post surgery in the early intervention groups and 18 weeks post surgery in the late intervention groups, and one-year follow-up. The values are expressed as mean ± standard deviations (SD). Paired $t$-tests were used to compare the physical outcomes between the early postoperative exercise intervention and the late postoperative exercise intervention. In the analysis, groups one and three were merged into one group (early postoperative exercise) and group two and four were merged into one group (late exercise intervention group). Paired $t$-tests were also performed to reveal trends in patients who exercised for more or less than 70% of the exercise sessions. A cut-off at 70% for adherence to exercise was used as a validity criteria for the included RCT in the ACSM guidelines for cancer patients (36). The overall effect of time on the patient-reported outcomes was evaluated using repeated measures analysis of variance (ANOVA) and was calculated using the mixed linear models. Estimated scale mean scores were reported as the mean with corresponding 95% CIs and compared to aged-matched reference data when available. The reference data was a random sample of 3,080 individuals, drawn from the Danish Civil Registration System for EORTC QLQ-C30 (113), while for SF-36 (114) it was a random sample of 6000 individuals, also drawn the Danish Civil Registration System. To analyze the changes in smoking, alcohol and physical activity habits, logistic, Poisson and multinomial logistic regression models were used, respectively. The clustered nature of the data was taken into account using generalized estimating equation (115,116), implemented in the generalized linear model (GENMOD). Wald tests were used to evaluate changes over time. Statistical significance was set at $p<0.05$ and all statistical analyses were conducted using SAS software, version 9.4 of the SAS System (Copyright © 2014, SAS Institute Inc., Cary, NC, U.S.A.).
Statistical Analyses in the Systematic Review (Paper IV)

For continuous outcomes, standardized mean differences (SMD) and the corresponding 95% CI were used for analysis as the included studies assessed the outcomes of interest in a variety of ways. To calculate the SMDs, the mean change scores and the corresponding SDs were extracted from the trials when these were reported. If mean change scores and/or SDs of the mean change scores were not reported, these were calculated based on the baseline and follow-up means and SDs, but only in cases where they were not provided, as recommended in the Cochrane Handbook (2011) (111). The calculated SDs of the mean change scores from baseline were estimated by imputing a correlation coefficient in the formula below to allow the use of paired data (117,118):

\[
SD_{change} = \sqrt{SD_{baseline}^2 + SD_{follow-up}^2 - (2 \times corr \times SD_{baseline} \times SD_{follow-up})}.
\]

When calculating the SDs of mean change scores, a correlation coefficients (r) is needed. As the correlation coefficients were not reported in the studies, correlation coefficients from similar populations were used concerning the following outcomes: VO\textsubscript{2}peak r=0.927 (119), 6MWD r=0.93 (89), SF-36 physical and mental component scores r=0.94 (120) and the EORTC QLQ-C30 physical functioning score r=0.85 (121). In cases with a discrepancy between the reported mean change scores and the reported data for baseline, the calculated mean change scores were used for analysis. If more than two time points were reported in the included studies, the follow-up closest to 12 weeks after initiation of the intervention, was selected as “short-term”. Long follow-up beyond six months was selected as “long-term”. The effect was interpreted based on the magnitude of SMD, using the Cohen’s guidelines: no effect under 0.2; small effect SMD = 0.2; medium SMD = 0.5; and large SMD = 0.8 (122).

All statistical analyses and forest plots were conducted in StataCorp 2013, Stata Statistical Software: Release 13 (StataCorp LP, College Station, TX, U.S.A.). Risk of bias summary and graphs were conducted in Review Manager (RevMan), version 5.3, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014. A summary of the findings in Paper IV was generated in GRADEpro GDT (GRADEpro Guideline Development Tool, McMaster University, 2015 (developed by Evidence Prime).

To calculate the overall treatment effect, a random-effects model was chosen using DerSimonian and Laird’s method (123). Clinical heterogeneity was considered by assessing differences among the trials concerning patient populations (e.g., age, degree of surgery and comorbidities) and exercise interventions (e.g., type, intensity, frequency, duration). The percentage of the
variability in effect estimates due to heterogeneity was evaluated using the I-squared test ($I^2$), which is suitable in the present review because it is independent of the number of trials. A higher percentage indicates statistical heterogeneity, and approximately 25% or less is considered to be low, around 50% is considered as moderate and 75% or above is high. Heterogeneity above 50% is interpreted as a considerable level of heterogeneity (124).

**Sensitivity Analysis**

To assess the effect of trials initiating exercise interventions early (within the first two weeks after surgery for lung cancer) compared to the effect of trials initiating exercise interventions later than two weeks after surgery, a sensitivity analysis was carried out between trials initiating exercise interventions before two weeks after surgery and trials initiating exercise later than two weeks. This sensitivity analysis was conducted on short-term follow-up. A cut-off at two weeks after surgery was a pragmatic approach based on clinical reflections concerning tissue healing and when exercising would be safe. The sensitivity analysis aimed at identifying the optimal time of onset of postoperative rehabilitation to patients with NSCLC.

**Ethical Considerations**

The feasibility study (Paper II-III) was reported according to the CONsolidated Standards of Reporting Trials (CONSORT) statement for non-pharmacologic interventions and the World Medical Association Declaration of Helsinki Declaration (125,126). All participants gave informed written consent prior to participation in any study procedures. The Danish National Committee on Health Research Ethics (H-3-2012-028) and the Danish Data Protection Agency approved the handling of data (2007-58-0015) in the feasibility study.

**Results from the Feasibility Study (Paper II-III)**

**Patient Characteristics and Recruitment**

The final number of patients screened for eligibility and referred for surgery was 180, of whom 124 were eligible. A total of 40 patients (32%) were included in the feasibility study and randomized as presented in the flow chart in Figure 5. Table 3 presents the characteristics of the 40 patients. The patients had a mean age of 68 years (table 3), the majority of them were retired (70%), 15% were currently employed, 5% unemployed, 5% enrolled in education, 2.5% off work
sick and 2.5% did not answer the question on working status. The most frequent comorbidities were hypertension, dyslipidemia, rheumatic disease and COPD. Sixteen patients had more than two comorbidities and five patients had no comorbidities. Twenty-five percent currently smoked, 70% were ex-smokers and 5% had never smoked. Twenty-eight percent stated that their level of alcohol consumption was above the DHA’s recommended level, which is more than seven units per week for females and over 14 units per week for males. The majority of patients (78%) had gone through VATS and nine patients (22%) had undergone a thoracotomy. Thirty-three percent (13 patients) were treated with adjuvant chemotherapy. The extent of resection was as follows: lobectomy (83%), pneumonectomy (2%), bilobectomy (5%), wedge resection (8%) and VATS segmental resection (2%). Patients who did not attend the study primarily reported that the reason was either due to logistical problems or concerns about their upcoming surgery (Figure 5).
Figure 5. Flow PROLUCA feasibility study

Table 3. Baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total n=40</th>
<th>Early exercise n=18</th>
<th>Late exercise n=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median</td>
<td>68 (36-85)</td>
<td>67 (36-79)</td>
<td>71 (56-86)</td>
</tr>
<tr>
<td>(range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 1</td>
<td>Group 2</td>
<td>Group 3</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>24 (60%)</td>
<td>10 (56%)</td>
<td>14 (64%)</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean (SD)</td>
<td>25 (5)</td>
<td>25 (5)</td>
<td>25 (4)</td>
</tr>
<tr>
<td>Academic professional degree &lt;3 years, n (%)</td>
<td>17 (43%)</td>
<td>6 (33%)</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Smoking history, n=40 (groups 1 and 3, n=18; groups 2 and 4, n=22)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoking, n (%)</td>
<td>10 (25%)</td>
<td>7 (39%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Never smoked, n (%)</td>
<td>2 (5%)</td>
<td>1 (6%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>28 (70%)</td>
<td>10 (55%)</td>
<td>18 (81%)</td>
</tr>
<tr>
<td>Years smoking, mean (SD)</td>
<td>41 (15)</td>
<td>44 (12)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>Presence of comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(five patients had none of the comorbidities below)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (38%)</td>
<td>6 (33%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>9 (23%)</td>
<td>4 (22%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (15%)</td>
<td>3 (17%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>8 (20%)</td>
<td>2 (11%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Rheumatic diseases, n (%)</td>
<td>12 (30%)</td>
<td>5 (28%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Previous other type of cancer, n (%)</td>
<td>6 (15%)</td>
<td>4 (22%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>4 (10%)</td>
<td>1 (6%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Medication, number of drugs, median (range)</td>
<td>3 (1-6)</td>
<td>2 (1-5)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁, L/s, mean (SD)</td>
<td>2.4 (0.6)</td>
<td>2.5 (0.5)</td>
<td>2.3 (0.6)</td>
</tr>
<tr>
<td>FEV₁, L/s, % predicted (SD)</td>
<td>94 (23.7)</td>
<td>95 (26.1)</td>
<td>93 (22.2)</td>
</tr>
<tr>
<td>FEV₁ /VC, %, mean (SD)</td>
<td>67.4 (8.7)</td>
<td>68 (6)</td>
<td>68 (10)</td>
</tr>
<tr>
<td>Cardiorespiratory capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitness, mL/kg/min, mean (SD)</td>
<td>19.4 (5)</td>
<td>21.5 (6)*</td>
<td>17.6 (4)*</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Peak oxygen uptake, L/min, mean (SD)</td>
<td>1.40 (0.39)</td>
<td>1.53 (0.33)*</td>
<td>1.28 (0.40)*</td>
</tr>
<tr>
<td>6MWD Meter (SD)</td>
<td>477 (81)</td>
<td>497 (92)</td>
<td>461 (70)</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I (a+b), n (%)</td>
<td>11 (27%)</td>
<td>5 (28%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Stage II (a+b), n (%)</td>
<td>24 (60%)</td>
<td>12 (67%)</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>Stage IIIa, n (%)</td>
<td>5 (13%)</td>
<td>1 (5%)</td>
<td>4 (18%)</td>
</tr>
</tbody>
</table>

**Safety**

No adverse events were reported or observed during the home-based preoperative exercise program or the postoperative exercise program, and no patients had spontaneous or unexpected reactions to exercising two weeks after surgery.

**Postoperative Complications, Recurrence, and Mortality**

Only one postoperative complication (pulmonary pneumatocele) occurred during the early exercise intervention and it was not evaluated as an adverse event caused by the exercise. All other postoperative complications were of a pulmonary and cardiac nature that occurred before the patients had initiated the exercise intervention. Within 30 days after surgery, the prevalence of pulmonary postoperative complications was 23% and was found to be highest in the group who initiated exercise two weeks after surgery (groups 1 and 3) (Table 4). Cardiac complications occurred in 13% of all complications and the distribution was even between the groups with early and late exercise. Recurrence was experienced in two patients and three patients died within the first year after surgery (Table 4).
Table 4. Postoperative complications, recurrence and mortality

<table>
<thead>
<tr>
<th>Pulmonary complications, n=40 (%)</th>
<th>9 (23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early, n=18 (%)</td>
<td>6 (33%)</td>
</tr>
<tr>
<td>Late, n=22 (%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Cardiac complications, n=40 (%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Early, n=18 (%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Late, n=22 (%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Recurrence, n=40 (%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Mortality, n=40 (%)</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

*Data collected 30 days after surgery
*Data collected at one-year follow-up

**Dropouts**

Eleven patients dropped out (27%) during the intervention, primarily due to either a lack of motivation to complete or side effects from the adjuvant chemotherapy. Patients who were treated with adjuvant chemotherapy were evenly distributed between the group of completers and the group of dropouts (Paper II). In the group of patients who exercised for 70-100% of the 24 exercise sessions, the prevalence of patients treated with adjuvant chemotherapy was lower compared to the group of patients who exercised 0-69% (Paper II). No difference was found concerning demographic data, stage of disease or type of surgery between the group of completers and the group of dropouts. The prevalence of dropouts was evenly distributed between the groups with early-initiated exercise and the group with late-initiated exercise (Table 5).

**Adherence to Home-based Preoperative Exercise**

Six out of 18 (30%) patients randomized to preoperative exercise were not able to receive instruction in preoperative home-based exercise. The contributory cause was a combination of medical procedures and lack of time prior to surgery, while one patient received instructions but did not start the program due to a lack of motivation. Eighteen were randomized to the home-based exercise program and the average number of days possible for exercise before surgery was eight, with a range between 2-15 days. Only three out of 12 patients managed to exercise daily prior to surgery (Table 5).
Adherence to Supervised Postoperative Group Exercise

The supervised group exercise program was completed by 73% of the patients. Adherence to the 24 group-based exercise sessions post surgery was ≥70% in 15 patients out of 29 (Table 5). Four patients out of the 29 did not start exercising; since the study is an intention-to-treat study, results from all 29 are provided. Additionally, analysis of the 25 patients who completed the exercise program post surgery was also carried out but the results did not change the significance of the results presented in Table 5. Consequently, the results for the completers alone are not included in the present thesis. Patients cancelled exercise sessions primarily because they were hospitalized/had appointments at the hospital, lacked motivation or did not have the time to exercise. Adherence was equal in the group with early-initiated exercise (groups 1 and 3) and in the group with late exercise (groups 2 and 4) (Table 5).

The average onset of exercise was 18 days post surgery in the early intervention group (groups 1 and 3), with a range of 13 to 29 days. In the late intervention group, the average onset of exercise was 47 days, with a range of 22 to 80. In the early intervention group, only one patient started exercise 49 days after surgery, which was close to the time of initiation of exercise in the late intervention (groups 2 and 4). As a result, this patient was no longer categorized as a patient in the early intervention group. Patients who performed preoperative exercise were evenly distributed between the clusters that exercised for at least 70%, or for less than 70%, of the postoperative sessions. During the 24 exercise sessions, the strength exercise was performed with the intensity at 67% (SD 20) of 1RM for the chest press and 69% (SD 22) of 1RM for the leg press. In the first four weeks of the 24 sessions, the intensity of the cardiorespiratory exercise was at 74% (SD 8) of the individually determined HRmax and in the last eight weeks, it was at 77% (SD 4) of the individually determined HRmax.
Table 5. Adherence to perioperative exercise

<table>
<thead>
<tr>
<th>Preoperative exercise (home-based) (n=18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instruction given to, n (%)</td>
</tr>
<tr>
<td>Possible days for exercise, mean (range)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Days of self-reported exercise out of days possible (%) (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ≥70%, n (%)</td>
</tr>
<tr>
<td>Exercise &lt;70%, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Postoperative exercise adherence to 24 sessions (group exercise) (n=29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ≥70%, n (%)</td>
</tr>
<tr>
<td>Exercise &lt;70%, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participation ≥70% in early and late postoperative intervention (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early exercise, n (%)</td>
</tr>
<tr>
<td>Late exercise, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drop-outs in early and late postoperative intervention (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early exercise, n (%)</td>
</tr>
<tr>
<td>Late exercise, n (%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initiation of exercise: Early (n=15) and late (n=16) intervention groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early, number of days after surgery, mean (range)</td>
</tr>
<tr>
<td>Late, number of days after surgery, mean (range)</td>
</tr>
</tbody>
</table>

Changes in Physiological Capacity

Changes in physiological capacity were evaluated in relation to adherence to exercise. Walking distance increased significantly post-intervention for patients who participated in at least 70% of the sessions, with a mean difference between baseline and post-intervention of 28 meters (95% CI: 4 to 51, \( p=0.0229 \)). At one-year follow-up no significant effect on walking distance was found. Results for the leg and chest press showed a significant improvement in strength for patients who participated in at least 70% of the sessions. This improvement was found to be 30 kilos for the leg press (95% CI: 5 to 55, \( p=0.0220 \)) and five kilos for the chest press (95% CI: 2 to 8, \( P=0.0029 \)) at post-intervention. The mean difference between baseline and one-year follow-up on the leg press was an improvement of 18 kilos (95% CI: 1 to 36, \( p=0.0443 \)) and for the chest press the improvement was four kilos (95% CI: 1 to 7, \( p= 0.0129 \)). Fitness decreased, independent of adherence to exercise, from baseline to post-intervention by 1.9 mL/kg/min (95%
CI: -3.9 to 0.2, *p*=0.0741) and the decrease was retained at 1.8 mL/kg/min (95% CI: -3.7 to 0.11, *p*=0.0637) at the one-year follow-up.

**Changes in HRQoL**

The FACT-L total score and LCS subscale showed a statistically significant improvement across the five time points (Figure 6a, *p*=0.0163; and 6b, *p*=0.0421). The EORTC-QLQ-C30 functional scales showed increasing levels of global QoL (Figure 7a, *p*=0.0032). Results from SF-36 showed improvements for the mental health component score (Figure 7b, *p*=0.0004). The SF-36 domain bodily pain showed no overall statistically significant difference between the five time points (*p*=0.1069), but post hoc comparisons indicated that scores six months and one year after surgery were higher than the baseline scores (7.3 and 7.6 points, respectively). For further results on patient-reported outcomes, see Paper III.

![FACT-L Total score](image1)

![FACT-L Lung cancer subscale](image2)

![EORTC-QLQ Global quality of life](image3)

![SF-36 Mental component score](image4)

Figure 6a and 6b. FACT-L total score, score range 0-136 (6a), high scores indicate good HRQoL, and FACT-L LCS (6b), score range 0-28, high scores indicate low level of symptoms reported.
Changes in Smoking, Alcohol, and Physical Activity Habits

Changes in smoking, alcohol and physical activity habits showed a reduction in the number of patients currently smoking, from 25% at baseline to 5% after the intervention, followed by an increase to 12% one year after surgery. These percentages did not differ significantly (Wald test $X^2 = 8.47$, degrees of freedom (df)=4, $P=0.0759$, P for trend 0.0579). A similar pattern was seen in connection with alcohol consumption. At baseline, 28% consumed more alcohol than DHA recommends. This amount dropped to 7% post-intervention, followed by an increase to 14% one year after surgery. Comparing the number of drinks per week using Poisson regression did not indicate significant differences across the five time points (Wald test $X^2 = 4.33$, df=4, $P=0.3634$, P for trend 0.1371). Physical inactivity dropped from 15% at baseline to 4% one year after surgery. Comparing the distribution of the ordinal variable in multinomial logit regression models adjusted for the level three months before diagnosis did not indicate significant differences across the five time points (Wald test $X^2 = 8.10$, df=4, $P=0.0881$, P for trend 0.6985).

Results from the Systematic Review (Paper IV)

Electronic databases were searched on the February 17, 2016 and resulted in 6191 hits: 1641 from MEDLINE, 3291 from Embase, 270 from the Cochrane Central Register of Controlled Trials (CENTRAL), 970 from CINAHL and 19 from PEDro. The number of duplicates was 1661, resulting in 4530 unique papers. Based on title and abstract, 4464 papers were excluded, resulting in 66 papers read in full text. Out of the 66, 62 studies were excluded as they did not meet the inclusion criteria. The present review included four RCTs involving 262 participants (65,127–129). Three of the studies randomized the participants into one of two groups: an exercise intervention or a control group (65,127,128). The fourth study randomized the participants into one of three groups: exercise intervention 1, exercise intervention 2 or a control group (129). This study was divided into two studies in the analysis, where each intervention group was compared to half of the control group (111). Twelve were in a language other than those listed in our criteria and three had missing data, which meant they were excluded. The first of the last-mentioned studies was contacted but the authors were unable to provide postoperative measurements of exercise capacity (130); the
second study was a conference article that was insufficient due to low completion of the intervention and a large amount of missing data (131); and the third one was unable to provide the missing data on exercise capacity and HRQoL (132). Figure 8 presents a flowchart of the search process based on the PRISMA template (133). For more details about excluded references, see Paper IV.

Figure 8. Study flow diagram

The studies which originated from the UK, Denmark, Belgium and Norway and were published from 2011–2015. Two of them conducted the interventions in a hospital setting after discharge (128,129), with participants in one study exercising during admission with subsequent home
training (127). In the fourth study, the intervention was conducted in local fitness centers after discharge (65). All four studies included mainly participants who had undergone lung resection for NSCLC. Both sexes were included and the mean age was above 60 years in all study groups. The majority of the participants went through open surgery (range 77–96%) and the lung cancer stages were equally distributed between control and exercise groups, except in one study, where four participants with stage IV NSCLC were randomized to the control group and none to the exercise group. For a summary of included studies, see further details in Paper IV.

Exercise interventions included a component with aerobic exercise and resistance training, except for intervention two in the three-armed RCT, which included exercise and whole body vibration (129). The intervention components varied in intensity, frequency and duration across the studies. The intensity of the aerobic exercises, which consisted of either walking or biking, varied from 60-95% of HRmax. The frequency of training varied from one session per week for 10 weeks (128) to three times a week for 12 (129) or 20 (65) weeks. The exercise interventions were initiated after five days (127), three weeks (128), 4-6 weeks (65) or within eight weeks (129) following lung resection.

Baseline measurements in Arbane et al’s (2011) (127) study were conducted pre-surgery as the study initiated exercise pre-surgery and until day five post surgery. In order to rule out variance due to operation outcomes, we decided in the present study to use the first measurement on day five post surgery as the “baseline” in the present review.

Additionally, Arbane et al’s (2011) results showed no statistical or clinical effect of early exercise captured by the day-five post surgery measurement, even though the intervention group had a mean distance that was 28 meters further than the control group (measured at day five postoperatively) (127). The minimal important difference (MID) in the 6MWD in patients with lung cancer is 42 meters (87).

The control groups received usual care consisting of a monthly telephone call from the research team, which provided education (127), one hour of individual instruction in home exercises (128), no advice beyond general information from the hospitals (65) and even discouraged improving their exercise tolerance with professional help (129).

Exercise capacity was reported in all four studies, two of which reported VO$_2$peak (65,129) and three of which reported 6MWD (127–129). HRQoL was reported in three studies, two of which reported SF-36 in physical and mental component scores (65,128), and one study reported the EORTC QLQ-C30 physical functioning score (129). One study only had one measurement of HRQoL post surgery, which is why that outcome was not extracted (127). All of the studies had
collected a short-term follow-up at completion of their interventions, and one study had collected an additional long-term follow-up one year after baseline (128).

**Risk of Bias**

Figure 9 presents the overall assessment of risk of bias across the studies, while Paper IV presents the risk of bias for the individual studies.

All the studies reviewed were at high risk of performance bias because blinding of participants is difficult in exercise interventions. The majority of studies were at high or unclear risk of detection bias and reporting bias as the outcome assessors were not blinded and the relevant predefined outcomes were not evaluated due to lack of completion of outcome measures or no trial registry. The section called “Summary of included studies” in Paper IV contains a detailed description of the assessment of risk of bias.

![Risk of bias graph](image)

**Figure 9. Risk of bias graph: review of authors’ assessment of each risk of bias item presented as percentages across all included studies**

**Effect of Intervention**

All meta-analyses were conducted using a random-effects model after assessment of clinical heterogeneity between studies, particular in the exercise interventions. VO2peak is considered the gold standard measurement of cardiorespiratory capacity, therefore when both VO2peak and 6MWD were available, VO2peak was chosen. Results, measured post-intervention, stated as short-term, showed a significantly higher exercise capacity in the intervention group compared to the control group (SMD 0.48; 95% CI 0.04 to 0.93), reflecting a small to moderate effect size (Figure 10.). The I² was 61.6%, suggesting moderate variations between intervention effects. The
study with a long-term follow-up showed no effect on exercise capacity after one year from baseline (SMD 0.09; 95% CI -0.44 to 0.61). The results are not illustrated.

The SF-36 physical component score was pooled in a meta-analysis with the EORTC QLQ-C30 physical functioning score. The physical component of HRQoL was significantly higher in the intervention group compared to the control group (SMD 0.50; 95% CI 0.19 to 0.82) when dealing with short-term effect, reflecting a moderate effect size (Figure 11). I² was 0%, suggesting a small variation between intervention effects.

According to the one study with long-term follow-up, there was no effect on the physical component of HRQoL in the long-term (SMD -0.27; 95% CI -0.78 to 0.25). The SF-36 mental component score was reported in two studies and pooled in a meta-analysis. There was no effect on the mental component of HRQoL (SMD 0.53; 95% CI -0.78 to 1.83) concerning short-term effect, nor at long-term follow-up (SMD -0.48; 95% CI -1.01 to 0.04). The results are not illustrated.

Only one study initiated exercise intervention early, within two weeks after surgery (127). This study showed no effect on exercise capacity in the short-term (SMD 0.09; 95% CI -0.57 to 0.74). In three studies that initiated exercise interventions later (65,128,129), >2 weeks after surgery, in contrast, the exercise capacity was significantly higher in the intervention group compared to the
control group in the short-term (SMD 0.58; 95% CI 0.07 to 1.09), reflecting a moderate effect size. There was no difference between the effect of late and early-initiated exercise intervention. $I^2$ for exercise interventions initiated late was 65.6%, suggesting moderate variation between intervention effects.

![Forest plot](image)

**Figure 11.** Forest plot: effect of the physical component of HRQoL in exercise group versus control group (short-term)

An overall low quality of the body of evidence was found in the present systematic review. Paper IV provides further information on the main findings and quality of the body of evidence for each result.

**Discussion**

**Summary of Main Findings**

This feasibility study showed that a high intensity interval exercise program starting two weeks after surgery in patients with NSCLC was safe and feasible. Recruitment of NSCLC patients to the rehabilitation intervention, with a focus on exercise, was challenging. The preoperative home-based exercise was found to be inconsistent and not feasible in a set-up where the time interval between referral and surgery (fast-track surgical program) was restricted to 14 days.
(Paper II-III). The systematic review showed that exercise improved exercise capacity and the physical component of HRQoL in the short-term, but no beneficial effect was found in the mental component of HRQoL. In the systematic review, it was not possible to draw conclusions about the effect of early-initiated postoperative exercise compared to late-initiated exercise due to the lack of well-conducted RCTs (Paper IV).

Safety
This feasibility study is the first study of its kind to initiate supervised high intensity interval exercise, in a non hospital setting, two weeks after surgery for NSCLC. The feasibility study demonstrated that the intervention was safe since no serious adverse events or other adverse events occurred during the intervention period. Only a few studies have initiated exercise interventions within two weeks after operation for NSCLC, and none of them included registration of adverse or serious adverse events (127,134–136). However, all of these studies were conducted in a hospital setting and none of these study prescribed high intensity interval exercise and the intervention was performed once daily (high to moderate intensity) from the first postoperative day until discharge from hospital (127,134,135). One study initiated an exercise intervention four days after discharge from hospital but the intervention were characterized as being home-based and unsupervised (136). In a feasibility study by Jones et al (2007), patients with NSCLC were recruited at least three weeks post surgery, with a mean of around 30 days after surgery, and the intervention consisted of high intensity cardiovascular exercise (64). This study stands out by reporting safety in relation to exercise and found neither adverse events nor serious adverse events in connection with the exercise (64).

High intensity interval exercises are shown to be superior to moderate intensity continuous exercise when it comes to inducing health benefits in healthy individuals (137). Due to this benefit and the safety of high intensity interval exercises in healthy individuals, this type of exercise has emerged in clinical populations, such as patients with DM (137). The acute cardiac response to high intensity interval exercise has been assessed in patients with coronary heart disease and no contraindications to high intensity interval exercise were observed (138,139). Also, in heart transplant recipients who completed an eight-week high intensity interval exercise program, the results showed significant improvements in cardiorespiratory capacity without adverse events occurring during the study (146). Notably, all patients in the studies mentioned above underwent a full medical screening and cardiopulmonary exercise test prior to participation (138–141). At the same time, it is important to stress that for patients with a recent
bypass surgery, the test was performed >3 months after the surgical procedure, and for heart transplant patients, >1 year post-transplantation, ensuring sufficient time for wound healing after a major surgical procedure.

Recent guidelines on physical activity and exercise for cancer survivors have not clarified the optimal time for initiation of exercise (78,104). For many years in the Danish health care system, the general practice has been to postpone initiation of any type of exercise, apart from mobilization, to six weeks after cancer surgery to allow sufficient time for wound healing. No evidence has been presented, however, to support this recommendation and the judgment of how early it is safe for a patient to start exercising after lung surgery often depends on the surgeon in charge. ACSM guidelines for cancer survivors state, quoted in Schmitz et al (2010), p. 1413: “Allow adequate time to heal after surgery. The number of weeks required for surgical recovery may be as high as 8 weeks” (142).

In 2007, Danish legislation specified that the local authorities were responsible for the rehabilitation of patients, including cancer patients, a task previously undertaken by hospitals (72). Since the aim of rehabilitation is to restore patients to the optimal level of functioning in their community and homes, it thus appears logical to perform rehabilitation in the patient’s immediate environment (143). Research has indicated that community-based rehabilitation can be just as beneficial for patients as hospital-based rehabilitation (144,145). Some of the safety concerns about cancer patients doing high intensity interval exercise in a non-hospital setting is the lack of access to blood samples, medical records and assistance in an emergency.

The ACSM guidelines for cancer patients state that prescribing exercise should be individualized according to pretreatment aerobic fitness, medical comorbidities, response to treatment and the immediate or persistent negative effects of treatment experienced at any given time (142). Previous studies in cancer patients during chemotherapy found that screening before exercise has a positive impact on the patients’ sense of safety during exercise (79,80).

In this feasibility study, every patient was screened prior to inclusion by the primary surgeon in accordance with the inclusion criteria. Additionally, a specialized cancer nurse and physiotherapist were in charge of the exercise sessions and the patients were screened prior to every exercise session for physical capability (see methods section). The completed screening did not result in any omission of patients from participating in the exercise sessions, which theoretically could have prevented serious adverse events or adverse events.

In healthy individuals, the health benefits of physical activity are well documented (147), even though recent research also indicates that exercise induces an acute risk of serious adverse events
This evidence also indicates, however, that the health benefits of routine physical activity by far outweighs the acute risk of serious adverse events (146). The acute risk is actually found to decrease with increased levels of physical activity, such that highly active individuals appear to have the lowest risk (two to five-fold lower). The incidence of adverse cardiovascular events in healthy individuals is below 0.01 per 10,000 participant hours (147). The transferability to lung cancer patients is unknown, but as many lung cancer patients are current or former smokers, they often have cardiovascular comorbidities, such as hypertension (38% in this study), dyslipidimia (23%) or atherosclerosis (unreported). Furthermore, 20% of the patients included had COPD. This feasibility study did not exceed a total of 1000 exercise sessions, which is why the risk of lung cancer patients experiencing a cardiovascular event is difficult to calculate in the same way as with healthy individuals.

**Postoperative Complications**

This feasibility study showed that initiating high intensity interval exercise two weeks after surgery for NSCLC does not increase or decrease the incidence of postoperative complications compared to the group with late-initiated exercise. Postoperative pulmonary complications following lung resection are associated with longer length of hospital stay, higher rate of intensive care unit admissions, higher 30-day readmissions and reduced overall survival, depending of the degree of resection (148–150), which is why prevention is of great importance. The ability to reduce postoperative pulmonary complications is of significant value to patients and to the healthcare system. A recent Cochrane review showed that in patients with operable lung cancer, preoperative exercise decreased the risk of postoperative pulmonary complications by 63%, reducing both intercostal catheter duration (by three days) and length of hospital stay (by four days), and also improved preoperative exercise capacity and FVC in patients undergoing lung resection (53). The Cochrane review stressed that the findings have to be interpreted with caution due to differences between the studies and small sample sizes. The same review found a number needed to treat for a beneficial outcome of four, which means that for every four patients performing preoperative exercise, one less patient will develop a postoperative pulmonary complication (53). In the PROLUCA feasibility study, only three out of 12 patients managed to exercise daily prior to surgery in a fast-track setting, which is why it is not possible to draw a conclusion about the effect of preoperative exercise on the incidence of postoperative complications.
Recruitment

The recruitment rate was 32% of the eligible patients, and the primary reason for them not attending was either logistical problems or concerns about their upcoming surgery. Similar exercise studies in patients with NSCLC show diversity in regards to the percent of recruited patients. Some studies report recruitment rates that are comparable to the one found in this study (64,128). Other studies report a much higher recruitment rate of around 65-80% (65,127), while the rate can also be found to be much lower, around 11% (54,134). How recruitment rates are reported, however, differs between the studies, as some reported patients out of eligible patients and others reported patients out of patients being assessed for eligibility (54,64,65,127,128,134). Logistical problems are one of the reasons often reported as a barrier to participation in rehabilitation (134). In research on cardiac rehabilitation, barriers to participation in rehabilitation program are categorized in three ways (151): 1) patient factors (e.g., lack of interest, lack of support from friends and family, reluctance to change lifestyle); 2) service factors (e.g., cost and reimbursement, location and accessibility, car parking); and 3) professional factors (e.g., knowledge and attitudes, referrals and prejudices) (151). The same barriers have been observed in the recruitment process in this feasibility study.

Adherence to the Preoperative Exercise

The stated hypothesis that preoperative home-based exercise is safe was supported since no serious adverse events were found. It could not be confirmed, however, that preoperative home-based exercise is feasible in patients with operable lung cancer, since adherence to the preoperative home-based exercise was inconsistent due to the short time interval between referral and surgery (fast-track surgical program). To our knowledge, not many studies have assessed the effect and adherence of a home-based exercise program prior to resection in patients with NSCLC being treated in a fast-track setting similar to the two weeks in this feasibility study. One study found good adherence to a four-week home-based preoperative exercise intervention as all of the included patients (n=16) completed more than 75% of the prescribed exercise sessions (152). Apart from the time difference between a four-week and this two-week exercise program, the patients included in the study by Coats et al (2013) were younger and diagnosed with early-stage lung cancer, compared to the patients included in this feasibility study (152). In Denmark, the maximum waiting time for lung cancer surgery is, by law, specified not to exceed two weeks. As a result, a four-week preoperative exercise program would not actually be possible in a Danish setting. The four-week preoperative waiting time until surgery
for lung cancer in the Canadian study by Coats et al (2013) brings into consideration that the difference between two and four weeks from diagnosis to surgery might not be that crucial. It could be interesting to investigate if similar survival rates for patients with NSCLC are found in countries where the preoperative waiting time is four weeks in stead of two weeks in Denmark. And also to examine if preoperative exercise intervention could have a positive impact on survival.

Preliminary evidence suggests that a high exercise capacity at the time of diagnosis of NSCLC is related to extended survival, but this has to be examined further (57,153). The postulated mechanism linking exercise with prolonged survival in lung cancer is the influence of exercise on the regulation of sex hormones, insulin/IGF and inflammatory markers (154). In addition, research on mice has investigated the mechanism that may link physical activity and exercise to cancer control and this research is of great importance to eventually recommending exercise as medicine for patients with cancer (155,156). Despite promising results with regards to preoperative exercise in NSCLC patients and its reduction of postoperative complications, Cavalheri & Granger’s (2017) systematic review rates the quality of evidence as low and highlights the need for further RCTs to investigate the effect of preoperative exercise on mortality and the cost/benefit of this intervention (53).

**Adherence to Postoperative Exercise**

The feasibility study confirmed the stated hypothesis, i.e., that high intensity interval exercise, in a non-hospital setting, initiated two weeks after surgery in NSCLC patients was feasible. The average onset of exercise was 18 days (range 13-29) post surgery in the early intervention group and 47 days (range 22-80) in the late intervention group. Despite several strategies to enhance adherence to the exercise sessions, 11 patients dropped out during the intervention, five patients (45%) from the early intervention groups (group 1 and 3) and six patients from the late intervention groups (group 2 and 4). The primary reason for dropping out was either lack of motivation to complete (n=4) or side effects from the adjuvant chemotherapy (n=3). Seventy-three percent of patients in the feasibility study completed the supervised group exercise, which is comparable to other exercise studies in patients with NSCLC, where the average percentage of patients who completed the study was around 80% (64,65,127–129). Although 73% of the lung cancer patients completed the group exercise, only 52% of them attended ≥70% of the sessions and 48% <70% of the group sessions. In other studies, the lung
cancer patients varied and the attendance rates are not described, making it impossible to calculate comparable rates (64,65,127–129).

According to Kamshoff et al (2014), high attendance rates in patients with different cancer diagnoses were defined as attending at least 80% of the sessions, and the effect of RCTs evaluating exercise programs depends largely on patients’ participation or exercise adherence (68). In this feasibility study, only 13 patients (33%) received chemotherapy. Due to the low number of patients, it is not possible to describe the barriers to participation in exercise. Three of the eleven dropouts, however, stated the reason to be side effects from adjuvant chemotherapy, which is why rehabilitation programs must focus on strategies to maintain exercise during treatment. A study in cancer patients found that high levels of fatigue and no previous experience with exercise influenced participation in exercise trials (68). Furthermore, minimizing practical barriers to participation, such as travel distance and flexible exercise schedules, were suggested in cardiac rehabilitation as promising strategies to enhance participation in future studies (151).

**Cardiorespiratory Capacity**

This feasibility study showed a trend towards a mean decrease in fitness of 1.9 mL/kg/min (95% CI: -3.9 to 0.2, p=0.0741) from baseline to post intervention and this decrease was retained at 1.8 mL/kg/min (95% CI: -3.7 to 0.11, p=0.0637) at one-year follow-up. Since this feasibility study is underpowered, the results must be interpreted with caution. Contrary to these findings, other studies investigating the cardiorespiratory effect of high intensity exercise in patients resected for NSCLC show an increase in fitness (61,62).

An RCT study found a between-groups difference of 3.4 mL/kg/min (95% CI 1.3 to 5.5 and p-value at 0.002) in favor of the exercising group (65). The baseline assessment was collected post surgery, which eliminates the impact of surgery on the exercise capacity measured. This is in contrast to this feasibility study, where the baseline assessment was measured within two weeks prior to surgery, which is also the case in other exercise studies measuring cardiorespiratory capacity in patients resected for NSCLC (132,157). It is therefore difficult to distinguish between the impact of the surgery and the exercise intervention. In addition, Edvardsen et al (2014) used a cardiorespiratory exercise protocol involving walking on an uphill treadmill, which might be more appropriate for use in patients resected for NSCLC (65).

A Canadian study in patients with breast cancer showed a 17% difference in cardiorespiratory capacity in favor of an uphill treadmill VO\textsubscript{2}max test compared to a cycling VO\textsubscript{2}max test (158). The study by Dolan et al (2012) found that experience and local muscular fatigue may have been
limiting factors during the cycling protocol rather than central fatigue of the cardiorespiratory system, thereby presenting an inaccurate level of cardiorespiratory capacity (158). Cycling requires a different skill than walking and in the study by Dolan et al (2012) they speculate, that the lack of experience in cycling influences the results (158). In Denmark the situation is different, as cycling is integrated in daily life and the general population are using bikes as a vehicle. Still it is not known if a treadmill is more appropriate for use in patients with NSCLC, with the intention to avoid local muscular fatigue before a central fatigue constrains further participation in the test.

An improvement in VO2peak of 15% is generally accepted as a clinically important change in healthy individuals but in lung cancer, an improvement of 11% may in fact be meaningful, especially in the context of severe deconditioning and high postsurgical morbidity (64). Data from this study does not indicate whether the fitness level was even lower immediately after surgery and thereafter increasing slowly over time. The starting point for the evaluation of the effect of training on cardiorespiratory capacity is not measured immediately before initiation of the exercise intervention, which is why this value may be lower than the value measured at baseline prior to surgery. This will result in an underestimation of the effect of the exercise intervention.

Another important difference between the study mentioned and this study is the duration of the intervention period and frequency of exercise sessions. In this Danish study, two exercise sessions every week for 12 weeks were chosen, which is used very commonly in the rehabilitation of patients with a variety of diagnoses, but in Edvardsen et al’s study (2014), they exercised three times a week for 20 weeks (65).

HR data showed that the patients in the present feasibility study were able to exercise with an intensity that was even higher than prescribed. In the first four weeks of the 24 sessions, the intensity of the cardiorespiratory exercise was 74% (SD 8) of individually determined HRmax (intended to be ~50-60%) and for the last eight weeks it was at 77% (SD 4) of individually determined HRmax (intended to be ~70-90%).

**Muscle Strength**

Results on muscular strength showed a significant improvement for patients exercising for at least 70% of the sessions. This improvement was found to be 30 kilos on the leg press (95% CI: 5 to 55, \( p=0.0220 \)) and five kilos on the chest press (95% CI: 2 to 8, \( p=0.0029 \)), measured post-intervention. Comparably, Edvardsen et al (2014), found a baseline mean in the intervention
group of 131.9 (SD±45.7) kilos on the leg press and a post-intervention mean of 159.3 (SD±48.4) kilos (65). Hence the improvement in this feasibility study is also found in other similar studies in patients resected for NSCLC, but diversities in the methods of measuring muscular strength makes it difficult to compare the results (127,159). The improvement is of great importance as muscle strength is inversely associated with all-cause mortality (160). Loss of muscle strength, a common occurrence in the elderly, is associated with increased mortality independent of age or other clinical and functional variables (160). Furthermore, research has shown that cancer patients have significant impairments in muscle strength regardless of disease stage when compared with healthy controls matched by age, sex, body mass index and/or physical activity level (161). Based on this, performing strength exercises is recommendable for not only lung cancer patients but for all patients with cancer.

**Walking Distance**

In this thesis, data on 6MWD showed a significant and clinically relevant increase of 28 meters (95% CI: 4 to 51 and \( p=0.0229 \)) from a baseline of 495 (SD ±63) meters to post-intervention for patients who participated in at least 70% of the sessions. Another study in the same group of patients found a 43% improvement in 6MWD after the intervention, but the baseline measured up to three months after surgery was only 351 meters (interquartile range: 240-436) (162). This indicates that the patients in the study by Spruit et al (2006) had a lower physical capacity at baseline than the patients in the PROLUCA feasibility study (162). In another study, Brocki et al (2014) found a decrease in walking distance to 76% of the preoperative values at day five post surgery in patients with NSCLC, while two weeks after surgery there was a partial recovery at 93% of preoperative values (128). The feasibility study measured the baseline prior to surgery, which is why it would be expected that the true baseline value before the exercise intervention is lower than the value measured preoperatively and that the subsequent increase would be correspondingly higher.

The 6MWD is the most widely used non-laboratory test to measure functional capacity in individuals with chronic lung disease, including those with lung cancer and COPD (54,87). Recent research estimated the MID for a deterioration of 6MWD in patients with lung cancer to be between 22 m and 42 m, or a change of 9.5%, which is consistent with the MID established in COPD populations (163,164). In sum, the three sections above verify the stated hypothesis that improvement in physical capacity in patients following surgery for lung cancer is achievable,
since improvements were found in muscular strength and in 6MWD but not in cardiorespiratory capacity.

HRQoL Outcomes
Overall, this feasibility study verifies the stated hypothesis that HRQoL improves significantly during the study period, from around two weeks prior to surgery until one year after surgery, in patients with NSCLC participating in an exercise intervention. This was demonstrated by the use of various validated patient-reported outcomes (see Table 1).

Results from FACT-L measurements showed that the total score improved significantly during the study \((p=0.0163)\) from a mean baseline score of 105 (95% CI: 99 to 112) to the highest reported level, a mean score of 114 (95% CI: 109 to 120), measured six months after surgery. The level of LCS (subscale in FACT-L) increased significantly \((p=0.0421)\) from a baseline score of 21 points (95% CI: 19 to 22) to the highest mean score, measured one year post surgery, of 23 (95% CI: 22 to 24). A high LCS score indicates a low level of symptoms and, as it has previously been demonstrated that a two to three point improvement in LCS is a clinically meaningful change in patients with NSCLC, the results are interpreted as such (165).

Results from the EORTC-QLQ-C30 showed that global QoL improved significantly \((p=0.0032)\) during the study from a mean baseline value of 65 (95% CI: 57 to 74) to the highest mean value measured six months post surgery of 82 points (95% CI: 75 to 88), which is nine points higher than the score in an age-matched Danish cohort in healthy individuals (mean score 73 ±SD 23) (113). Braun et al (2011) found that in patients resected for NSCLC, a 10-point increase in global QoL was associated with a 9% increase in survival (166). A difference of five to 10 points represents a small but clinically meaningful change, 10 to 20 points a moderate change and more than 20 points a larger clinically meaningful change seen from the patient’s perspective (167).

As a result, the improvement found in this feasibility study can be interpreted as a significant and moderate clinically important change. However, the findings of the present feasibility study must be interpreted with caution since the lack of a control group weakens any conclusion regarding the effect of this intervention.

Additionally, results from the SF-36 found that the mental health component score improved significantly during the study period \((p=0.0004)\) to a mean level of 53 points (95% CI: 49 to 58) measured at both the six-month and one-year follow-up. These findings are one point below the mean mental health component score in an age-matched random sample of 6000 individuals.
drawn from the Danish Civil Registration System (114), which is in contrast with recent findings in a Danish RCT on operable lung cancer patients, where a significant improvement in the mental health component score was not found (157). This is in contrast to this study, where the mental health component score improved significantly and stayed unchanged at one year follow-up.

The same study by Brocki et al (2014), however, found an improvement in the SF36 physical health component score, with a difference between the intervention group and the control group of 3.76 points (95% CI: -0.1;7.62, \(p=0.06\)) in favor of the intervention group (128), as well as in the baseline values measured approximately three weeks after surgery. Brocki et al’s study (2014) found that the tendency toward improvement in the physical health component score post-intervention was reversed 12 months after surgery, where the control group presented slightly better measures overall (128). In this thesis, there was, however, a decrease from baseline measured preoperatively to one year after surgery in the physical health component score, but the results were not significant (\(p=0.5327\)) (results not presented). Again, the impact of surgery does not indicate whether the physical health component score had been even lower immediately after surgery and thereafter increased slowly over time.

**Changes in Smoking, Alcohol and Physical Activity Habits**

Results from the feasibility study showed that smoking and alcohol habits decreased, leading to fewer smokers and fewer patients with an alcohol intake above the recommended amount of \(\leq 7\) units per week for women and \(\leq 14\) for men, in the period from baseline to post-intervention. This effect, however, reversed one year after surgery without reaching the baseline. The level of sedentariness dropped from 15 to 4% during the intervention period. The changes in smoking, alcohol and physical activity habits were not statistically significant, but the results are of clinical importance and underline the need for optimizing maintenance of lifestyle changes after rehabilitation.

Research in patients with NSCLC found that 40% of them did not meet physical activity recommendations measured at the time of diagnosis and six months after unless they were participating in a specific exercise intervention (55). Furthermore, after six months, the same patients had a decline in physical activity, functional capacity and strength compared to healthy individuals. This is further confirmed by another study showing that NSCLC patients had postoperatively longer periods of sedentary behavior than healthy controls (168).
Effect of Early Postoperative Exercise

Results from the meta-analysis showed that postoperative exercise interventions improved exercise capacity (SMD 0.48; 95% CI 0.04 to 0.93) and the physical component of HRQoL (SMD 0.50; 95% CI 0.19 to 0.82) in the short-term, but no beneficial effect was found on the mental component of HRQoL. Only a single study has evaluated the long-term effect and showed no effect on either physical capacity or HRQoL (128). These findings are comparable to the findings in a previous systematic review, where the exercise capacity was significantly higher in the intervention group compared to the control group (MD 50 m; 95% CI 15 to 85 m) (49). This systematic review included RCTs with different measures of exercise capacity or HRQoL, which is why comparing the results in the calculated SMD was difficult. The Cavalheri et al’s systematic review (2014), found no significant difference in HRQoL between the intervention and the control groups (SMD 0.17; 95% CI -0.16 to 0.49), contrary to the findings in this systematic review, which might be due to diversity in the design. Cavalheri et al (2014) included studies with various designs that included a few RCTs, only one of which met the inclusion criteria of the review in this thesis. In addition, two new RCTs with a total of 131 patients were included. Another difference between other systematic reviews, including Cavalheri et al (2014) and this systematic review, is the inclusion of studies dealing with both pre and postoperative exercise (49, 61, 169, 170).

This systematic review is the first of its kind to examine the effect of postoperative exercise in patients with NSCLC after lung resection, including solely RCTs and with postoperative outcome measurements only included. In this way, the impact of the surgery is eliminated from the effect of the intervention, but one may expect lower baseline assessments postoperatively, due to sequelae to the operation, as compared to levels measured preoperatively. Other previous systematic reviews confirmed that both pre and postoperative exercise was associated with positive results for exercise capacity and some HRQoL domains (49, 61, 169, 170). The quality of the evidence provided by the RCTs included in the meta-analysis has been rated, according to GRADE, as low or very low, mainly because of some serious risks of bias, inconsistency in effect estimates and imprecision, as the small sample sizes caused wide CIs. Consequently, the results of this review must be interpreted with caution.

The systematic review in this thesis could only identify sparse research that encompasses knowledge about the influence of early initiation of exercise after lung cancer surgery. Only one study initiated the exercise intervention within two weeks following surgery, which is why it is not possible to evaluate whether or not early-initiated exercise will improve the effect of exercise
capacity and HRQoL. As a result, the study contained a home-based non-supervised training program following discharge, which potentially could have lowered adherence to the intervention, reducing its effect (127). Accordingly, hypothesis number four could not be confirmed. Despite the fact that no effect could be found, an early-initiated intervention could be beneficial due to several reasons. One is the reduction of the postoperative period with inactivity and research from cardiac rehabilitation shows favourable effects of exercise initiated in the acute phase following myocardial infarction when compared to late onset of exercise (171). One study has shown that exercise may facilitate wound healing via neuroendocrine regulation among healthy older adults participating in an exercise intervention compared to a control group (172). Therefore, exercise may also have beneficial effects on patients recovering from a lung resection since wound healing is found to be accelerated.

**Methodological Considerations**

A methodological concern is the chronology of studies in the papers included in the thesis, which at first might appear as a reversed way of doing traditional clinical research. A classic approach would start out with a systematic review, followed by a feasibility study and leading to an RCT, but the research approach always depends on the research question being asked (173). This thesis, started out with a concept paper describing the intended PROLUCA RCT study. Due to a low recruitment rate in a surgical fast-track setting for operable lung cancer patients, the preoperative exercise intervention was judged to be problematic. The decision was consequently made to shift from an RCT to a feasibility study investigating the original perioperative design on a smaller scale while simultaneously changing the focus from effect to safety and feasibility. Another methodological concern is the lack of a postoperative assessment performed immediately before initiation of exercise. This could have revealed a more precise result of the intervention, since the impact of the surgery would be isolated. This approach would require taking into account the choice of cardiorespiratory exercise tests since it has not yet been clarified whether it is safe to perform a maximum performance test two weeks after surgery in patients undergoing thoracic surgery.

Another methodological concern is that a feasibility study is not designed to evaluate the effect of the intervention but instead is meant to evaluate safety and feasibility. Moreover, a feasibility study includes a small sample size, which is why the use of statistical tests may be problematic because of the risk of finding or not finding statistically significant results. Therefore, results from a feasibility study must be interpreted with caution.
**Strengths and Limitations**

This thesis has several limitations, one of which is the low recruitment rate in the feasibility study, which could possibly result in a selection bias and perhaps indicate that the intervention was only feasible in a selected group of NSCLC patients as the population included might not be representative of the population of patients undergoing surgery for NSCLC. Further on, the selection bias could influence the options available for implementing these results in a clinical setting. It might be that the patients choosing to participate in the present study represent a group with better physical fitness than the group not participating in the study. Unfortunately, it has not been possible to collect data on the patients eligible for the study but not included, although it could have been of great value to compare participants and non-participants with regards to demographics, smoking status, presence of comorbidity and pulmonary function. A comparison of the patients included in this feasibility study with cohort studies in patients with NSCLC reveals similarities regarding age, sex, pulmonary function and comorbidities (174,175).

Another limitation is the quality of the smoking information in this feasibility study, which only reports years of smoking and not the intensity. A more precise way of reporting the exposure to tobacco is pack-years of smoking (176), which is calculated by multiplying the average number of packs of cigarettes smoked per day (intensity) by the number of years the person has smoked (176). This method is widely used within the health care system.

One of the strengths is that the study was conducted in a municipality, which has been legally responsible for the rehabilitation of various patient categories since 2007. This strengthens the applicability of the intervention to general clinical practice. The rehabilitation systems for cancer patients in Nordic countries (Denmark, Norway, Finland, Sweden, Iceland, Germany and the Netherlands) are based on a similar, multidimensional and multidisciplinary understanding of cancer rehabilitation (72), which also enhances the transferability of the results.

Another strength is the comprehensive literature search on lung cancer and exercise carried out by two review authors that resulted in sufficiently identifying relevant studies and successfully obtained missing data. Additionally, the investigative effort put into finding on-going or unpublished studies improved the probability that all relevant studies were found. This was done by searching trial registrations and contacting recognised authors in the research field. The language criteria for exclusion may have limited the inclusion of additional studies. The three studies excluded due to missing data also represent a limitation, as their effect estimates could have influenced the results of this review.
Conclusion

This thesis showed that early, supervised, group-based high intensity interval exercise is both safe and feasible in patients with operable NSCLC. High intensity interval exercise, in a non-hospital setting, initiated two weeks after lung resection was achievable. The preoperative home-based exercise was not feasible in the present setting due to the short time interval between referral and surgery. Results from the feasibility study showed that HRQoL and muscle strength improved significantly during the study period, from time of diagnosis until one year after resection in patients with NSCLC participating in rehabilitation. Results from the systematic review also showed that exercise interventions for patients resected for NSCLC improved exercise capacity and the physical component of HRQoL in the short-term, based on results from a meta-analysis. Due to the lack of well-conducted RCTs, it was not possible draw any conclusions about the effect of early-initiated postoperative exercise compared to late-initiated exercise.

Perspectives

Inactivity in lung cancer patients is known to be associated with worse outcomes in HRQoL and symptom burden (177). The challenges experienced in recruiting lung cancer patients to the exercise intervention in the feasibility study is not a unique issue related to lung cancer but a general challenge in the field of clinical research on rehabilitation (178). This recruitment issue should not prevent further research within this area since the consequences of being sedentary are critical (146), especially in lung cancer patients. With the significant cancer burden and rising cancer costs, rehabilitation is still an inexpensive cancer therapy (179). Supplementary qualitative research in preoperative exercise for NCSLC patients highlights the need for psychosocial support during the period from diagnosis to surgery, which also supports the idea of some kind of a preoperative intervention (180). Therefore, future research should continuously focus on how to motivate and encourage lung cancer patients in all stages, as well as lung cancer survivors, firstly, to stop smoking and, secondly, to be more physically active (179). Additionally, research that identifies how to motivate subgroups of lung cancer patients that are at greater risk of remaining sedentary during and after treatment is warranted (178). Discovering that high intensity interval exercise is safe in patients two weeks after surgery for lung cancer is important since it might prevent physical inactivity in the postoperative period and
this could potentially lead to a better outcomes in physical capacity and HRQoL in both the short and long-term, which previous research indicates is affected in operable lung cancer patients (49). The results of PROLUCA RCT II will reveal the actual effect of an early exercise intervention initiated two weeks after surgery compared to a late-initiated exercise intervention in patients with operable lung cancer based on the parameters physical capacity and HRQoL. As a result, this thesis, in combination with the PROLUCA RCT II study, will add valuable knowledge to the quest for finding the best rehabilitation methods for patients with NSCLC.

The Danish health care system has another challenge not covered by this thesis, but still important for the patients. Lung cancer incidence is found to be inversely associated with educational, occupational and income-based socioeconomic status regardless of adjustments for smoking (181). Thus, even in the Danish health care system, which has free, equal access to health services, disadvantaged groups are less likely to receive rehabilitation services (182). Additionally, another Danish study found that early-stage NSCLC patients who lived alone and had a low income were less likely to undergo surgery compared to those who had a high income or who lived with a partner, even after control for possible explanatory factors (183). Research in lung cancer and socioeconomic status underlines the need for efforts to ensure optimal treatment of lung cancer patients with a low social status (184). This thesis thus also bolsters arguments for ensuring that all lung cancer patients are referred to rehabilitation regardless of their social status.
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Appendices

— Paper I

— Paper II

— Paper III

— Paper IV
Perioperative rehabilitation in operation for lung cancer (PROLUCA) – rationale and design

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Abstract

Background: The purpose of the PROLUCA study is to investigate the efficacy of preoperative and early postoperative rehabilitation in a non-hospital setting in patients with operable lung cancer with special focus on exercise.

Methods: Using a 2x2 factorial design with continuous effect endpoint (Maximal Oxygen Uptake (VO2peak)), 380 patients with non-small cell lung cancer (NSCLC) stage I-IIIa referred for surgical resection will be randomly assigned to one of four groups: (1) preoperative and early postoperative rehabilitation (starting two weeks after surgery); (2) preoperative and late postoperative rehabilitation (starting six weeks after surgery); (3) early postoperative rehabilitation alone; (4) today’s standard care which is postoperative rehabilitation initiated six weeks after surgery. The preoperative rehabilitation program consists of an individually designed, 30-minute home-based exercise program performed daily. The postoperative rehabilitation program consists of a supervised group exercise program comprising cardiovascular and resistance training two-hour weekly for 12 weeks combined with individual counseling. The primary study endpoint is VO2peak and secondary endpoints include: Six-minute walk distance (6MWD), one-repetition-maximum (1RM), pulmonary function, patient-reported outcomes (PROs) on health-related quality of life (HRQoL), symptoms and side effects of the cancer disease and the treatment of the disease, anxiety, depression, wellbeing, lifestyle, hospitalization time, sick leave, work status, postoperative complications (up to 30 days after surgery) and survival. Endpoints will be assessed at baseline, the day before surgery, pre-intervention, post-intervention, six months after surgery and one year after surgery.

Discussion: The results of the PROLUCA study may potentially contribute to the identification of the optimal perioperative rehabilitation for operable lung cancer patients focusing on exercise initiated immediately after diagnosis and rehabilitation shortly after surgery.

Trial Registration: NCT01893580

Keywords: Cancer, Rehabilitation, Exercise, Lung cancer, NSCLC

Background

Lung cancer is one of the most frequently occurring cancer diagnoses with the highest mortality rate [1]. Lung cancer is divided into Small-Cell Lung Carcinoma (SCLC) and Non-Small Cell Lung Carcinoma (NSCLC). Surgery is at present the primary treatment for NSCLC. According to the Danish Register of Lung Cancer 2011, the 2-year survival was 62% and the 5-year survival 42% following radical surgery for lung cancer [2]. Modern surgical treatment includes both minimal invasive surgery, e.g. video-assisted thoracoscopic surgery (VATS), and open surgery such as thoracotomy. An increasing proportion of lung cancer patients are operated by VATS technique in both Europe and the US. At Copenhagen University Hospital (Rigshospitalet), more than 60% of all lung cancers patients are operated by VATS [2]. Improved surgical techniques combined with effective adjuvant chemotherapy have led to a significant survival benefit in individuals with NSCLC [3,4]. Postoperative complications are experienced by 25% of the patients.
with NSCLC [2], and the risk of developing postoperative complications during the first two weeks after surgery has been reported to depend on different factors, e.g. preoperative cardiorespiratory capacity, measured as VO₂peak [1,5]. The physiological consequences of ageing and inactivity combined with the cancer disease and the treatment of cancer result in a marked reduction in VO₂peak and functional capacity [6-8]. Other factors such as smoking [9], alcohol consumption [10], nutritional status [11] and comorbidity [12] are predictors of postoperative complications. The treatment of NSCLC and other types of cancer is complex and potentially lethal. Accordingly, side effects are now recognized as a subject of major clinical importance [13]. The side effects may comprise physical and psychological as well as social distress with symptoms such as reduced cardiorespiratory capacity, paresthesia, post-thoracotomy pain syndrome, fatigue, anxiety, and depression [14-16]. The late side effects are long-lasting or even chronic and may result in restrictions in activity of daily living and reduced quality of life [5,17-23].

A Cochrane systematic review from 2012 indicates that exercise in patients with a variety of cancer diagnoses may have beneficial effects on HRQoL [24]. This is supported by a Danish randomized controlled trial with 269 cancer patients (different diagnoses) according to which patients receiving chemotherapy tolerate intensive physical exercise and experience reduced fatigue, depression, and nausea [25]. In general, rehabilitation in cancer patients based on physical exercise perioperatively has been shown to increase HRQoL and physical activity, and at the same time reduce the side effects of the treatment [24,26-33]. There is consistent evidence from 27 observational studies that physical activity is associated with reduced all-cause, breast cancer-specific, and colon cancer-specific mortality [34].

Clinical studies of preoperative physical exercise in patients with operable NSCLC are sparse. However, a recent prospective feasibility study on 25 patients with NSCLC reports that the patients tolerate 30 minutes of preoperative intensive cardiovascular exercise 5 times/week. The study finds that exercise significantly improves VO₂peak and 6MWD [35]. Two other studies indicate that rehabilitation including preoperative exercise can improve physical and psychological outcome in patients with NSCLC [36,37]. The effect of postoperative physical exercise in patients with lung cancer has been investigated briefly. The studies differ in type of intervention, dose and timing of intervention, and the research is primarily based on case studies and studies with few and heterogeneous participants [36]. Two non-randomized feasibility studies observed that supervised moderate to high intensity cardiovascular exercise initiated four weeks after surgery is safe and feasible for operable lung cancer patients. The intervention consisted of three weekly cycling sessions for a period of 14 weeks, and participation was associated with a significantly improved HRQoL [38,39].

In a prospective study of 45 lung cancer patients, exercise on ergometer bikes 30 minutes daily, initiated two weeks after end of cancer treatment (including both surgery and chemotherapy), was reported to result in a pronounced improvement in exercise capacity and functional status [40]. The results are confirmed by other studies [41,42]. Another randomized study of 53 lobectomized lung cancer patients showed retention of muscle strength in the intervention group in which the patients participated in mobilization and strength exercise twice daily during admission followed by a 12-week long home exercise program. HRQoL (EORTC questionnaire) and physical capacity (measured by 6MWD) were unchanged [43]. Overall, these studies indicated that postoperative exercise may have a positive effect on physical capacity and HRQoL in NSCLC. A systematic review from 2011 concluded that pre- and postoperative exercise is safe and feasible for NSCLC patients and associated with a positive effect on physical capacity and, to some extent, HRQoL [26]. However, the main part of the studies quoted in the review are small case series and the only randomized study in the review observes no difference between the intervention and the control group [26]. In summary, several studies indicate that postoperative exercise of NSCLC patients is safe and associated with improvement of fitness and self-reported outcome such as HRQoL and fatigue [27,44]. Positive effects of perioperative exercise interventions are more pronounced with moderate- to vigorous-intensity versus mild-intensity exercise programs. More research is required to fully understand the potential effect of exercise over time and to determine essential attributes of exercise (mode, intensity, frequency, duration, and timing) by cancer type and cancer treatment [24].

To our knowledge the present Perioperative Rehabilitation in Operation for Lung CAnCer (PROLUCA) study is the first study to investigate the clinical effects of pre- and early postoperative rehabilitation in NSCLC patients. In PROLUCA a randomized clinical trial, the efficacy of pre- and early postoperative rehabilitation is compared with the effect of rehabilitation initiated six weeks after surgery (usual care) in a non-hospital setting.

The aim of PROLUCA is to identify the optimal timing of exercise to improve VO₂peak in postoperative NSCLC patients. The specific aims are: (1) comparison of combined preoperative home-based exercise with postoperative exercise regarding VO₂peak and patient-reported outcomes (PROs), (2) comparison of early postoperative exercise (initiated as early as two weeks after surgery) with usual care regarding VO₂peak and PROs.
Methods

Participants and settings
The study will recruit and randomize 380 patients (95 patients/study arm) with histologically or cytologically confirmed NSCLC, stage I-IIIa (TNM classification v. 7 [45]) or strong substantiated suspicion of NSCLC, referred for surgery. All subjects are assigned for curative lung cancer surgery at Department of Cardiothoracic Surgery, Copenhagen University Hospital (Rigshospitalet). The inclusion and exclusion criteria are described in Table 1: Subject Eligibility Criteria in the PROLUCA Trial.

Procedure
The study is conducted in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement for non-pharmacologic interventions and the Helsinki Declaration [49]. Informed consent is obtained from all participants prior to initiation of any study procedures. The study is approved by The Danish National Committee on Health Research Ethics (H-3-2012-028) and the Danish Data Protection Agency (2007-58-0015).

The study flow is presented in Figure 1 Study Flow PROLUCA. Using a 4-arm, randomized design, potential subjects will be identified and screened for eligibility and informed about PROLUCA by the study research coordinators at the involved hospitals (Bispebjerg University Hospital and Gentofte Hospital). After referral to intended curative lung cancer surgery at Copenhagen University Hospital (Rigshospitalet), the subjects are contacted by telephone and provided with a review of the study. If the subjects accept to participate, the baseline assessment is performed at Copenhagen Centre for Cancer and Health. At baseline the following assessments are performed: (1) PROs described in Table 2 Data Assessment Schedule in the PROLUCA Trial, (2) anthropometric data, (3) 6MWD, (4) muscle strength (1RM in chest- and leg-press machines), (5) pulmonary function test, and (6) cardiopulmonary exercise test (VO2peak). All baseline assessments will be completed as close to time of diagnosis as possible and repeated the day before surgery, pre-intervention (6MWD, pulmonary function, FACT-L), post-intervention, and at follow-up six months and one year after surgery.

Group allocation (Randomization)
Following the successful completion of baseline assessments, participants will be randomly allocated, on an individual basis, to one of the four exercise intervention groups:

Group 1: Preoperative home-based exercise and postoperative rehabilitation initiated as early as two weeks after surgery.

Group 2: Preoperative home-based exercise and postoperative rehabilitation initiated six weeks after surgery.

Group 3: Postoperative rehabilitation initiated as early as two weeks after surgery.

Group 4: Postoperative rehabilitation initiated six weeks after surgery (Usual practice as control group).

The random allocation sequences will be concealed from all study personnel and performed by Copenhagen Trial Unit, Centre for Clinical Intervention Research. A permuted block design with allocation weight of 1:1:1:1 will be used to generate the treatment assignments. Randomly allocated participants will remain in the same group for the entire duration of the intervention, as expressed in Figure 2 PROLUCA Study Timeline. To ensure similarity of randomized groups at baseline, patient randomization will be stratified based on type of surgery, VATS versus thoracotomy surgery.

Blinding
It is not possible to blind the participants to their actual treatment allocation, since participants are aware whether...
they initiate preoperative exercise and whether their postoperative exercise starts two or six weeks after surgery. All study personnel collecting data and doing the statistical analyses of the data are, however, blinded to the patient allocation, and the patients are strictly informed not to reveal their group allocation to the test personnel.

Exercise training protocols (General considerations)

Preoperative exercise
The home-based exercise program is individually designed for each of the participants randomized to a preoperative intervention. The ultimate goal of the preoperative home-based exercise program is to ensure that the patients perform cardiovascular exercise of moderate-vigorous intensity (~60-80% of maximum heart rate (HRmax)) for at least 30 minutes every day until surgery. The preoperative period varies in length and the intention is not to exceed 14 days. The preoperative exercise is monitored by a heart rate sensor (Polar Team 2 System, with off-line transmitters) and an exercise diary logbook.

Postoperative rehabilitation
The postoperative intervention consists of a supervised 12-week rehabilitation program containing 24 group-based exercise sessions, three individual counseling sessions, and three group-based lessons in health-promoting behavior. If the participants have special needs in terms of smoking cessation, nutritional counseling or patient education, this is offered too.

The postoperative physical exercise consists of an individually prepared supervised strength exercise – and a group-based cardiovascular exercise twice a week (60 minutes/session) on non-consecutive days for 12 weeks, a total of 24 sessions, containing the following elements:

Warm-up (five minutes) and cardiovascular exercise (25 minutes) on ergometer bike (BODY BIKE Classic Supreme©), individually prepared strength exercise (25 minutes) carried out using five machines (Technogym”), leg press, chest press, leg extension, pull to chest, pull-down (upper body). The practical aim of strength exercise is to complete three series of 5–12
sets. Trained physiotherapists and cancer nurse specialists supervise the training program following the recommended principles [50]. All exercise sessions will include supervised breathing exercises combined with stretching and relaxation techniques (five minutes). All the cardiorespiratory exercise is designed such that participants begin exercising at a low intensity (~50%-60% of individually determined HRmax) which is subsequently increased to more moderate to vigorous intensity (~70%-80% of individually determined HRmax).

The ultimate goal for the postoperative exercise is two group-based exercise sessions per week, with a cardiorespiratory intensity for the first four weeks at ~50-60% of individual HRmax. The next eight weeks the intensity increases to moderate-high intensity at ~70-90% of individually determined HRmax. The heart rate will be monitored continuously throughout the cardiorespiratory exercise using heart rate monitors and software (Polar Team2 Pro©). All interventions will be individually tailored to each participant and following the principles of

Table 2 Data assessment schedule in the PROLUCA trial

<table>
<thead>
<tr>
<th></th>
<th>Baseline a</th>
<th>Flw-up b</th>
<th>Flw-up c</th>
<th>Flw-up d</th>
<th>Flw-up e</th>
<th>Flw-up f</th>
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<tr>
<td>Anthropometric data and cancer disease</td>
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<td>Physiological measurements</td>
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<td>Cardiorespiratory capacity (VO2peak)</td>
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<td>One-repetition-maximum (1RM)</td>
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<td>Heart rate (HR), Blood pressure (BP)</td>
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<td>Spirometric (FEV1/FEV1%)</td>
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<td>Patient-reported outcome</td>
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<td>Health-related quality of life (EORTC QLQ-C30, FACT-L)</td>
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<td>FACT-L</td>
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<td>Sickness absence and work status</td>
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<td>Other measurements</td>
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<td>Perioperative complications</td>
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<tr>
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<td>Histological diagnosis and TNM staging</td>
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<td>X</td>
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</table>

*Baseline (0 week).
*Flw-up (Follow-up): Preoperation (the day before surgery).
*Flw-up (Follow-up): Pre-intervention (2/6 weeks after surgery).
*Flw-up (Follow-up): Post-intervention (14/18 weeks after surgery).
*Flw-up (Follow-up): Six months after surgery.
*Flw-up (Follow-up): One year after surgery.

Figure 2 PROLUCA Study Timeline (three intervention groups and one control group).
adherent, or resistance training prescription guidelines for adults as recommended by the American College of Sports Medicine (ACSM) [50]. The ultimate goal for the exercise prescription is to exercise with an intensity of ~60-80% of 1 RM two times a week for 12 weeks. To ensure progression every second week, the load is progressively increased and the number of repetitions are reduced starting out at 12 repetitions in three sets progressing to 10 repetitions in three sets to a final of eight repetitions in three sets. The progression is documented in a study exercise log file for registration of the intensity of all sessions along with data on blood pressure prior to exercise.

**Adherence Considerations**
To maximize adherence, several strategies will be employed including telephone-based follow-ups. The patients are provided free parking in front of the center and transport expenses are covered. The high degree of scheduling flexibility allows participants to perform test at a convenient time and work around other competing demands such as medical appointments, work, and family commitments.

**Study endpoints and assessments**

**Primary endpoint**
VO\(_2\)peak is evaluated by an incremental test using an electromagnetically braked cycle ergometer (Lode Corival Ergometer©). Inspired and expired gases are analyzed breath-by-breath by a metabolic cart (JAEGER MasterScreen CPX©). Subjects begin pedaling at seven watts and resistance increases after a predefined 10 watts ramp protocol until exhaustion or a symptom-limited VO\(_2\)peak is achieved (pain, dizziness, anxiety etc.). This regimen has previously been demonstrated to be appropriate for measuring VO\(_2\)peak in prior studies in patients with ankylosing spondylitis [51]. Other similar VO\(_2\)peak protocols are found appropriate for measuring VO\(_2\)peak in NSCLC [38,39,52].

**Secondary endpoints**

**Patient-reported outcomes (PROs)** PROs will include HRQoL, symptoms and side effects, anxiety and depression, well-being, distress, lifestyle, sickness absence, work status, and social support. HRQoL is assessed using the integrated system of the European Organization for Research and Treatment in Cancer (EORTC) for assessing the HRQoL of cancer patients participating in international clinical trials and devised through collaborative research. The EORTC QLQ-C30 assesses patient symptoms and HRQoL in lung cancer patients [53]. Symptoms and side effects will be assessed using the EORTC–LC13, which is an additional page to the EORTC–QLQ specifically designed to cover a wide range of lung cancer patients varying in disease stage and treatment modality [54]. EORTC measures single items and the scales range in score from 0 to 100. A high scale score represents a higher response level. A high score for a functional scale represents a high/healthy level of functioning and a high score for the global health status/quality of life represents a high HRQoL. However, a high score for a symptom scale/item represents a high level of symptomatology or problems [53,54]. HRQoL will also be assessed using the Functional Assessment of Cancer Therapy - Lung (FACT-L) scale that contains four subscales for physical (7-items), functional (7-items), emotional (6-items), social/family well-being (7-items) plus a lung cancer specific subscale (15-items) which will be summed to obtain the FACT-L score (all 42 items) [55].

General well-being is assessed using the 36-Item Short Form Health Survey (SF-36), standard recall (four weeks). The SF-36 includes eight scales measuring general health with two summary scales; physical and mental component scales [56,57]. To assess psychological well-being, the Hospital Anxiety and Depression Scale (HADS) with 14 items will be administered, designed to measure general anxiety and depression for use in investigations of patients with physical illness [58]. The distress thermometer is a validated measure of distress and consists of a single item, with responses ranging from 0 to 10 [59].

The Multidimensional Scale of Perceived Social Support (MSPSS) is a 12-item scale assessing social support. Each item is answered on a seven-point Likert scale, from one: Very strongly disagree, to seven: Very strongly agree. The scale yields three subscale scores, for Family, Friends, and Significant Others, and a Total score, which is confirmed in a confirmatory factor analysis [60]. In other different cancer studies, all the above-mentioned validated instruments were found appropriate and easy to administer [35,52,59,61].

**Physiological measurements**
Physiological measurements will include: (1) functional capacity, (2) pulmonary function, (3) cardiovascular O\(_2\) delivery, and (4) muscle strength. (1) functional capacity will be measured by a six-minute walking distance (6MWD) test carried out over a pre-measured distance of 22 m and in accordance with the American Thoracic Society (ATS) statement [62]. The 6MWD test has demonstrated good reliability and validity in patients with chronic obstructive lung disease [63], a patient group with similar symptomatology and pathophysiology. (2) Pulmonary Function will be determined by assessing the Forced Expiratory Volume in one second (FEV\(_1\)), and the FEV\(_1\)/FVC\(_\text{ratio}\) which is the ratio of FEV\(_1\) to the Forced Vital Capacity (FVC) using a Triple V digital volume sensor® connected to JAEGER MasterScreen CPX®. All pulmonary function
tests will be performed in a standing position and according to the ATS guidelines [48]. (3) Arterial O2 Saturation will be assessed at rest and continuously during exercise using pulse oximetry (Nellcor, OxiMax N-65®), which provides the most accurate non-invasive assessment of blood arterial O2 saturation levels. Muscle strength is measured by 1RM [64] using machines (Technogym™) that includes leg press (lower extremity) and chest press (pectoral muscles).

Disease-related outcomes
In all patients lung cancer subtype, stage and extent of surgery will be related to the effect of exercise and rehabilitation interventions.

Tracking and monitoring of adverse events
Tracking and monitoring of adverse events are assessed as follows: (1) before every intervention- and test-session, all patients will receive face-to-face supervision by a specialized trained cancer nurse discussing any potential negative side effects of the intervention assignment. All injuries and adverse events (e.g., knee pain, back pain) will be recorded as unintended events. In addition, heart rate and blood pressure are recorded prior to every intervention session and repeated if any adverse events should occur during exercise.

Statistical considerations
Sample size calculation
This randomized phase II trial will accrue 380 subjects with operable NSCLC over an accrual period of ~2 years. The present design consists of four intervention groups with operable NSCLC over an accrual period of ~2 years. This randomized phase II trial will accrue 380 subjects required in each group (power: 80%), giving a total inclusion of 380 patients.

For each of the primary and secondary endpoints, three separate t-tests will be used to compare each experimental arm to the control arm in mean change across time of the endpoint. For each endpoint, the overall alpha level will be controlled at a two-sided 0.05 by using Holm’s procedure [65]. That is, Holm’s procedure first ranks the three p-values from lowest to highest. The first (lowest) p-value has to be less than 0.05/3 (0.0167) to be significant and permit continuation to the other t-tests. The Holm’s procedure continues sequentially in this fashion using alpha levels of 0.05/2 (0.025) and 0.05/1 (0.05) for the remaining two t-tests, respectively. Power for this study is defined as the probability that at least one of the three t-tests of the arm effect on VO2peak is significant; in other words, power is the probability that the first of the 3 ordered t-tests are significant. We assume that change in VO2peak will have a standard deviation of 4.0 mL kg⁻¹ min⁻¹ as observed in previous research [27,36]. Statistical power depends upon the configuration of mean change in VO2peak across the 4 arms. Thus, for example, 80% power is obtained when the mean change in VO2peak across Arms 1, 2, 3, and 4 is 0.60, 0.60, 2.10, and 0.0 (mL kg⁻¹ min⁻¹), respectively.

Analytic plan
The intention-to-treat analysis includes all randomized participants in their randomly assigned allocations. The intervention group assignment will not be altered based on the participant’s adherence to the randomly allocated study arm. Patients who are lost-to-follow-up are included in the analysis (intention to treat). For the primary analysis, a multiple regression model will be used to assess a change in VO2peak on study group, the baseline value of the endpoint, and other pertinent baseline variables that may influence change in the study endpoints (e.g., comorbid conditions/medications, self-reported exercise history, age). Data from PROs will be presented as mean, standard deviation (SD), median and inter-quartile range (IQR) and all change scores (value at follow-up minus value at baseline) will be presented with a 95% confidence interval.

Discussion
The aim of PROLUCA is to contribute with important knowledge about the efficacy of pre- and early postoperative rehabilitation in patients with NSCLC in a non-hospital setting.

The decision to target newly diagnosed patients with NSCLC was primarily based on the fact that these patients are not often examined in relation to the effect of rehabilitation, although they generally have a good performance status and prognosis after surgery and adjuvant chemotherapy. In consequence, the issue of NSCLC survivorship is becoming an increasingly important aspect of the multidisciplinary care of this patient group and the demands for knowledge correspondingly important.

The need for rehabilitation becomes obvious by the fact that NSCLC patients are subject to a marked decrease in cardiorespiratory capacity due to a combination of age and comorbidity and reinforced by the use of adjuvant cancer treatment [6]. It is well known that good preoperative cardiorespiratory capacity leads to better postoperative conditions resulting in less postoperative complications in patients with NSCLC [1,5]. Further studies are also warranted on other physical effects of exercise and how to commit this group of cancer patients to a more active lifestyle.

Studies focusing on the effects of exercise interventions pre- and postoperatively are required to fully understand the potential effect of exercise over time. The optimal
characteristics of exercise (mode, intensity, frequency, duration, and timing) have yet to be determined [24].

No published research in cancer rehabilitation has investigated the best timing of rehabilitation in patients with NSCLC in a randomized clinical trial. Qualitative studies have pointed out that cancer patients may experience transition points during time of illness to which they are particularly vulnerable: (1) diagnosis, (2) operation and hospitalization, (3) transition from hospital to daily life, and (4) return to daily life [66-72]. The timing of rehabilitation has also been indicated to of importance when it comes to motivation toward a healthier lifestyle in patients with a variety of cancer diagnoses [73]. The ‘teachable moment’ is a term used in e.g. research in breast cancer patients describing the transition that takes place when the patients are diagnosed. This transition can modify barriers and motivate the patient; thus timing of rehabilitation is of great importance for the outcome [74].

The PROLUCA study aims at revealing the impact of timing of rehabilitation on VO2peak and health-promoting behavior in patients with NSCLC. The effect six months and one year after surgery is measured. VO2peak is chosen as the primary endpoint as this test provides the gold standard (direct) assessment of cardiopulmonary capacity [13]. In a hospital setting it would have been interesting to test cardiopulmonary capacity as early as two weeks postoperatively, but as the intervention in PROLUCA is carried out in a non-hospital setting, this is not possible due to safety reasons. According to the Danish Health Act from 2007 the responsibility for rehabilitation of all patients with a decrease in functional capacity lies with the municipalities unless medical assistance is needed. The same is true of patient-targeted prevention.

The patients perform a VO2peak test preoperatively and again after the intervention. The first test acts as a surrogate parameter for the starting point, and PROLUCA is therefore not capable of clarifying what happens to VO2peak shortly after surgery. Research indicates that VO2peak spontaneously recovers to a limited degree at approximately 6 months after surgery, and stabilizes at approximately 3 months after surgery and pulmonary resection. Another study finds a 13% decrease in VO2peak ~6 months after surgery [75]. As this study compares the preoperative VO2peak with postoperative VO2peak value 6 months after surgery, the best estimate possible is chosen.

To obtain a patient population as close to normal daily practice as possible where patients are suffering from a variety of comorbidity, PROLUCA limits the amount of exclusion criteria. This makes PROLUCA unique compared to other studies whose selection of patients is distinct. Therefore the results of PROLUCA may contribute importantly to daily clinical practice.

With the increasing interest in the field of exercise oncology research, more studies are now focusing on the application of exercise as a concomitant intervention alongside anti-cancer therapies.

Summary

Even though rehabilitation, with focus on exercise, is widely recommended to cancer patients, information concerning timing and dose of exercise rehabilitation is lacking when it comes to patients operated for NSCLC. To our knowledge no previous studies have been published in which postoperative rehabilitation is initiated as early as two weeks after surgery for NSCLC. Furthermore, there is a distinct need for trials including NSCLC patients, since this group of patients is especially vulnerable due to a high burden of comorbidity, risk of relapse of the cancer disease and consequences of both surgical and oncological treatment. In addition, the patient population included in PROLUCA is as close to those seen in normal daily practice as possible. This makes PROLUCA unique compared to other studies whose selection of patients is distinct, and the results of the PROLUCA study may contribute importantly to daily clinical practice.

Abbreviations

VO2peak: Maximal oxygen uptake; NSCLC: Non-small cell lung carcinoma; HRmax: Heart rate max; 6 MWD: Six-minute walk distance; 1 RM: One-repetition-maximum; PROs: Patient-reported outcomes; HRQoL: Health related quality of life; SCLC: Small-cell lung carcinoma; VATS: Video-assisted thoracoscopic surgery; TTN: Tumor node metastasis; ACSM: American College of Sports Medicine; EORTC: The European Organization for Research and Treatment in Cancer; FACT-L: Functional assessment of cancer therapy – lung; SF-36: 36-item short form health survey; HADS: Hospital anxiety and depression scale; ATS: American Thoracic Society; FEV1: Forced expiratory volume in one second; FVC: Forced vital capacity; FEV1/ FVC: Which is the ratio of FEV1 to the FVC.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

MSS: conception and design, drafting of manuscript and final approval for publication. KT: conception and design, drafting of manuscript and final approval for publication. JVP: conception and design, drafting of manuscript and final approval for publication. MM: conception and design and final approval for publication. MC: conception and design and final approval for publication. MM: conception and design and final approval for publication. KT: conception and design, drafting of manuscript and final approval for publication. HL: conception and design and final approval for publication. MSS: conception and design, drafting of manuscript and final approval for publication. All authors read and approved the final manuscript.

Acknowledgements

The study is supported by grants from The Center for Integrated Rehabilitation of Cancer patients (CIRE), a center established and supported by The Danish Cancer Society and The Novo Nordisk Foundation, and the study is supported by the Copenhagen University Hospital, the Faculty of Health Sciences, University of Copenhagen, and is secured by funding from The Municipality of Copenhagen. The authors thank Karl Bang Christensen, Associate professor, Department of Biostatistics, University of Copenhagen, for his valuable assistance concerning biostatistics.
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Received: 10 July 2013 Accepted: 13 May 2014

Published: 4 June 2014

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Cite this article as: Sommer et al.: Perioperative rehabilitation in operation for lung cancer (PROLUCA) – rationale and design. BMC Cancer 2014, 14:404.

doi:10.1186/1471-2407-14-404

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Perioperative rehabilitation in operable lung cancer patients (PROLUCA)

**This declaration concerns the following article:**


**The PhD student’s contribution to the article:**

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Signature of the PhD student and the principal supervisor:

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Perioperative Rehabilitation in Operable Lung Cancer Patients (PROLUCA): A Feasibility Study

Maja S. Sommer, MHS, PT1, Karen Trier, RN, MR1, Jette Vibe-Petersen, MD1, Malene Missel, RN, MScN2, Merete Christensen, MD2, Klaus R. Larsen, MD, PhD3, Seppo W. Langer, MD, PhD2, Carsten Hendriksen, MD2, Paul Frost Clementsen, MD2,4, Jesper H. Pedersen, MD, DMSc2, and Henning Langberg, PhD, DMSc2

Abstract

Introduction. Surgical resection in patients with non–small cell lung cancer (NSCLC) may be associated with significant morbidity, functional limitations, and decreased quality of life. Objectives. The safety and feasibility of a preoperative and early postoperative rehabilitation program in patients operated for NSCLC was determined in a nonhospital setting, with focus on high-intensity interval exercise. Methods. Forty patients with biopsy-proven NSCLC stages I to IIIa referred for surgical resection at the Department of Cardiothoracic Surgery RT, Rigshospitalet, University of Copenhagen, were randomly assigned to 1 of 4 groups (3 intervention groups and 1 control group). The preoperative intervention consisted of a home-based exercise program, while the postoperative exercise program comprised a supervised group exercise program involving resistance and high-intensity interval cardiorespiratory exercise 2 hours weekly for 12 weeks combined with individual counseling. The study endpoints were inclusion rate, adherence, and number of adverse events. Results. Forty patients (of 124 screened; 32%) were included and randomized into the 4 groups. The postoperative exercise was completed by 73% of the patients randomized to this intervention. No adverse events were observed, indicating that the early postoperative exercise program is safe. The preoperative home-based exercise program was not feasible due to interfering diagnostic procedures and fast-track surgery that left only 1 to 2 weeks between diagnosis and surgery. Conclusion. The early postoperative exercise program for patients with NSCLC was safe and feasible, but in a fast-track set up, a preoperative home-based exercise program was not feasible for this population.

Keywords
lung cancer, exercise, rehabilitation, NSCLC, perioperative intervention

Submitted Date: 8 September 2015; Revised Date: January 13 2016; Acceptance Date: 21 January 2016

Introduction

Among the most common cancers, lung cancer has the highest mortality rate of cancer worldwide.1 Most cases are non–small cell lung cancer (NSCLC). Accurate staging of NSCLC is crucial for allocation to surgical treatment, which may be curative in cases of localized disease (stages I and II) and for selected patients with locally advanced disease (stage IIIA).2 The recommended treatment of disseminated NSCLC and small cell lung cancer involves chemotherapy and radiation therapy.2

The number of long-term survivors after treatment of NSCLC is increasing.3 Surgical resection is still associated with potentially significant morbidity, functional limitations, and decreased quality of life. Therefore, evidence-based rehabilitation may be an important tool to improve outcome and quality of life in this group of patients.4,5 Systematic reviews suggest that pre- and postsurgical exercise in patients with NSCLC, compared with usual

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care, is associated with improved cardiopulmonary exercise capacity, increased muscle strength, as well as reduced fatigue, postoperative complications, and length of hospital stay.6-8 These reviews emphasize that an optimal exercise program is still to be determined and that prospective research in this area is needed.5-8

Preoperative exercise offered to NSCLC patients attracts attention because it may improve longevity and decrease risk of postoperative complications, but research in this field differs in design, type of intervention, and dose of exercise. The research is primarily based on case studies and studies with few and heterogeneous patients.9,11 In addition, recent research highlights the need for psychosocial support during the period from diagnosis to surgery.12

Evidence shows that postoperative exercise for NSCLC patients is both safe and associated with improvement of cardiopulmonary capacity and self-reported outcomes such as health-related quality of life and fatigue.13 Still more research is required to understand the potential effect of exercise on NSCLC patients and to determine how individual components such as mode, intensity, frequency, duration, and timing may contribute.7

Barriers for participating in rehabilitation and maintaining lifestyle changes are, for example, high symptom burden, such as side effects to the adjuvant treatment, and high prevalence of comorbidity, especially chronic obstructive pulmonary disease.14 The timing of rehabilitation is important when it comes to motivating patients to perform and sustain lifestyle changes.15 The teachable moment is a term used to describe a health event that motivates individuals to adopt to a healthier lifestyle.15

Silver et al defined cancer rehabilitation as medical care that should be integrated throughout the oncology care continuum and delivered by trained rehabilitation professionals who have it within their scope of practice to diagnose and treat patients’ physical, psychological and cognitive impairments in an effort to maintain or restore function, reduce symptom burden, maximize independence and improve quality of life in this medically complex population.16,p36(p16)

Thus, the focus of this article is the evaluation of the exercise part in a rehabilitation program to patients with operable lung cancer.

The advantages of performing exercise during adjuvant treatment are better physical and mental status and a reduction of side effects to the adjuvant chemotherapy. These advantages are found in a variety of cancer patients.17,19

To our knowledge, no published research has studied whether initiating high-intensity interval exercise is safe in a nonhospital setting as early as 2 weeks after an operation for NSCLC. Our assumption is that introducing exercise before initiation of adjuvant chemotherapy, thereby laying the groundwork for better adherence to the exercise program, is advantageous compared to an exercise program initiated during adjuvant chemotherapy. We assume that NSCLC patients are willing and able to participate in home-based exercise prior to surgery and also hypothesize that patients attending preoperative home-based exercise are more prepared to participate in high-intensity interval exercise after surgery.

**Aim of the Study**

The overall aim of this feasibility study was to investigate the safety and feasibility of preoperative and early postoperative rehabilitation in a nonhospital setting, with focus on exercise, in patients undergoing surgery for lung cancer.

**Methods**

**Patients and Settings**

The PROLUCA feasibility study included 40 patients (age ≥18 years) with biopsy-proven NSCLC, stages I to IIIa assigned for curative surgery at the Department of Cardiothoracic Surgery, Rigshospitalet, University of Copenhagen. The inclusion criteria were the following: assigned for curative lung cancer surgery, at least 18 years old, performance status 0 to 2 (World Health Organization),21 resident of the City of Copenhagen or a surrounding municipality, able to read and understand Danish, and approval by primary surgeon. The exclusion criteria were the following: the presence of metastatic disease or surgical inoperability, diagnosis of lung cancer not verified by biopsy, severe cardiac disease, and contraindications to maximal exercise testing as recommended by the American Thoracic Society and by exercise testing guidelines for cancer patients.22

**Procedure**

The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement for nonpharmacologic interventions and the World Medical Association Declaration of Helsinki.23,24 Written informed consent was obtained from all patients prior to initiation of any study procedures. The study was approved by the Danish National Committee on Health Research Ethics (File No. H-3-2012-028) and the Danish Data Protection Agency (File No. 2007-58-0015).

The study design is presented in Figure 1. Using a 4-arm, randomized design, potential subjects were identified and screened for eligibility and contacted by the study research coordinators at the referral departments at Bispebjerg and Gentofte Hospitals. After referral to surgery, the subjects were contacted by telephone and informed of the purpose and design of the study. Next, written informed consent was
obtained and baseline assessment was performed at the Copenhagen Centre for Cancer and Health. At baseline the following assessments were performed (Table 1): (1) anthropometric data and tumor node metastasis (TNM) stage, (2) cardiorespiratory capacity expressed as maximal oxygen uptake (VO2peak) evaluated by an incremental test using an electromagnetically braked cycle ergometer (Lode Corival Ergometer, Groningen, Netherlands) where inspired and expired gases were analyzed breath-by-breath by a metabolic cart (JAEGER MasterScreen CPX, Care Fusion, San Diego, CA), (3) 6-minute walk distance (6MWD), (4) muscle strength measured by a 1 repetition maximum (1RM) in chest and leg press, (5) pulmonary function test (spirometry), and (6) patient-reported outcomes. All baseline assessments were completed as close to the time of diagnosis as possible and were repeated the day before surgery, postintervention, and at follow-up 6 months and 1 year after surgery. Assessments at pre-intervention were 6MWD, pulmonary function, and Functional Assessment of Cancer Therapy–Lung (FACT-L).

Group Allocation (Randomization)
Following the successful completion of baseline assessments, patients were randomized and allocated, on an individual basis, to 1 of the 4 exercise intervention groups:

1. Preoperative and postoperative exercise initiated 2 weeks after surgery
2. Preoperative and postoperative exercise initiated 6 weeks after surgery
3. Postoperative exercise initiated 2 weeks after surgery
4. Current standard care, postoperative exercise initiated 6 weeks after surgery

The random allocation sequences were concealed from all study personnel and performed by Copenhagen Trial Unit, Centre for Clinical Intervention Research. Randomly allocated patients remained in the same group for the entire duration of the intervention.

The intention-to-treat analysis included all randomized participants in their randomly assigned allocations. The intervention group assignment was not altered based on the participant’s adherence to the randomly allocated study arm. Patients who were lost to follow-up were included in the analysis (intention-to-treat).

Exercise Training Protocols

Preoperative Exercise. Individually designed according to functional status and comorbidity for each patient randomized to the preoperative intervention, the home-based exercise program consisted of 30 minutes of cardiorespiratory exercise daily until surgery. The exercise period varied in length due to the time available before surgery. The preoperative exercise was monitored by a heart rate monitor and software (Polar Team2, Polar Electro Oy, Kempele, Finland) and an exercise diary logbook.

Postoperative Exercise. The postoperative exercise intervention was a part of the rehabilitation services available at a rehabilitation center described in Figure 2. Every participant was initially screened for rehabilitation needs following a professional rehabilitation guide covering the following topics: disease specific, social network, relatives, psychological, existential, diet, smoking, alcohol, physical activity, sexuality, sleep, and stress. The rehabilitation guide was based on the theoretical framework by the World Health Organization on International Classification of Functioning,25 the “self-efficacy theory” by
Integrative Cancer Therapies

Bandura, and motivational interviewing by Miller. The exercise intervention consisted of 24 group-based exercise sessions combined with 3 individual counseling sessions and 3 group-based lessons in health-promoting behavior. If the patients had special needs in terms of smoking cessation, nutritional counseling, or patient education, this was also offered as part of the rehabilitation. The postoperative exercise consisted of individually tailored, supervised strength exercise and group-based cardiorespiratory exercise twice a week (60 minute/session) on nonconsecutive days for 12 weeks, for a total of 24 sessions. It included the following exercises.

Warm-up (5 minutes) and cardiorespiratory exercise (25 minutes) on an ergometer bike (BODY BIKE Classic Supreme, TKO, Houston, TX), individually tailored strength exercise (25 minutes) carried out using 5 machines (Technogym, Cesena, Italy), leg press, chest press, leg extension, pull to chest, and pull down (upper body). Trained physiotherapists and cancer nurse specialists supervised the training program following principles recommended by the American College of Sports Medicine. All exercise sessions included supervised breathing exercises combined with stretching and tension-release techniques (5 minutes). All interventions were individually tailored to each patient and followed the principles of aerobic or resistance training prescription guidelines for adults as recommended by the American College of Sports Medicine. The high-intensity interval exercise consisted of a warm-up period where the participants aimed at reaching a level at 85% of individually determined HRmax (5 minutes) followed by a short rest (1 minute). The duration of the high-intensity interval exercises was 25 minutes. In each interval

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<td>Smoking history, N = 40 (groups 1 and 3, n = 18; groups 2 and 4, n = 22)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoking, n (%)</td>
<td>10 (25%)</td>
<td>7 (39%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Never smoked, n (%)</td>
<td>2 (5%)</td>
<td>1 (6%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Ex-smoker, n (%)</td>
<td>28 (70%)</td>
<td>10 (55%)</td>
<td>18 (81%)</td>
</tr>
<tr>
<td>Years smoking, mean (SD)</td>
<td>41 (15)</td>
<td>44 (12)</td>
<td>38 (13)</td>
</tr>
<tr>
<td>Presence of comorbidity (5 patients had none of the comorbidities mentioned below)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>15 (38%)</td>
<td>6 (33%)</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>9 (23%)</td>
<td>4 (22%)</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>6 (15%)</td>
<td>3 (17%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>COPD, n (%)</td>
<td>8 (20%)</td>
<td>2 (11%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Rheumatic diseases, n (%)</td>
<td>12 (30%)</td>
<td>5 (28%)</td>
<td>7 (32%)</td>
</tr>
<tr>
<td>Other type of cancer, n (%)</td>
<td>6 (15%)</td>
<td>4 (22%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Depression, n (%)</td>
<td>4 (10%)</td>
<td>1 (6%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>Medication, number of drugs, median (range)</td>
<td>3 (1-6)</td>
<td>2 (1-5)</td>
<td>3 (2-6)</td>
</tr>
<tr>
<td>Pulmonary function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEV₁ (L/s), mean (SD)</td>
<td>2.4 (0.6)</td>
<td>2.5 (0.5)</td>
<td>2.3 (0.6)</td>
</tr>
<tr>
<td>FEV₁ (L/s), % predicted (SD)</td>
<td>94 (23.7)</td>
<td>95 (26.1)</td>
<td>93 (22.2)</td>
</tr>
<tr>
<td>FEV₁/VC (%), mean (SD)</td>
<td>67.4 (8.7)</td>
<td>68 (6)</td>
<td>68 (10)</td>
</tr>
<tr>
<td>Cardiorespiratory capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fitness (mL/kg/min), mean (SD)</td>
<td>19.4 (5)</td>
<td>21.5 (6)</td>
<td>17.6 (4)</td>
</tr>
<tr>
<td>Peak oxygen uptake (L/min), mean (SD)</td>
<td>1.40 (0.39)</td>
<td>1.53 (0.33)</td>
<td>1.28 (0.40)</td>
</tr>
<tr>
<td>6MWD, mean (SD)</td>
<td>477 (81)</td>
<td>497 (92)</td>
<td>461 (70)</td>
</tr>
<tr>
<td>TNM stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I (a + b), n (%)</td>
<td>11 (27%)</td>
<td>5 (28%)</td>
<td>6 (27%)</td>
</tr>
<tr>
<td>Stage II (a + b), n (%)</td>
<td>24 (60%)</td>
<td>12 (67%)</td>
<td>12 (55%)</td>
</tr>
<tr>
<td>Stage IIIa, n (%)</td>
<td>5 (13%)</td>
<td>1 (5%)</td>
<td>4 (18%)</td>
</tr>
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</table>

Abbreviations: n, number; SD, standard deviation; COPD, chronic obstructive lung disease; FEV₁, forced expiratory volume in 1 second; VC, vital capacity; 6MWD, 6-minute walk distance.

*P > .05.
(1-2 minutes), the participants aimed at reaching a level of 85% to 100% of individually determined HRmax in each interval followed by a short rest (1 minute). The high-intensity interval exercise was followed by a cool down period (2 minutes).

The ultimate goal for the postoperative exercise was 2 group-based exercise sessions per week, with a cardiorespiratory intensity for the first 4 weeks of approximately 50% to 60% of individual HRmax. In the next 8 weeks, the intensity was increased to moderate-high intensity at approximately 70% to 90% of individually determined HRmax. The ultimate goal of the strength exercise program was to exercise with an intensity of approximately 60% to 80% of 1RM 2 times a week for 12 weeks. To ensure progression, every other week the load was progressively increased and the number of repetitions reduced, starting out at 12 repetitions in 3 sets, progressing to 10 repetitions in 3 sets, to a final of 8 repetitions in 3 sets. The protocol study by Sommer et al describes the pre- and postoperative interventions in further detail.29

**Adherence Considerations**

To maximize adherence, several strategies were employed: telephone-based follow-up, free parking in front of the center, and remuneration for transport expenses. A high degree of scheduling flexibility allowed patients to perform tests at a convenient time to allow space for competing demands such as medical appointments, work, and family commitments.

**Study Endpoint and Assessment**

**Tracking and Monitoring of Adverse Events.** Tracking and monitoring of adverse events took place as follows: before every intervention and test session, all patients received face-to-face supervision by a specialist cancer nurse to discuss any potential negative side effects of the intervention. All injuries and adverse events (eg, knee pain, back pain) were recorded as unintended events. In addition, heart rate and blood pressure were recorded prior to every intervention session and repeated if any adverse events occurred during exercise.

**Adherence to the Program.** Reasons for not attending the program were assessed immediately after the participants decided not to participate or decided to drop out of the program. The assessment was performed by specially trained cancer staff and conducted either by phone or face-to-face.
Adherence to exercise sessions was monitored by trained staff, and reasons for not attending a session were assessed immediately after absence from exercise.

**Statistical Analysis**

Descriptive statistics and paired *t* tests were calculated using SAS/STAT software. Statistical significance was set at *P* < .05. Baseline values of the study populations were compared with values measured at postintervention and 1-year follow-up. The values are expressed as mean ± standard deviation (SD). Paired *t* tests were also performed to reveal tendencies in patients who exercised for more or less than 70% of the exercise sessions. Cardiac rehabilitation normally sets the cutoff for adherence to both the number of training sessions prescribed and the duration of the prescribed program as at least 80%. In cancer rehabilitation, there is no standard practice on how to set adherence to an exercise intervention. Based on the small number of participants in this study, we chose a cutoff value for adherence as at least 70% of the exercise sessions.

**Results**

**Study Population and Characteristics**

A total of 180 patients were screened for eligibility, 124 of whom were eligible. Forty patients (32%) were included and randomized. Table 1 presents the baseline characteristics of the 40 patients included and of the pooled subgroups with either early (groups 1 + 3) or late (groups 2 + 4) exercise intervention. The 2 most frequent reasons given by patients for not attending the study were either logistical ones or that the patients had too much to think about prior to surgery (Figure 3). The 40 patients included in the study had a mean age of 68 years, and the majority were retired (Table 1). The most frequent comorbidities (registered from the medical records) were hypertension, dyslipidemia, rheumatic disease, and chronic obstructive pulmonary disease. Five patients had no comorbidity, and 16 patients were categorized as having multiple morbidities. At baseline, 70% were ex-smokers, and 25% currently smoked. The baseline cardiopulmonary capacity of the included patients was 19.4 mL/kg/min and a forced expiratory volume in 1 second (FEV1) at 2.4 L/s and a FEV1/vital capacity [VC] at 67.4%; Table 1).

The VO2peak and fitness measured at baseline was significantly higher in the early exercise group compared to the late exercise group (Table 1).

Nine patients (22%) underwent open thoracotomy surgery, of which 3 participated in early exercise group and 6 participated in late exercise group. Thirty-one (78%) patients received video-assisted thoracic surgery and 13 (33%) received adjuvant chemotherapy (9 in early exercise groups and 4 in late exercise groups).

The types of operation that were performed were primarily lobectomy (83%); only 1 pneumonectomy was performed (2%). The patient that had a pneumonectomy was randomized to the early intervention group and had an adherence to the exercise program of 80%. Other types of operations performed were bilobectomy (5%), wedge resection (8%), and video-assisted thoracic surgery, and chronic obstructive pulmonary disease. Five patients had no comorbidity, and 16 patients were categorized as having multiple morbidities. At baseline, 70% were ex-smokers, and 25% currently smoked. The baseline cardiopulmonary capacity of the included patients was 19.4 mL/kg/min and a forced expiratory volume in 1 second (FEV1) at 2.4 L/s and a FEV1/vital capacity [VC] at 67.4%; Table 1).

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the late intervention (groups 2 and 4) was initiated. As a result, this patient could no longer be categorized in the early initiation of exercise group.

The distribution of patients who performed preoperative exercise was evenly distributed between patients who exercised for at least 70% or for less than 70% of the postoperative sessions. The mean intensity of the strength exercise was for the chest press 67% (SD 20) of 1RM and for leg press 69% (SD 22) of 1RM during the 24 exercise sessions. The intensity of the cardiorespiratory exercise for the first 4 weeks was at 74% (SD 8) of individual determined maximum heart rate and for the last 8 weeks at 77% (SD 4) of individual determined maximum heart rate.

**Dropouts.** Eleven patients dropped out during the intervention, primarily due to either lack of motivation to complete or side effects to the adjuvant chemotherapy. Patients receiving adjuvant chemotherapy were evenly distributed between completers and dropouts (Table 3). The prevalence of patients receiving adjuvant chemotherapy was lower in patients who exercised for 70% to 100% of the 24 exercise sessions compared to patients who exercised 0% to 69% (Table 3). There was no difference between completers and dropouts regarding demographic data, stage of disease, or type of surgery. Dropouts were evenly distributed between the groups who initiated exercise 2 and 6 weeks after surgery (Table 2).

**Postoperative Complications, Recurrence, and Mortality**

Out of all of the registered pulmonary and cardiac complications, only one occurred during the exercise intervention and it involved pulmonary pneumatocele and was not evaluated as an adverse event caused by the exercise. All other pulmonary and cardiac complications occurred before the patients initiated the exercise intervention. The overall prevalence of pulmonary postoperative complications within 30 days after surgery was 23% and was highest in the early exercise group (groups 1 and 3; Table 4). The prevalence of cardiac complications was 13%, and the distribution of cardiac complications was evenly distributed between early and late exercise. Two patients experienced recurrence and 3 patients died within the first year after surgery (Table 4).

**Changes in Physiological Capacity**

Table 5 shows the results of physiological capacity change scores from baseline to postintervention and from baseline
There was a significant increase postintervention in walking distance (P = .0229) for patients who participated in at least 70% of the sessions. This effect on walking distance was not reproduced at the 1-year follow-up. There was a significant improvement in strength for patients who participated in at least 70% of the sessions. This improvement was found for leg press in both the postintervention and at the 1-year follow-up (P = .0220 and P = .0443). Correspondingly, the improvement for chest press was also significant (P = .0029 and P = .0129).

Independent of adherence to exercise, there was a trend in mean decrease in fitness of 1.9 mL/kg/min from baseline to postintervention (P = .0741). This trend was retained at the 1-year follow-up (P = .0637).

### Discussion

This feasibility study showed that rehabilitation with high-intensity interval exercise initiated 2 weeks after surgery in NSCLC patients in a nonhospital setting was safe and feasible. The preoperative home-based exercise was inconsistent and not feasible in the present setup due to the short time interval between referral and surgery (fast-track surgical program).

### Preoperative Home-Based Exercise

To our knowledge only one study has investigated the effect of a home-based exercise training program prior to surgery in patients who are potentially candidates for lung resection, but the patients were younger and diagnosed with early-stage lung cancer compared to the patients in the present study. Coats et al found good adherence to a 4-week home-based exercise intervention as all of the included patients (n = 16) completed more than 75% of the prescribed exercise sessions. In Denmark, the maximum waiting time for surgery after a diagnosis of lung cancer is, by law, specified not to exceed 2 weeks. Therefore, a 4-week preoperative training program would not be possible.
Table 5. Physiological Capacity Change Scores (Evaluated in Relation to Adherence to Exercise).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Baseline (N = 40)</th>
<th>Baseline (n = 29)</th>
<th>Baseline (n = 28)</th>
<th>Difference Between Baseline and Postintervention</th>
<th>Difference Between Baseline and 1-Year Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO2peak (L/min)</td>
<td>1.40 (0.39)</td>
<td>1.35 (0.54)</td>
<td>1.38 (0.40)</td>
<td>−0.12 (−0.27 to 0.03)</td>
<td>−0.09 (−0.21 to 0.02)</td>
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<tr>
<td>Exercise ≥70%</td>
<td>1.45 (0.45)</td>
<td>1.45 (0.55)</td>
<td>1.35 (0.44)</td>
<td>−0.08 (−0.26 to 0.11)</td>
<td>−0.07 (−0.25 to 0.11)</td>
</tr>
<tr>
<td>Exercise &lt;70%</td>
<td>1.37 (0.35)</td>
<td>1.21 (0.48)</td>
<td>1.41 (0.37)</td>
<td>−0.19 (−0.50 to 0.12)</td>
<td>−0.12 (−0.30 to 0.06)</td>
</tr>
<tr>
<td>Fitness (mL/kg/min)</td>
<td>19.4 (4.8)</td>
<td>18.8 (6.4)</td>
<td>18.4 (2.9)</td>
<td>−1.9 (−3.9 to 0.2)</td>
<td>−1.8 (−3.7 to 0.11)</td>
</tr>
<tr>
<td>Exercise ≥70%</td>
<td>19.2 (5.3)</td>
<td>18.1 (5.7)</td>
<td>17.7 (3.1)</td>
<td>−1.3 (−3.3 to 0.7)</td>
<td>−1.3 (−4.35 to 1.7)</td>
</tr>
<tr>
<td>Exercise &lt;70%</td>
<td>19.6 (4.5)</td>
<td>19.8 (7.7)</td>
<td>19.2 (2.5)</td>
<td>−2.8 (−8 to 2.4)</td>
<td>−2.4 (−5.2 to 0.3)</td>
</tr>
<tr>
<td>6MWD (m)</td>
<td>477 (81)</td>
<td>512 (80)</td>
<td>517 (92)</td>
<td>16 (−3 to 35)</td>
<td>22 (−9 to 53)</td>
</tr>
<tr>
<td>Exercise ≥70%</td>
<td>495 (63)</td>
<td>526 (67)</td>
<td>507 (113)</td>
<td>28 (4 to 51)</td>
<td>20 (−30 to 69)</td>
</tr>
<tr>
<td>Exercise &lt;70%</td>
<td>465 (90)</td>
<td>486 (101)</td>
<td>531 (59)</td>
<td>−7 (−43 to 29)</td>
<td>25 (−16 to 67)</td>
</tr>
<tr>
<td>IRM Leg (kg)</td>
<td>107 (39)</td>
<td>121 (46)</td>
<td>130 (58)</td>
<td>9 (−3 to 22)</td>
<td>21 (5 to 37)</td>
</tr>
<tr>
<td>Exercise ≥70%</td>
<td>112 (41)</td>
<td>140 (67)</td>
<td>133 (51)</td>
<td>30 (5 to 55)</td>
<td>18 (1 to 36)</td>
</tr>
<tr>
<td>Exercise &lt;70%</td>
<td>104 (39)</td>
<td>100 (28)</td>
<td>118 (47)</td>
<td>−6 (−21 to 9)</td>
<td>10 (−12 to 33)</td>
</tr>
<tr>
<td>IRM Chest (kg)</td>
<td>34 (13)</td>
<td>36 (13)</td>
<td>37 (16)</td>
<td>3 (0 to 6)</td>
<td>3 (0 to 6)</td>
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<tr>
<td>Exercise ≥70%</td>
<td>33 (12)</td>
<td>39 (15)</td>
<td>35 (14)</td>
<td>5 (2 to 8)</td>
<td>4 (1 to 7)</td>
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<tr>
<td>Exercise &lt;70%</td>
<td>34 (15)</td>
<td>30 (8)</td>
<td>40 (18)</td>
<td>−2 (−7 to 4)</td>
<td>2 (−4 to 7)</td>
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<td>FEV1, L/s (SD)</td>
<td>2.4 (0.6)</td>
<td>2.2 (0.5)</td>
<td>2.2 (0.4)</td>
<td>−0.2 (−0.4 to 0)</td>
<td>−0.2 (−0.3 to 0)</td>
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<tr>
<td>FEV1/VC, % (SD)</td>
<td>67.4 (8.7)</td>
<td>66.7 (10.9)</td>
<td>63.9 (8.4)</td>
<td>−1.3 (−3.8 to 1.2)</td>
<td>−6.3 (−9.5 to −3)</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; CI, confidence interval; 6MWD, 6-minute walk distance; FEV1, forced expiratory volume in 1 second; VC, vital capacity.

Some possible advantages of home-based preoperative programs are greater flexibility and convenience for patients, low time consumption, and more manageable financially compared to preoperative interventions in an outpatient setting.32,33 In our study, 28% of eligible patients found physical activity before surgery unmanageable in the fast-track setting. In the present feasibility study, patients who performed preoperative exercise were evenly distributed between patients who exercised for at least 70% or for less than 70% of the postoperative sessions, which indicates that preoperative home-based exercise had no influence.

Preoperative exercise is a component in the emerging medical discipline called Prehabilitation.34 Silver and Baima define prehabilitation as a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairments, and provide interventions that promote physical and psychological health to reduce the incidence and/or severity of future impairments.34(p716)

The potential benefit of prehabilitation to cancer patients and the research within this area seems promising in terms of reducing morbidity, improving physical and psychological function, and decreasing hospital readmissions.34 Supervised Group Exercise After Surgery

In a nonhospital setting, the present study is the first to demonstrate that supervised, group-based high-intensity interval exercise initiated 2 weeks after surgery is safe in NSCLC patients. The present study also demonstrates that the patients could exercise with the average intensity we have prescribed. The intensity of the cardiorespiratory exercise was for the first 4 weeks at 73% of individual determined HRmax. These results indicate that the patients in the present study were able to exercise with a higher intensity than the 50% to 60% we prescribed.

Previous research concerning early postoperative exercise in operable lung cancer patients is based on studies with limited intensity and duration of exercise. In the majority of the studies, the exercise is initiated the day after operation and carried out during hospitalization. These studies find that exercising shortly after an operation for NSCLC is safe, but the studies are characterized by having small sample sizes.35-37 Recently published research investigated the efficacy of home-based postoperative exercise, but the interventions in these studies are characterized by low-intensity exercise interventions.38,39 The present study found a higher prevalence of pulmonary complications in the group that initiated exercise 2 weeks after surgery, but since the complications occurred before exercise was initiated there was no causal relation. The prevalence of pulmonary and cardiovascular postoperative complications in the present study is comparable to other findings in a cohort...
study by Boffa et al.\(^{40}\) Edvardsen et al carried out a randomized clinical trial (RCT) in NSCLC patients, where the intervention was initiated 4 to 6 weeks after surgery and carried out in a fitness center near the patients’ home. In addition to demonstrating significant improvements in both physical performance and health-related quality of life, the study found the intervention to be safe, with only one adverse event reported (a hip fracture).\(^{41}\) Thus, with regard to safety their study supports our results.

Missel et al interviewed patients with operable NSCLC and found that motivation for participation in an exercise program depended on patient expectations concerning the physical benefits and the comfort of having health care professionals present.\(^{12}\) This underlines the importance of having specialized cancer nurses and physiotherapists to manage the exercise instead of attending a public fitness center.

Seventy-three percent of patients in the present study completed the supervised group exercise and adherence to the program exceeded 70% in half of the patients. In the study by Edvardsen et al, mean adherence to the exercise intervention was 88%, but technically some participants could exceed 100%. Other studies reported an adherence of around 50% to 55%.\(^{42,43}\) The present study found no difference between early and late intervention in terms of adherence or dropouts. Among the patients receiving adjuvant chemotherapy, only 2 patients (n = 13) managed to exercise for at least 70% of the sessions, indicating the difficulty of attending exercise during adjuvant chemotherapy.

In the present study, 33% of the patients received adjuvant chemotherapy, which is comparable to the NSCLC population in Denmark.\(^{3}\) Edvardsen et al\(^{41}\) found that patients receiving the last courses of chemotherapy had to postpone their training sessions until they had completed the adjuvant treatment. In contrast, Jones et al\(^{44}\) found good adherence in the same group of patients receiving chemotherapy, but the effect of the intervention was inferior to the findings in the study by Edvardsen et al,\(^{41}\) and the second most frequent reason for dropping out of the present study was side effects of the adjuvant treatment, reported by 27% of the total number of dropouts. The prevalence of patients receiving adjuvant chemotherapy was highest in the group with early exercise. These results show that exercising during adjuvant treatment is feasible and supported by findings in inoperable lung cancer as well as other cancer diagnoses.\(^{17,19}\)

The present study found a significant improvement in strength for patients who exercised for at least 70% of the sessions. This improvement was found for leg and chest press, both postintervention and at the 1-year follow-up and is comparable to the findings of the RCT by Edvardsen et al,\(^{41}\) where the same significant improvement in leg press was found (mean difference at 29.5 kg \(P > .001\)). This improvement is of great importance as muscle strength is inversely associated with all-cause mortality.\(^{45}\) Our feasibility study also found a trend toward a mean decrease in fitness of 1.9 mL/kg/min from baseline to postintervention. These findings are not supported in other studies published in NSCLC patients. Since the study is underpowered, the results must be interpreted with caution.

### Strength and Limitations

The strength of this study is the precise surveillance of adverse events, the reported reasons for dropping out, and the precise detection of postoperative complications. Additional strengths are the use of well-validated objective measurements, blinded professionals collecting data, and the statistical analysis.

The fact that only 32% of the eligible patients participated in the present study can result in a selection bias because the present population might not be representative of the population operated on for NSCLC in Denmark. The low recruitment rate could also affect possibilities to implement these results in a clinical setting. It might be that the patients choosing to participate in the present study represents a group with better physical fitness than the group that did not want to participate in the study. A comparison of the patients in the present study with cohort studies in patients with NSCLC reveals similarities regarding age, sex, pulmonary function, and comorbidities.\(^{40,46}\)

A methodological weakness of this study is that blinding participants to their actual treatment allocation was not possible since participants were aware of whether they initiated preoperative exercise and whether their postoperative exercise started 2 or 6 weeks after surgery. Another limitation in the present study is the low number of participants and thereby the risk of finding or not finding statistically significant results when using a \(t\) test to analyze the mean difference from baseline to postintervention and from baseline to 1 year after surgery. Therefore, the result from the present study must be interpreted with caution. It is also very important to emphasize that the \(t\) test only allows us to investigate the effect on a certain time point and we cannot conclude anything about the effect over time.

### Conclusion

This study shows that patients with operable NSCLC are able to initiate high-intensity interval group exercise 2 weeks after lung resection in a nonhospital setting. Early, supervised, group-based high-intensity interval exercise is both safe and feasible. In the study setting, the preoperative home-based exercise was not feasible due to low recruitment rate and the short time interval between referral and surgery. Our findings are currently under investigation in an RCT study examining the effect of a postoperative exercise intervention initiated either 2 or 14 weeks after surgery. To
ensure a higher inclusion rate, the preoperative exercise intervention has been omitted.

**Declaration of Conflicting Interests**
The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding**
The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by grants from the Center for Integrated Rehabilitation of Cancer Patients (CIRE), which was established by and receives support from the Danish Cancer Society and the Novo Nordisk Foundation.

**References**

DECLARATION OF CO-AUTHORSHIP

**Information on PhD student:**

<table>
<thead>
<tr>
<th>Name of PhD student</th>
<th>Maja Schick Sommer</th>
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<tr>
<td>Date of birth</td>
<td>08/12-1976</td>
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<tr>
<td>Work place</td>
<td>Copenhagen Centre for Cancer and Health</td>
</tr>
<tr>
<td>Principal supervisor</td>
<td>Professor Henning Langberg</td>
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**Title of PhD thesis:**

Perioperative rehabilitation in operable lung cancer patients (PROLUCA)

**This declaration concerns the following article:**


**The PhD student’s contribution to the article:**

*please use the scale (A,B,C) below as benchmark*)

<table>
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<th>(A,B,C)</th>
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<td>2. Planning of the experiments and methodology design, including selection of methods and method development</td>
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<td>3. Involvement in the experimental work</td>
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<td>4. Presentation, interpretation and discussion in a journal article format of obtained data</td>
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*Benchmark scale of the PhD student’s contribution to the article

| A. refers to: | Has contributed to the co-operation | 0-33 % |
| B. refers to: | Has contributed considerably to the co-operation | 34-66 % |
| C. refers to: | Has predominantly executed the work independently | 67-100 % |

**Signature of the co-authors:**

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Changes in Health-Related Quality of Life During Rehabilitation in Patients With Operable Lung Cancer: A Feasibility Study (PROLUCA)

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Abstract
Introduction: Surgical resection in patients with non–small cell lung cancer (NSCLC) may be associated with significant morbidity, functional limitations, and decreased quality of life. Objectives: The objective is to present health-related quality of life (HRQoL) changes over time before and 1 year after surgery in patients with NSCLC participating in a rehabilitation program. Methods: Forty patients with NSCLC in disease stage I to IIIa, referred for surgical resection at the Department of Cardiothoracic Surgery RT, Rigshospitalet, were included in the study. The rehabilitation program comprised supervised group exercise program, 2 hours weekly for 12 weeks, combined with individual counseling. The study endpoints were self-reported HRQoL (Functional Assessment of Cancer Therapy–Lung, European Organization for Research and Treatment in Cancer–Quality of Life Questionnaire–QLQ-C30, Short-Form-36) and self-reported distress, anxiety, depression, and social support (National Comprehensive Cancer Network Distress Thermometer, Hospital Anxiety and Depression Scale, Multidimensional Scale of Perceived Social Support), measured presurgery, postintervention, 6 months, and 1 year after surgery. Results: Forty patients were included, 73% of whom completed rehabilitation. Results on emotional well-being (P < .0001), global quality of life (P = .0032), and mental health component score (P = .0004) showed an overall statistically significant improvement during the study. Conclusion: This feasibility study demonstrated that global quality of life, mental health, and emotional well-being improved significantly during the study, from time of diagnosis until 1 year after resection, in patients with NSCLC participating in rehabilitation.

Keywords
lung cancer, exercise, rehabilitation, NSCLC, HRQoL

Submitted date: 20 May 2016; Revised Date: 3 August 2016; Acceptance Date: 6 August 2016

Introduction
Health-related quality of life (HRQoL), including physical, psychological, and social functioning, has become an important topic in clinical oncology during and after treatment for lung cancer.1 Furthermore, many randomized controlled trials include HRQoL measures as a valid and useful endpoint in addition to the traditional clinical outcomes of, for example, mortality and morbidity.2 As predictor of survival, HRQoL reflects how patients with lung cancer experience the impact of the cancer disease and its treatment on their quality of daily living, thus making HRQoL an important clinical outcome.3-6 Kurtz et al.7 describe the connection between physical symptoms as a result of the disease combined with subsequent treatment and decline in physical function and its

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effect on emotional well-being. They find that the severity of cancer-related symptoms, restrictions in social functioning, and radiation treatment were the primary predictors of depressive symptoms in elderly lung cancer patients during the first year after diagnosis. As a result, early identification of psychosocial difficulties in patients with non–small cell lung cancer (NSCLC) is recommended. Lowery and colleges also hypothesize that the decline in HRQoL in postsurgical NSCLC survivors reflects a decline in the physical component more than a decline in the emotional component of HRQoL.8

Factors negatively associated with HRQoL following lung cancer surgery include the extent of resection,9 postoperative pain,10 degree of comorbidity,10 distressed mood,11 and fatigue.12 Cerfolio and Bryant observed that pneumonectomy leads to worse HRQoL than lobectomy and that preoperative HRQoL is an important predictor of postoperative HRQoL.13

Despite a history of lung cancer, most cancer survivors appear to believe that they have good to excellent health, and although many lung cancer survivors already practice behaviors associated with a healthy lifestyle, there are still many who do not and who may need help in selected areas.14 Engaging in physical activity among lung cancer survivors is particularly low during the early posttreatment period. Lung cancer survivors who currently meet physical activity guidelines report better quality of life in multiple domains than less active individuals, but as most lung cancer survivors do not meet physical activity guidelines, they may benefit from interventions promoting regular physical activity.1

The overall aim of this feasibility study was to investigate the safety and feasibility of preoperative and early postoperative rehabilitation in a nonhospital setting, with a focus on exercise, in patients undergoing surgery for lung cancer. Sommer et al15 recently reported on this topic. The aim of this article is to present HRQoL changes over time before and 1 year after surgery in the same population of patients with NSCLC participating in a rehabilitation program.

Methods

Patients and Settings

The Perioperative Rehabilitation in Operation for Lung Cancer (PROLUCA) feasibility study included 40 patients. The inclusion criteria were the following: biopsy-proven diagnosis of NSCLC, scheduled for surgery with curative intention, at least 18 years of age, World Health Organization performance status 0 to 2,16 resident of the City of Copenhagen or a surrounding municipality, able to read and understand Danish, and approval by the primary surgeon. The exclusion criteria were the following: presence of metastatic disease or surgical inoperability, diagnosis of lung cancer not verified pathologically, severe cardiac disease, and contraindications to maximal exercise testing as recommended by the American Thoracic Society and by exercise testing guidelines for cancer patients.17,18

Procedure

The study was conducted in accordance with the Consolidated Standards of Reporting Trials (CONSORT) statement for nonpharmacologic interventions and the World Medical Association Declaration of Helsinki.19,20 Written informed consent was obtained from all patients prior to initiation of the study procedure. The study was approved by the Danish National Committee on Health Research Ethics (File No. H-3-2012-028) and the Danish Data Protection Agency (File No. 2007-58-0015).

The study comprised a 4-arm, randomized feasibility design. Patients were referred from 2 medical departments to the Department of Cardiothoracic Surgery, Rigshospitalet.

Baseline assessment included physical tests and patient-reported outcomes and was performed at the Copenhagen Centre for Cancer and Health. HRQoL was assessed at the following 5 time points:

1. Baseline assessments completed as close to the time of diagnosis as possible
2. Presurgery assessments completed the day before surgery
3. Postintervention assessments completed 2 to 14 days after the last exercise session
4. Six-month assessments completed as close as possible to 26 weeks after surgery
5. One-year assessments completed as close as possible to 52 weeks after surgery

Group Allocation (Randomization)

Following the successful completion of baseline assessments, patients were randomized and allocated, on an individual basis, to 1 of the 4 exercise intervention groups, as described in the study protocol by Sommer et al.21 Around half of the patients initiated the postoperative exercise 2 weeks after surgery and the other half 6 weeks after surgery.

The intention-to-treat analysis included all randomized participants in their randomly assigned allocations. The intervention group assignment was not altered based on the participant’s adherence to the randomly allocated study arm. Patients who were lost to follow-up were included in the analysis (intention-to-treat).

Postoperative Exercise Training Protocol

The postoperative exercise intervention was a part of the rehabilitation services available at a rehabilitation center,
described in Figure 1. Every participant was initially screened for rehabilitation needs using a professional rehabilitation guide covering the following topics: disease specific, social, network, relatives, psychological, existential, diet, smoking, alcohol, physical activity, sexuality, sleep, and stress. The theoretical framework of the rehabilitation guide was based on World Health Organization on International Classification of Functioning, Bandura’s self-efficacy theory, and Miller’s motivational interviewing. The exercise intervention consisted of 24 group-based exercise sessions combined with 3 individual counseling sessions and 3 group-based lessons in health-promoting behavior. If the patients had special needs in terms of smoking cessation, nutritional counseling, or patient education, this was also offered as part of the rehabilitation. The postoperative exercise consisted of individually tailored, supervised strength exercise and group-based cardiorespiratory exercise twice a week (60 minutes/session) on nonconsecutive days for 12 weeks, for a total of 24 sessions.

Sommer et al describe the details of the exercise intervention and the physiological results of the PROLUCA feasibility study.

Adherence Considerations
To maximize adherence, several strategies were employed: telephone-based follow-up, free parking in front of the center, and remuneration for transport expenses. A high degree of scheduling flexibility allowed patients to perform tests at a convenient time to allow space for competing demands such as medical appointments, work, and family commitments.

Patient-Reported Outcomes
Patient-reported outcomes included HRQoL, symptoms and side effects, anxiety and depression, well-being, distress, lifestyle, and social support, which were measured at 5 time points: baseline, presurgery, postintervention, and 6 months and 1 year after surgery. HRQoL was assessed using the integrated system of the European Organization for Research and Treatment in Cancer (EORTC), which is often used in cancer patients participating in international clinical trials and devised through collaborative research. The EORTC QLQ (Quality of Life Questionnaire) C30 assesses patient symptoms and HRQoL in cancer patients. Symptoms and side effects were further assessed using the EORTC-QLQ-LC (Lung Cancer) 13, which is an additional page to the EORTC-QLQ specifically designed to cover a wide range of lung cancer patients varying in disease stage and treatment modality. EORTC measures single items, and the scoring scale ranges from 0 to 100. A high score for a functional scale represents a high/healthy level of functioning, and a high score for the global quality of life represents a high HRQoL. However, a high score for a symptom scale/item represents a high level of symptomatology or problems. A difference of 5 to 10 points in the scores represents a small change, 10 to 20 points a moderate change, and greater than 20 points a large clinically significant change from the patient’s perspective.

HRQoL was also assessed using the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale. FACT-L contains 4 subscales for physical well-being (7 items), social/family well-being (7 items), emotional well-being (6 items), and functional well-being (7 items), while
the 7-item FACT-L lung cancer subscale (LCS) assesses symptoms commonly reported by lung cancer patients (eg, shortness of breath, loss of weight, tightness in chest). The trial outcome index (TOI) is derived by adding scores on the physical well-being and functional well-being subscales to the lung cancer subscale. All FACT-L items are rated on a 5-point Likert-type scale ranging from 0 = “Not at all” to 4 = “Very much,” and scores range from 0 to 24 (emotional well-being), 0 to 28 (other 4 subscales), 0 to 84 (TOI), and 0 to 136 (total score). Higher scores represent better quality of life or fewer symptoms. General well-being was assessed using the 36-item Short Form Health Survey (SF-36) version 1, standard recall (4 weeks). SF-36 includes 8 scales measuring general health with 2 summary scales: physical and mental component scales. Psychological well-being was assessed using the Hospital Anxiety and Depression Scale (HADS), which has 14 items designed to measure general anxiety and depression in patients with physical illness. The National Comprehensive Cancer Network (NCCN) Distress Thermometer is a validated measure of distress and consists of a single item, with responses ranging from 0 to 10. The NCCN Distress Thermometer was used to assess distress, and the Multidimensional Scale of Perceived Social Support (MSPSS) was used to assess social support. MSPSS is a 12-item scale that uses a 7-point Likert-type scale ranging from 1 = “Very strongly disagree” to 7 = “Very strongly agree.” The scale yields 3 subscale scores for family, friends, and significant others, in addition to a total score, which is verified with a confirmatory factor analysis. In addition to the MSPSS questionnaire, 7 questions on support from other cancer patients were collected. In other cancer studies, the above-mentioned validated instruments were found appropriate and easy to administer.

**Statistical Analysis**

Repeated-measures analysis of variance was performed using the MIXED Procedure, SAS/STAT software, version 9.3. The clustered nature of the data was taken into account by specifying a heterogeneous autoregressive (1) covariance structure. The overall effect of time was evaluated using an F test. Estimated scale mean scores are reported as mean with corresponding 95% confidence intervals (CIs) and compared to reference data when available. We used Danish reference data for the EORTC QLQ-C30 and the SF-36. For smoking, alcohol, and physical activity habits we used logistic, Poisson, and multinomial logistic regression models, respectively. The clustered nature of the data was taken into account using generalized estimating equations, as implemented in the GENMOD procedure in SAS/STAT software, version 9.3. Wald tests were used to evaluate changes over time.

**Results**

**Study Population and Baseline Characteristics**

A total of 180 patients referred for surgery were screened for eligibility, 124 of whom were eligible. Forty patients (32%) were included and randomized in accordance with the flow chart shown in Figure 2. Table 1 shows the characteristics of the 40 patients included in the study. The mean age was 68 years, 15% were currently employed, and the majority were retired (Table 1). The most frequent comorbidities were hypertension, dyslipidemia, rheumatic disease, and chronic obstructive pulmonary disease (COPD). Five patients had no comorbidity, and 16 patients had more than 2 comorbidities. At baseline, 70% were ex-smokers and 25% were currently smoking. Eleven patients reported that their level of alcohol consumption was above 7 units per week for females and above 14 units per week for males, which is the maximum weekly intake recommended by the Danish National Board of Health. Five patients reported they were sedentary before time of diagnosis. Nine patients (22%) underwent thoracotomy, and 31 (78%) patients had video-assisted thoracic surgical resection (VATS). Thirteen (33%) received postoperative (adjuvant) chemotherapy. The extent of resection was lobectomy (83%), pneumonectomy (2%), bilobectomy (5%), wedge resection (8%), and VATS segmental resection (2%).

The 2 most frequent reasons given by patients for not attending the study were either logistical problems or concerns about the coming surgery (Figure 2).

**Dropouts**

Eleven patients dropped out during the intervention, primarily due to lack of motivation or due to side effects to adjuvant chemotherapy. There was no difference between completers and dropouts regarding demographic data, stage of disease, or type of surgery.

**Changes in Health-Related Quality of Life**

The FACT-L emotional well-being showed a statistically significant improvement across the 5 time points (Figure 3A, P < .0001). The results from FACT-L lung cancer subscale, TOI, and the total score also showed a statistically significant improvement across the 5 time points (Figure 3B, P = .0421; Figure 3C, P = .0376; and Figure 3D, P = .0163). The EORTC-QLQ-C30 functional scales showed increasing levels of global quality of life and emotional well-being (Figure 4A, P = .0032, and Figure 4B, P = .0006). Results from the SF-36 showed improvements for the mental health component score (Figure 5A, P = .0004) and for the domain scores for role physical function, vitality, and mental health during the study period (Figure 5B,
Changes in Symptom Scales

Results for the 5 time points in EORTC symptom scales showed no differences across time points in any of the reported symptoms (results not shown).

Changes in Level of Anxiety, Depression, and Distress

Results from HADS and Distress Thermometer demonstrated a significant reduction in the level of anxiety, depression and distress, role of distress during the study period, and the greatest reduction was found 6 months after surgery (Figure 6A, $P = .0003$; Figure 6B, $P = .0062$; Figure 7A, $P = .0006$; and Figure 7B, $P = .0005$).

Changes in Perceived Social Support

The changes in perceived social support showed no overall statistically significant difference between the 5 time points in any of the subscales for support from significant others, family, friends, or in the total sum across the 12 items (results not shown). The baseline scores for all MSPSS subscales were high at baseline (Table 1) and during the study (results not shown). Changes in perceived support from other cancer patients were statistically significant during the study period (Figure 8; $P < .0001$).

Changes in Smoking, Alcohol, and Physical Activity Habits

The changes in smoking, alcohol and physical activity habits showed a reduction in the number of patients currently smoking from 25% at baseline to 5% after the intervention, followed by an increase to 12% one year after surgery. These percentages did not differ significantly (Wald test $\chi^2 = 8.47$, degrees of freedom ($df$) = 4, $P = .0759$, $P$ for trend=.0579). A similar pattern was seen in connection with alcohol consumption. At baseline, 28% consumed more alcohol than recommended by the Danish National Board...
Integrative Cancer Therapies of Health. This amount was reduced to 7% postintervention, followed by an increase to 14% one year after surgery. Comparing the number of drinks per week using Poisson regression did not indicate significant differences across the 5 time points (Wald test $\chi^2 = 4.33$, $df = 4$, $P = .3634$, $P$ for trend .1371). Physical inactivity dropped from 15% at baseline to 4% one year after surgery. Comparing the distribution of the ordinal variable in multinomial logit regression models adjusted for the level 3 months before diagnosis did not indicate significant differences across the 5 time points (Wald test $\chi^2 = 8.10$, $df = 4$, $P = .0881$, $P$ for trend .6985).

Discussion

This feasibility study demonstrated that global quality of life and domains representing emotional or mental well-being improved significantly during the study period, from prior to surgery until 1 year after resection, in patients with NSCLC participating in rehabilitation. Results from the EORTC-QLQ-C30 showed that global quality of life improved significantly during the study and to a level higher than the level in an age-matched Danish cohort.38 Braun et al found that, in patients with NSCLC, every 10-point increase in global quality of life was associated with a 9% increase in survival.5 The present study found a 17-point increase in the domain global quality of life from baseline to 6 months after surgery and a 13-point decrease in the domain smoking history.

Table 1. Baseline Characteristics.

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<td>Female, n (%)</td>
<td>24 (60%)</td>
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<td>Body mass index, kg/m², mean (SD)</td>
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<td>Academic professional degree &lt;3 years, n (%)</td>
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<td>Smoking history</td>
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<td>Currently smoking, n (%)</td>
<td>10 (25%)</td>
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<td>Never smoked, n (%)</td>
<td>2 (5%)</td>
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<td>Ex-smoker, n (%)</td>
<td>28 (70%)</td>
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<td>Years smoking, mean (SD)</td>
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<td>Presence of comorbidity (5 patients had none)</td>
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<td>Hypertension, n (%)</td>
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<td>Diabetes, n (%)</td>
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<td>Atrial fibrillation, n (%)</td>
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<td>COPD, n (%)</td>
<td>8 (20%)</td>
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<td>Rheumatic diseases, n (%)</td>
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<td>Other type of cancer, n (%)</td>
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<td>Depression, n (%)</td>
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<td>Medication, number of drugs, median (range)</td>
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<td>FACT-L health-related quality of life scores, mean (SD)$^a$</td>
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<tr>
<td>Physical well-being</td>
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<td>17.0 (5.1)</td>
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<td>Functional well-being</td>
<td>19.1 (7.3)</td>
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<td>FACT-L lung cancer subscale</td>
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<td>Trial outcome index</td>
<td>64.9 (14.0)</td>
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<td>Total score</td>
<td>104.7 (19.9)</td>
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<td>EORTC-QLQ functional scales, mean (SD)$^b$</td>
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<td>Global quality of life (global health status)</td>
<td>65.6 (24.0)</td>
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<td>Physical functioning</td>
<td>88.0 (17.4)</td>
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<td>SF-36 health-related quality of life scores, mean (SD)$^b$</td>
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<td>Physical component score</td>
<td>50.3 (10.2)</td>
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<td>Mental component score</td>
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<td>Role physical function</td>
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<td>Bodily pain</td>
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<td>Role emotional</td>
<td>62.2 (37.8)</td>
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<tr>
<td>Mental health</td>
<td>66.5 (21.9)</td>
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Abbreviations: COPD, chronic obstructive pulmonary disease; EORTC-QLQ, European Organization for Research and Treatment in Cancer—Quality of Life Questionnaire; FACT-L, Functional Assessment of Cancer Therapy–Lung; HADS, Hospital Anxiety and Depression Scale; MSPSS, Multidimensional Scale of Perceived Social Support; NCCN, National Comprehensive Cancer Network; SF-36, Short-Form Health Survey; SD, standard deviation.

$a$ Score range 0 to 24, 0 to 28, 0 to 84, 0 to 136. High scores indicate good health-related quality of life or fewer symptoms.

$b$ Score range 0 to 100. High scores indicate good health-related quality of life.

$c$ Score range 0 to 7. High scores indicate high level of support.

$d$ Score range 0 to 21. High scores indicate high levels of anxiety and depression.

$e$ Score range 0 to 10. High scores indicate high levels of distress and role of distress.
increase from baseline to 1 year after surgery. According to a study by Osoba, a difference of 5 to 10 points represents a small significant change, 10 to 20 points a moderate change, and greater than 20 points a larger clinically significant change from the patient’s perspective. Therefore, the improvement found in the present study is interpreted as a moderate change.

For 178 patients operated for NSCLC with no subsequent recurrence, Kenny et al found a substantial initial deterioration in the physical dimensions and global quality of life, with an improvement to baseline levels between hospital discharge and 2 years after diagnosis. The study by Kenny et al was, in contrast to this study, not designed to evaluate participation in rehabilitation but examined the role of position emission tomography in preoperative assessment. The findings in the present study showed an improvement from baseline to postintervention, with an additional increase 6 months after surgery, in global quality of life, which may be interpreted as an effect of the present rehabilitation program, although the lack of a control group weakens the conclusion.

In the present study, results from the SF-36 demonstrated that the mental health component score and the scores from the following domains: role physical function, vitality, and...
Integrative Cancer Therapies

mental health improved significantly during the study period. The domain bodily pain showed that the patients experienced less pain over time during the study period and also less pain compared to an age-matched Danish cohort. Brocki et al confirm this improvement postintervention and also found an effect in the bodily pain domain related to a supervised outpatient exercise program. They also found a trend in favor of the intervention for role physical function and the physical health component score. In contrast to our findings, the tendency in the study of Brocki was reversed at 12 months after surgery, with the control group presenting overall slightly better measures.
Brunelli et al found that patients with NSCLC were below the norm population in the physical health component score. In addition, their study showed a decline in the same score 1 month after surgery returning to preoperative values 3 months after surgery.44

In contrast to the findings of Brunelli et al, the results from this study showed that the physical health component score was higher at baseline and 1 year after surgery compared to an age-matched Danish cohort.39 A reasonable explanation could be selection bias, as we cannot rule out that patients participating in this study represent a group with better physical fitness than the group refusing to participate. The mental health component score improved form baseline level below the norm population to the same level as the norm population 6 months after surgery. Moller and Sartipy found in a cohort of patients with NSCLC that mental health component summary scores below the mean

**Figure 5C.** Short Form Health Survey (SF-36) Vitality. Score range 0 to 100. High scores indicate good health-related quality of life. CI, confidence interval.

**Figure 6A.** Hospital Anxiety and Depression Scale (HADS) Anxiety. Score range 0 to 21. Low scores indicate low level of anxiety. CI, confidence interval.

**Figure 5D.** Short Form Health Survey (SF-36) Mental health. Score range 0 to 100. High scores indicate good health-related quality of life. CI, confidence interval.

**Figure 6B.** Hospital Anxiety and Depression Scale (HADS) Depression. Score range 0 to 21. Low scores indicate low level of depression. CI, confidence interval.
of the age- and gender-matched normal population were associated with a 3-fold increase in the risk of death. 6

Results from FACT-L showed that emotional well-being improved significantly during the study. The improvement in emotional well-being postintervention is similar to the effect found in patients with advanced lung cancer participating in rehabilitation. 45

The improvement in TOI (5 points) and lung cancer subscale (2 points) are according to Cella et al clinically meaningful for patients with NSCLC. 46 Cella and colleagues demonstrated that a 2- to 3-point change in LCS and a 5- to 6-point change in TOI was a clinically meaningful change in patients with NSCLC. 46 As this feasibility study is under-powered, no conclusions can be drawn.

As only 33% of the patients (n = 13) were treated with chemotherapy, it is not possible in this study to evaluate the influence of chemotherapy on HRQoL.

According to Zigmond and Snaith, HADS anxiety and depression subscale scores can be classified as normal (0-7), mild (8-10), moderate (11-14), or severe (15-21). 32 The levels of anxiety and depression in the present study are therefore judged to be normal, but the level of anxiety still showed a decrease in the anxiety score between baseline and 6 months after surgery, which reversed between 6 months and 1 year after surgery without reaching the baseline level. This tendency was not observed in levels of depression.

Results from distress (NCCN Distress Thermometer) showed the same pattern as HADS regarding anxiety, the scores showing parallel fluctuations. This indicates a correlation between anxiety and distress, which was also found in a study by Bidstrup et al. 33 The present study showed that the level of anxiety decreased 6 months after surgery, but reversed 1 year after surgery without reaching the baseline level. This pattern was not found in patients with COPD, where the level of anxiety increased with time. 47

According to parameters from a study by Zimmet et al, concerning social support, the results from the present study can be interpreted as high social support at baseline and during the study period. 48 Zimmet et al found that a mean score ranging from 1 to 2.9 represents a low level of support, a score of 3 to 5 moderate support, and 5.1 to 7 high support. 48 This is in contrast to a Danish study by Quist et al that involved a similar intervention where social well-being decreased. 45 The patients participating in their study had advanced lung cancer, and their condition and disease stage differ from the.
patients participating in the present study. The significant increase in support from other cancer patients during our study could hypothetically have a connection to the improvement in emotional well-being and reflects the value of establishing a social network. A qualitative study by Missel et al, in the present population, found that group training had social benefits, such as patients experiencing a sense of belonging and that exercising with others in a similar circumstance is meaningful due to the sense of community created.49

The level of patients reporting being sedentary dropped from 15% to 4% during our study. Granger et al found that 40% of patients with NSCLC did not meet physical activity recommendations at time of diagnosis and after 6 months; without a specific exercise intervention, these patients experienced a decline in physical activity, functional capacity, and strength compared to healthy individuals.50 Cavalieri et al found that patients with NSCLC treated with lobectomy were more sedentary than healthy age-matched controls.51 Results from the present study on smoking and alcohol habits showed a decrease in the number of smokers and patients with an intake above the recommended amount from baseline to postintervention, but this effect reversed 1 year after surgery without reaching the baseline. The present changes in smoking, alcohol, and physical activity habits were not statistically significant, but the results are of clinical importance and they underline the need for optimizing maintenance from rehabilitation.

Strengths and Limitations

The strengths of this study are the use of well-validated HRQoL questionnaires and the analysis of the consumption of alcohol and tobacco from the time of diagnosis to 1 year after surgery.

A methodological weakness is the low number of participants and the absence of a control group, since it leaves out the possibility of concluding on the effect of the intervention.

The fact that only 32% of the eligible patients participated in the present study limits the generalization of the results, as the patients might not be representative of the population operated for NSCLC in Denmark. The low recruitment rate could also affect the results, because participation in the study could be related to patients with better performance status and physical fitness compared with the group not participating. However, a comparison of the baseline characteristics of the patients in the present study with cohort studies in patients with NSCLC reveals similarities regarding age, sex, pulmonary function, and comorbidities.52,53

Conclusion

This feasibility study demonstrated that global quality of life, mental health, and emotional well-improved significantly during the study, from time of diagnosis until 1 year after resection, in patients with NSCLC participating in rehabilitation. There was a reduction in distress and anxiety and smoking and alcohol habits from baseline to after the intervention, followed by an increase 1 year after surgery, which underlines the need for continued rehabilitation initiatives. The clinical implication of these results is awareness from the health care professionals in supporting patients with operable lung cancer to maintain the achieved lifestyle changes throughout life.

Acknowledgments

The authors would like to thank the patients who participated in this study and the staff at Copenhagen Centre for Cancer and Health for their work during the data collection. We would also like to acknowledge the staff at the collaborating hospitals for their assistance during data collection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study is supported by grants from the Center for Integrated Rehabilitation of Cancer Patients (CIRE), which was established and is supported by the Danish Cancer Society and the Novo Nordisk Foundation. Funding has also been provided by Rigshospitalet, University of Copenhagen; the Faculty of Health and Medical Sciences, University of Copenhagen; and the City of Copenhagen. CopenRehab is also supported by a grant from the City of Copenhagen.

References


correction to Paper III

Figure 5A. will be replaced with this figure in the next edition of the Journal of Integrative Cancer Therapy and the published article will be updated at the time of print issue.
# DECLARATION OF CO-AUTHORSHIP

**Information on PhD student:**

<table>
<thead>
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<th>Maja Schick Sommer</th>
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<td><a href="mailto:mss@kraeftcenter-kbh.dk">mss@kraeftcenter-kbh.dk</a></td>
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<tr>
<td>Date of birth</td>
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<tr>
<td>Principal supervisor</td>
<td>Professor Henning Langberg</td>
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**Title of PhD thesis:**

Perioperative rehabilitation in operable lung cancer patients (PROLUCA)

**This declaration concerns the following article:**


**The PhD student’s contribution to the article:**

(please use the scale (A,B,C) below as benchmark*)

<table>
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<th>(A,B,C)</th>
</tr>
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<td>1. Formulation/identification of the scientific problem that from theoretical questions need to be clarified. This includes a condensation of the problem to specific scientific questions that is judged to be answerable by experiments</td>
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<tr>
<td>2. Planning of the experiments and methodology design, including selection of methods and method development</td>
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<td>3. Involvement in the experimental work</td>
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<tr>
<td>4. Presentation, interpretation and discussion in a journal article format of obtained data</td>
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*Benchmark scale of the PhD student’s contribution to the article

A. refers to: Has contributed to the co-operation 0-33 %

B. refers to: Has contributed considerably to the co-operation 34-66 %

C. refers to: Has predominantly executed the work independently 67-100 %

**Signature of the co-authors:**

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<td>10/12/17</td>
<td>Henning Langberg</td>
<td>Professor</td>
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| Date: 21/12/17  
PhD student: | Date: 15/12/17  
Principal supervisor: |
EFFECT OF POSTSURGICAL REHABILITATION PROGRAMMES IN PATIENTS OPERATED FOR LUNG CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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From the 1Copenhagen Centre for Cancer and Health, City of Copenhagen, 2CopenRehab, Section of Social Medicine, Department of Public Health, Faculty of Health and Medical Sciences, University of Copenhagen, 3University Hospitals Centre for Health Research (UCSF), Rigshospitalet, 4Department of Occupational- and Physiotherapy, Copenhagen University Hospital, 5Department of Respiratory Medicine, Bispebjerg University Hospital, 6Department of Cardiothoracic Surgery RT, Rigshospitalet and 7Department of Public Health, Section of Social Medicine, University of Copenhagen, Copenhagen, Denmark. #These 2 authors contributed equally and should be considered as first authors.

Objective: To review the evidence concerning the effects of postoperative exercise interventions on exercise capacity and health-related quality of life following resection for non-small cell lung cancer, and to review whether different initiation times of exercise produce different effects on exercise capacity.

Data sources: Comprehensive literature search of MEDLINE, Embase, CENTRAL, CINAHL and PEDro.

Study selection: Randomized controlled trials examining the effects of exercise interventions were eligible for inclusion.

Data extraction: Postoperative outcome measurements were extracted and the quality of evidence was graded using Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.

Data synthesis: Four randomized controlled trials were identified involving 262 participants. Short-term follow-up (12–20 weeks) showed significantly higher exercise capacity and physical component of health-related quality of life in the intervention group (standardized mean difference (SMD) 0.48; 95% confidence interval (CI) 0.04–0.93) compared with the control group (SMD 0.50; 95% CI 0.19–0.82). There was no difference between the effect of late- and early-initiated exercise intervention.

Conclusion: Exercise has a small-to-moderate effect at short-term follow-up on exercise capacity and the physical component of health-related quality of life in patients operated for lung cancer. The long-term effects of exercise capacity are unknown. Early-initiated exercise programmes (2 weeks post-operation) did not show an effect on exercise capacity. These findings should be interpreted with caution.

Key words: non-small cell lung cancer; exercise; health-related quality of life.

Accepted Oct 5, 2017; Epub ahead of print Jan 25, 2018

J Rehabil Med 2018; 50: 236–245

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Lung cancer is one of the most common malignancies worldwide, and the leading cause of cancer-related death (1). Pulmonary resection is currently the most effective curative treatment when non-small cell lung cancer (NSCLC), stage I, II, IIIA, is diagnosed. Surgery is performed using either an open approach (thoracotomy) or minimally invasive video-assisted thoracoscopic surgery (VATS) (2). Improvements in earlier preoperative staging, better surgical techniques and more effective adjuvant treatment have enhanced survival (3). Lung cancer surgery is associated with morbidity, functional limitations and decreased quality of life (4).

As a result, evidence-based rehabilitation may be a key component to improve outcome and quality of life in these patients (4, 5). An emerging discipline in rehabilitation of lung cancer survivors, exercise intervention, is associated with benefits that may improve the health of long-term cancer survivors and extend survival (6).

Studies demonstrate lower levels of physical activity among individuals diagnosed with NSCLC compared with healthy individuals, yet the physical activity level decreases further during the first 6 months following diagnosis (7).

The increase in population of lung cancer survivors signifies the need to improve their health. Barriers for participating in rehabilitation and maintaining lifestyle changes are, for example, high symptom burden, such as side-effects to the adjuvant treatment, and high prevalence of comorbidity, especially chronic obstructive pulmonary disease (COPD) (8).

Exercise initiated early in the treatment trajectory is found to be beneficial for operable lung cancer patients (9, 10). In a population diagnosed with myocardial infarction, early-initiated exercise in the acute phase has shown greater benefits on exercise capacity than is the case in exercise interventions initiated in a later treatment phase (11).

Systematic reviews investigating the effects of pre- and post-surgical exercise interventions in patients with NSCLC show that exercise may increase exercise capacity of people following lung resection for...
NSCLC (6, 12, 13). However, to date, no systematic reviews have been done investigating the effects of post-surgical exercise interventions for patients with NSCLC focusing on high-quality evidence and only post-operative outcomes to eliminate the impact of the surgery (no pre-operative baseline measurements). Furthermore, no previous reviews have focused on whether the effect would differ due to different initiation times for postoperative exercise in patients with NSCLC. The present review hypothesized that early initiation of exercise (within 2 weeks) following lung resection would increase the effect on exercise capacity compared with later initiation of exercise.

The primary objective was to systematically review the literature for the effect of postoperative exercise interventions on exercise capacity in patients following lung resection for NSCLC. A secondary aim was to review the effect of exercise interventions on health-related quality of life (HRQoL) and to determine whether different initiation times of exercise either enhanced or decreased exercise capacity in patients following lung resection.

**METHODS**

The protocol for this systematic review was registered in the PROSPERO database (registration number CRD42016027412). The Cochrane Handbook for Systematic Reviews of Interventions (14) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (15) were applied during preparation of this review.

**Inclusion criteria**

Randomized controlled trials (RCT) assessing the effects of postoperative exercise interventions in patients undergoing resection for NSCLC, in which participants were allocated to receive exercise compared with a control group, were included. Studies and abstracts published in English, one of the Scandinavian languages, or German were eligible for inclusion. Inclusion criteria were trials with participants receiving any type of lung resection performed with VATS or thoracotomy procedures. To avoid comparison of effect measures in different populations, trials were included only if at least 50% of the population had resectable NSCLC. Trials were included if the interventions comprised any type of exercise involving bodily movements produced by skeletal muscles (aerobic exercise, resistance exercise, ambulation or mobility exercise) initiated within 1 year after lung resection.

Supervised and/or unsupervised exercise performed individually or in groups were also eligible intervention criteria. Type, intensity, frequency and duration of the exercise interventions were not a constraint, but were recorded where possible. Control groups were considered eligible if they contained non-intervention control, usual care, waiting list control or add-on treatments.

**Outcomes**

VO_{peak} is considered the gold standard for the measurement of cardiorespiratory fitness and 6MWD is often used in pulmonary rehabilitation programmes to quantify exercise capacity, both recommended for use in clinical oncology research (16–19). The primary outcome of the present review was any measure of maximum exercise capacity (16). Exercise capacity measures included peak oxygen consumption (VO_{peak}) and 6-minute walk distance (6MWD), measured as primary or secondary outcomes in the included studies. The secondary outcome of interest was HRQoL assessed by 1 of the most commonly used questionnaires for thoracic surgery patients: Generic 36-Item Short Form Health Survey (SF-36) (20), cancer-specific European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30) (21), and the disease-specific patient-reported outcome Functional Assessment of Cancer Therapy-Lung (FACT-L) (22). The European Society of Thoracic Surgeons defines these questionnaires as the most appropriate for thoracic surgery patients.

Only postoperative outcome measurements were extracted, in order to examine the effect of postoperative exercise eliminating the impact of surgery and to compare effect sizes across studies. The inclusion criteria are summarized in Table I.

**Selection of studies**

A comprehensive literature search of MEDLINE, Embase, CENTRAL, CINAHL and PEDro. The literature search matrix used for MEDLINE (shown in Appendix SI1) was adapted for use in the other databases (search strategies shown in Appendix SV1). The Search strategy focused on 2 overall clusters: NSCLC and rehabilitation, with their associated synonyms, combined with AND, as shown in Appendix SI1. No limitations were used in the electronic searches to avoid unintended exclusion of relevant trials.

In order to identify additional trials all reference lists of all primary studies and review articles were screened. Experts in the field of exercise and NSCLC were contacted in order to identify unpublished research. A search was also carried out of clinicaltrials.gov to identify ongoing, as yet unpublished, trials.

All references identified were imported into the web-based software platform cvidence.org. Selection of trials, risk of bias assessment, and extraction of data were managed with this software. Two review authors (MB, MS) independently...
Data extraction and management

Two review authors (MB, MS) independently extracted data using a predefined form based on the Cochrane Collaboration’s checklist of items to consider in data extraction (14). Data included details of the trials, participant characteristics and results at postoperative time points. Disagreements on extraction of data were resolved by discussion.

Two review authors (MB, MS) independently assessed the risk of bias of all included trials, evaluated as either high, low or unclear risk of bias using the Cochrane Collaboration’s tool for assessing risk of bias (14). High risk of bias indicated that there was a high risk that the results would either overestimate or underestimate the true intervention effect, while low risk of bias indicated the opposite. Unclear risk of bias denoted either a lack of information or uncertainty concerning the potential of bias. Disagreements were resolved by discussion, or when necessary, a third review author (JC) was consulted and agreement reached.

Statistical analyses

For continuous outcomes standardized mean differences (SMD) and the corresponding 95% confidence intervals (95% CI) were used in the analysis. To calculate the SMDs the mean change scores and the corresponding standard deviations (SDs) were extracted from the included trials when these were reported. Where mean change scores and/or SDs of the mean change scores were not applied, they were calculated based on the baseline and follow-up means and SDs, as recommended in the Cochrane Handbook (14). The calculated SDs of the mean change scores from baseline were estimated by imputing a correlation coefficient in the formula below to allow the use of paired data (23, 24):

$$SD_{change} = SD_{baseline} + SD_{follow-up} - (\times corr \times SD_{baseline} \times SD_{follow-up})$$

Correlation coefficients were used in the calculation of SDs of mean change scores in the following outcomes: VO2peak and the corresponding standard deviations (SDs) were extracted from the included trials when these were reported. Where mean change scores and/or SDs of the mean change scores were not applied, they were calculated based on the baseline and follow-up means and SDs, as recommended in the Cochrane Handbook (14). The calculated SDs of the mean change scores from baseline were estimated by imputing a correlation coefficient in the formula below to allow the use of paired data (23, 24):

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$$SD_{change} = SD_{baseline} + SD_{follow-up} - (\times corr \times SD_{baseline} \times SD_{follow-up})$$

Electronic databases were searched on 17 February 2016 and resulted in a total of 6,191 hits: 1,641 from MEDLINE, 3,291 from Embase, 270 from the Cochrane Central Register of Controlled Trials (CENTRAL), 970 from CINAHL and 19 from PEDro. The number of duplicates was 1,661, resulting in 4,530 unique articles. Based on the title and abstract, 4,464 articles were excluded, resulting in 66 articles read in full text. Of these, 62 studies were excluded as they did not meet the inclusion criteria. The present review included 4 RCTs involving 262 participants (32–35). Three of the studies randomized the participants into 1 of 2 groups: an exercise intervention or a control group (32–34). The fourth study randomized the participants into 1 of 3 groups: exercise intervention 1, exercise intervention 2 or a control group (35). This study was divided into 2 studies in the analyses, in which each intervention group was compared with half the control group (14). Twelve studies were in a language other than those listed in our criteria and 3 had missing data. The first
of the last-mentioned studies was contacted, but it
was unable to provide postoperative measurements
of exercise capacity (36); the second was a confer-
cence article that was insufficient due to low
completion of the intervention and a high number
of missing data (37); and the third was unable to
provide the missing data on exercise capacity and
HRQoL (38). Fig. 1 presents a flowchart of the
search process based on the PRISMA template (15).
Details of the excluded references are shown in
Appendix SII1.

The studies, based in the UK, Denmark, Belgium
and Norway, were published in 2011–2015. Two of
the studies conducted the interventions in a hospital
setting after discharge (33, 35), while participants in
one study exercised during admission with subsequent
home training (32). In the fourth study the interven-
tion was conducted in local fitness centres after
discharge (34).
All 4 studies included mainly participants who had undergone lung resection for NSCLC. Both sexes were included and the mean age was over 60 years in all study groups. The majority of the participants went through open surgery (range 77–96%), and the lung cancer stages were equally distributed between control and exercise groups, except in one study, where 4 participants with stage IV NSCLC were randomized to the control group and none to the exercise group. For 4 studies pre-surgery until day 5 post-surgery. In order to rule-out variance due to operation outcomes we decided in the present study to use the first measurement to decide in the present study to use the first measurement.

Exercise interventions included a component with aerobic exercise and resistance training, except for intervention 2 in the 3-armed RCT, which included exercise and whole-body vibration (35). The intervention components varied in intensity, frequency and duration across studies. The intensity of the aerobic exercises, which consisted of either walking or biking, varied from 60% to 95% of maximum heart rate. The frequency of training varied from 1 session per week for 10 weeks (33) to 3 times a week for 12 (35) or 20 (34) weeks. The exercise interventions were initiated after 5 days (32), 3 weeks (33), 4–6 weeks (35) or 20 (34) weeks. The exercise interventions were initiated after 5 days (32), 3 weeks (33), 4–6 weeks (35) or 20 weeks (34) following lung resection. Baseline measurements in Arbane et al.’s study (32) were conducted pre-surgery, since the study initiated exercise pre-surgery until day 5 post-surgery. In order to rule-out variance due to operation outcomes we decided in the present study to use the first measurement on day 5 post-surgery as the “baseline” in the present review.

In addition, the results by Arbane et al. (32) showed no statistically or clinically effect of early exercise

### Table III. Characteristics of included studies and participants

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number Ex/c</th>
<th>Mean age (years)</th>
<th>Female</th>
<th>Surgery (n)</th>
<th>Thor/VATS</th>
<th>Additional treatment</th>
<th>Primary outcome</th>
<th>Secondary outcome</th>
<th>Baseline</th>
<th>Follow-up</th>
<th>Analysis</th>
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<td>27/26</td>
<td>65.4/62.6</td>
<td>NR</td>
<td>51/2</td>
<td>NR</td>
<td>QLQ-LC13</td>
<td>6MWD</td>
<td>Day 5 (originally 12 weeks pre-operative)</td>
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<tr>
<td>Brocki 2014 et al.</td>
<td>41/37</td>
<td>64/65</td>
<td>32/46</td>
<td>60/18</td>
<td>Any adjuvant: 16/18</td>
<td>SF-36 physical</td>
<td>6MWD</td>
<td>3 weeks</td>
<td>4 months + 1 year</td>
<td>ITT</td>
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<tr>
<td>Edvardsen 2015 et al.</td>
<td>30/31</td>
<td>64.6/65.9</td>
<td>33/28</td>
<td>51/10</td>
<td>Radio: 3/4</td>
<td>VO peak (n=30/31)</td>
<td>SF-36 physical</td>
<td>4–6 weeks</td>
<td>20 weeks</td>
<td>ITT: VO peak Per protocol: SF-36 + EORTC (unpublished data)</td>
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<tr>
<td>Salhi 2015 et al.</td>
<td>a+b24/24</td>
<td>b+63/64</td>
<td>b+6/6</td>
<td>NR</td>
<td>Radio: 4/3</td>
<td>6MWD</td>
<td>VO peak EORTC QLQ-C30 physical functioning</td>
<td>Within 8 weeks</td>
<td>12 weeks</td>
<td>ITT: 6MWD Per protocol: EORTC</td>
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* a: intervention group 1, b: intervention group 2, c: not included in review due to absence of 2 postoperative measurements. c: control group; Ex: exercise group; NR: not reported; Thor: thoracotomy; VATS: video-assisted thoracoscopic surgery; Radio: radiotherapy; Chemo: chemotherapy; EORTC: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; SF-36: 36-Item Short Form Health Survey; VO2peak: peak oxygen consumption; 6MWD: 6-minute walk distance; ITT: intention-to-treat.

### Table IV. Characteristics of included exercise interventions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Length of intervention</th>
<th>Duration of session</th>
<th>Exercise type</th>
<th>Intensity</th>
<th>Frequency</th>
<th>Supervised/unsupervised</th>
<th>Inpatient/Group</th>
<th>Individual Control group</th>
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<tr>
<td>Arbane 2011 et al.</td>
<td>12 weeks (+5 days)</td>
<td>5–10 min per exercise</td>
<td>Aerobic (walking, marching, recumbent bike) + resistance (weights)</td>
<td>60–80% MHR</td>
<td>2×/day</td>
<td>Both</td>
<td>Both</td>
<td>Individual</td>
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<tr>
<td>Edvardsen 2015 et al.</td>
<td>20 weeks</td>
<td>60 min</td>
<td>Warm-up + aerobic (walking uphill on treadmill), progressive resistance training (machines), inspiratory muscle training</td>
<td>3×/week</td>
<td>Supervised</td>
<td>Outpatient Individual</td>
<td>No advice about exercise beyond general information from the hospital</td>
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<tr>
<td>Salhi 2015 et al.</td>
<td>12 weeks</td>
<td>20 min aerobic + NR in resistance</td>
<td>Aerobic (biking or treadmill)</td>
<td>Resistance (machines)</td>
<td>Whole-body vibration (vibration platform)</td>
<td>Aerobic (biking or treadmill)</td>
<td>3×/week</td>
<td>Supervised</td>
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* Intervention 1, ‡Intervention 2, §Education content unknown. MHR: maximum heart rate; RPE: Borg Rating Perceived Exertion (range 6–20); REP: repetitions; RM: repetition max; Wmax: watt max.
captured by the day 5 post-surgery measurement, even though the intervention group had a mean distance that was 28 m longer than the control group (measured at day 5 post-operatively). The minimal important difference in the 6MWD in patients with lung cancer is 42 m (39).

The control groups received usual care, consisting of a monthly telephone call from the research team, which provided education (32), 1 h of individual instruction in home exercises (33), no advice beyond general information from the hospitals (34) and even discouraged to improving their exercise tolerance with professional help (35).

Exercise capacity was reported in all 4 studies, 2 of which reported VO2peak (34, 35) and 3 of which reported 6MWD (32, 33, 35). HRQoL was reported in 3 studies, 2 of which reported SF-36 in physical- and mental component scores (33, 34), and 1 of which reported the physical functioning score of the EORTC QLQ-C30 (35). One study did only have one measurements of HRQoL post-surgery, which is why that outcome was not extracted (32). All of the studies had collected a short-term follow-up at completion of their interventions, and 1 study had collected an additional long-term follow-up 1 year after baseline (33).

The overall assessment of risk of bias across the studies is presented in Fig. 2, while the risk of bias for the individual studies is presented in Appendix SIII. All of the studies reviewed were at high risk of performance bias because blinding of participants is difficult in exercise interventions. The majority of studies were at high or unclear risk of detection bias and reporting bias as the outcome assessors were not blinded and the relevant predefined outcomes were not evaluated due to lack of completion of outcome measures or no trial registry. The section called “Summary of included studies” in Appendix SIV contains a detailed description of the assessment of risk of bias.

**Effect of intervention**

All meta-analyses were conducted using a random-effects model after assessment of clinical heterogeneity between studies, especially in exercise interventions. VO2peak is considered the gold standard measurement of cardiorespiratory fitness research, therefore when both measurements were available VO2peak was chosen. Results at completion of the intervention periods, stated as short-term, showed a significantly higher exercise capacity in the intervention group compared with the control group (SMD 0.48; 95% CI 0.04–0.93), reflecting a small-to-moderate effect size (Fig. 3). The F was 61.6%, suggesting moderate variations between intervention effects. The study with a long-term follow-up showed no effect on exercise capacity after 1 year from baseline (SMD 0.09; 95% CI –0.44 to 0.61), the results are not illustrated.

The SF-36 physical component score was pooled in a meta-analysis with the EORTC QLQ-C30 physical functioning score. The physical component of HRQoL was significantly higher in the intervention group.
compared with the control group (SMD 0.50; 95% CI 0.19–0.82) in the short-term, reflecting a moderate effect size (Fig. 4). The I² was 0%, suggesting a small variation between intervention effects.

According to the one study with long-term follow-up, there was no effect on the physical component of HRQoL in the long-term (SMD –0.27; 95% CI –0.78 to 0.25). The results are not illustrated in the present review. The SF-36 mental component score was reported in 2 studies and pooled in a meta-analysis. There was no effect on the mental component of HRQoL (SMD 0.53; 95% CI –0.78 to 1.83) in the short-term, nor at long-term follow-up (SMD –0.48; 95% CI –1.01 to 0.04). The results are not illustrated.

Only one study initiated exercise intervention early, within 2 weeks after surgery (32). This study showed no effect on exercise capacity in the short-term (SMD 0.09; 95% CI –0.57 to 0.74), as illustrated in Fig. 5. In 3 studies that initiated exercise interventions later (33–35), >2 weeks after surgery, in contrast, the exercise capacity was significantly higher in the intervention group compared with the control group in the short-term (SMD 0.58; 95% CI 0.07–1.09), reflecting a moderate effect size (Fig. 5). There was no difference between effect of late and early initiated exercise intervention. The I² for exercise interventions initiated late was 65.6%, suggesting moderate variation between intervention effects.

The main findings and quality of the body of evidence for each result is presented in the summary of findings (Table II).

**DISCUSSION**

This meta-analysis showed that exercise improved exercise capacity and the physical component of HRQoL in the short-term, but no beneficial effect was found on the mental component of HRQoL. Only one study evaluated the long-term effects and found no effect on either physical capacity or HRQoL (33). Early-initiated exercise programmes, within 2 weeks after lung resection, did not show an effect on exercise capacity. These findings must be interpreted with caution due to the heterogeneity of exercise programmes, methodological limitations, some significant risks of bias, small samples and the low number of studies included.

**Overall completeness and applicability of evidence**

As exercise capacity appears to be a valuable prognostic indicator for patients with NSCLC, and the clinical finding that exercise capacity increases during exercise in patients following lung resection is highly important (40). Until now referral for rehabilitation following lung resection has been based on an individual evaluation of rehabilitation needs. Numbers of referrals made is unpublished, but a survey from Australia and New Zealand reports that <25% of patients are referred to pulmonary rehabilitation after lung resection (41). The inadequate level of referrals is due to the lack of well-designed studies to confirm the role of supervised exercise training in facilitating postoperative recovery in this patient population (41).

The large variations in the exercise programmes, in terms of moderate-to-high intensity ranging from 60% to 90% of heart rate maximum (HRmax), frequency ranging from twice a day to 3 times a week, and duration from 5 min per exercise to a 60-min full session, influence the findings in the present review and limit the clinical applicability.

Differences in physical activity recommendations across the control groups may have influenced the effect sizes. Potential contamination of exercise in some of the control groups may have influenced, and most likely reduced, the effect of the relevant studies.

The present review did not clarify whether early initiation of exercise, within 2 weeks following lung resection, is more effective than exercise initiated later, which was hypothesized *a priori*. One study initiated exercise intervention within 2 weeks following surgery and therefore this analysis may not illustrate the true effect. Thus, the study contained a home-based non-supervised training programme following discharge, which potentially could have lowered adherence to the intervention, reducing its effect (32).

As a result it is not possible to evaluate whether early-initiated exercise training will improve the effect in exercise capacity and HRQoL.

The recruitment rates were low in 2 out of 6 studies (33, 35), potentially having caused a selected group of participants, e.g. the healthiest, the youngest and
the fittest, to participate compared with those uninterested. Characteristics of the populations in the studies are therefore not necessarily consistent with a representative sample of patients with operable NSCLC. Information about eligible patients not interested in participating would be of great clinical interest with regard to applicability.

Quality of evidence
The quality of evidence provided by the studies included in the analysis has been rated, according to GRADE, as low or very low, mainly because of some serious risks of bias, inconsistency in effect estimates and imprecision, as the small sample sizes caused wide confidence intervals. Consequently, the results must be interpreted with caution.

Strengths and limitations of the review process
A strength of this review is the comprehensive literature search by 2 review authors, which optimized sufficient identification of relevant studies, and successfully obtaining missing data.

In addition, the investigative work done to find ongoing, unpublished studies by searching trial registrations and contacting recognized authors in the research field improves the probability that all relevant studies were found. The number of studies excluded due to the language criteria, however, probably limited the inclusion of further studies. The 3 studies excluded due to missing data also represent a limitation, as their effect estimates could have influenced the results of this review.

One of the excluded studies found that 6MWD improved by 35 m from preoperative baseline to post-intervention, the control group showed a decline by 59 m ($p = 0.024$) (38). Another study found no differences between the intervention group (homebased exercise plus 5 days with exercise in hospital) and the control group (36). What the 2 studies have in common is no post-operative baseline-outcomes to eliminate the impact of surgery; therefore it is difficult to compare the results with the results of this review.

The excluded study by Jacobsen et al. was a conference article that did not report any results (37). If the pooled data from the various instruments (VO\textsubscript{2peak} and 6MWD) used to assess exercise capacity did not measure the same outcomes, the results of the review may be biased. A recent study shows a difference in pulmonary oxygen when comparing 6MWD and the cardiopulmonary exercise test in patients with NSCLC following lung resection (17).

Studies on patients diagnosed with either chronic obstructive pulmonary disease or chronic heart failure, in contrast, found no differences in VO\textsubscript{2peak} obtained using either the pulmonary oxygen uptake test or the 6MWD (42–44).

Including the most commonly used and recommended questionnaires for measuring HRQoL in thoracic surgery patients could represent a strength as well as a limitation. The decision was made to maintain a high level of methodological quality, which is why the 3 questionnaires listed were considered useful for the population, though SF-36 has not been validated for patients with lung cancer. A limitation is the pooled data from the physical component domain of HRQoL, since it was assessed using instruments with different target groups, as one was a generic HRQoL questionnaire (SF-36) and the other a cancer-specific HRQoL questionnaire (EORTC QLQ-C30).

The EORTC QLQ-C30 physical functioning domain has shown a substantial convergent correlation with all of the 4 SF-36 physical summary component subdomains ($r > 0.50$) (45). The moderate similarity of the 2 instruments may have biased the result of the physical component of HRQoL, presenting the risk of an overestimate or underestimate of real effect.

The use of imported correlation coefficients in the calculation of SDs of mean differences in 2 of the included studies may have had an impact on the results. These SDs are estimates calculated based on changes found in previous studies with similar populations of patients with other cancer diagnoses (26). The SF-36 scores in that study were also reported to be similar to SF-36 scores for patients with chronic diseases, such as chronic obstructive pulmonary disease, hypertension and congestive heart failure (26). This method of estimating the SDs could decrease the reliability of the reported results, due to an element of imprecision in the estimates (14). However, the estimated SD becomes a better replacement of the real SD compared with the use of an unpaired SD of the mean change.

Agreements and disagreements with other studies or reviews
A significant improvement in 6MWD was confirmed in a previous systematic review evaluating the effect of exercise interventions in patients with NSCLC following lung resection (12). In contrast baseline outcome measures from pre- and post-surgery were included where the present review has all outcome measures conducted post-surgery to eliminate the impact of lung surgery and focus entirely on the effect of rehabilitation. In addition, the present review included 2 new RCTs with a total of 131 participants. Other previous systematic reviews confirmed that both pre- and post-operative exercise was associated with positive benefits on exercise capacity and some domains of HRQoL (6, 46). Different study designs were included in the pre-
vious reviews, including a few RCTs, only one of which met the inclusion criteria of the current review (32).

During completion of the current review, a new review by Ni et al. (13) (evaluating the effects of pre- and post-operative exercise interventions) was published supporting our findings, in contrast their review included all study designs, as well as pre- and post-operative measurements.

The present review does not find that exercise improves the mental domain of HRQoL compared with usual care for patients having undergone lung resection; however, there might be a trend towards the direction of positive effects, but the confidence intervals indicate that these effects are very uncertain. The findings are in contrast to previous research in patients with COPD, patients with other cancer diseases and qualitative research in patients undergoing lung resection for NSCLC (9). One of the possible reasons for this is how HRQoL was assessed, as SF-36 is a generic HRQoL questionnaire, or the lack of statistical power in the studies in the present review.

This review is the first to examine the effects of postoperative exercise training in patients with NSCLC following lung resection with inclusion of postoperative outcome measurements alone. This method does not include the involvement of the surgery on the outcomes. Inclusion of solely RCTs improves the quality of evidence. Moreover, this review is the first to focus on the effects of early-initiated exercise, although, due to lack of studies, this analysis did not lead to any conclusion regarding this question.

**Conclusion**

This review found that exercise may have beneficial effects on exercise capacity and the physical component of HRQoL among patients following lung resection for NSCLC. However, since there are risks of bias, inconsistency and imprecision of findings, these results should be interpreted with caution.

Despite the overall low quality of the body of evidence, health professionals should consider referring patients with NSCLC to an exercise programme following lung resection. Further research is needed to confirm the efficacy of exercise intervention in people with NSCLC, and whether these effects can be maintained beyond the active intervention period. Additional research is required to investigate when exercise intervention should be initiated following lung resection to obtain the best result and prevent or minimize postoperative impairments. This knowledge may contribute to the design of future exercise research in patients with operable NSCLC.

**REFERENCES**

# DECLARATION OF CO-AUTHORSHIP

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This declaration concerns the following article:


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*Benchmark scale of the PhD student’s contribution to the article*

- A. refers to: Has contributed to the co-operation 0-33 %
- B. refers to: Has contributed considerably to the co-operation 34-66 %
- C. refers to: Has predominantly executed the work independently 67-100 %

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