Physiotherapy interventions and outcomes following lung cancer surgery

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ÖREBRO UNIVERSITY

BARBARA C BROCKI

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Abstract

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The aim of this thesis was to evaluate the effect of exercise training and inspiratory muscle training and to describe pulmonary function, respiratory muscle strength, physical performance and health-related quality of life (HRQoL) following lung cancer surgery.

  Study I was a randomised controlled trial including 78 patients radically operated for lung cancer. The intervention group received 10 sessions of supervised exercise training in addition to home-based exercise; the control group was instructed on home-exercise alone. Supervised compared to non-supervised exercise training did not result in differences between groups in HRQoL, except for the SF-36 bodily pain domain four months after the surgery. No effects of supervised training were found for any outcome after one year. **Study II** was descriptive and was based on the study I sample. We evaluated the course of recovery of HRQoL and physical performance up to one year following surgery. All patients improved HRQoL and physical performance one year after the surgery, reaching values comparable to a reference healthy population. The walked distance was positively associated with the SF-36 domain for physical functioning. **Study III** was descriptive, included 81 patients and evaluated the influence of surgery on respiratory muscle strength, lung function and physical performance two weeks and six months after surgery. We found that respiratory muscle strength was not affected after the second postoperative week and that muscle-sparring thoracotomy did not deteriorate respiratory muscle strength, compared to video-assisted thoracic surgery. Compared to preoperative values, physical performance was recovered, whereas lung function remained reduced six months postoperatively. **Study IV** was a randomised controlled trial including 68 patients at high risk of developing postoperative pulmonary complications (PPC). This study evaluated the effects of two weeks of postoperative inspiratory muscle training in addition to breathing exercises and early mobilisation on respiratory muscle strength and the incidence of PPC. Additional inspiratory muscle training did not increase respiratory muscle strength, but improved postoperative oxygenation. Respiratory muscle strength was recovered in both groups two weeks postoperatively.

Keywords: lung cancer, surgery, quality of life, exercise, inspiratory muscle training, physical performance, pulmonary complications.

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List of papers

This dissertation is based on the following studies, which will be referred to in the text by their Roman numerals:

Study I
Brocki BC, Andreasen J, Nielsen LR, Nekrasas V, Gorst-Rasmussen A, Westerdahl E
Short and long-term effects of supervised versus unsupervised exercise training on helth-related quality of life and functional outcomes following lung cancer surgery – A randomised controlled trial
Lung Cancer 2014;83:102-108

Study II
Brocki BC, Westerdahl E, Andreasen JJ, Souza DSR
Improvements in physical performance and health-related quality of life one year after radical operation for lung cancer
Cancer Treat Commun 2015;4:65-74
DOI:10.1016/j.ctrc.2015.05.004

Study III
Brocki BC, Westerdahl E, Langer D, Souza DSR, Andreasen JJ
Respiratory muscle strength is not affected two weeks and six months following pulmonary resection
In manuscript

Study IV
Brocki BC, Andreasen JJ, Langer D, Souza DSR, Westerdahl E
Postoperative inspiratory muscle training in addition to breathing exercises and early mobilisation improves oxygenation in high risk patients after lung cancer surgery – A randomised controlled trial
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Abbreviations

ASA	American Society of Anesthesiologists
CG	Control group
COPD	Chronic obstructive pulmonary disease
DLCO	Diffusing capacity for carbon monoxide
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
HRQoL	Health-related quality of life
IG	Intervention group
IMT	Inspiratory muscle training
MIP	Maximal inspiratory pressure
MEP	Maximal expiratory pressure
NRS	Numeric rating scale
PEP	Positive expiratory pressure
PPC	Postoperative pulmonary complications
RMS	Respiratory muscle strength
RCT	Randomised controlled trial
SpO_2	Peripheral oxygen saturation
6MWT	6-minute walk test
SF-36	Short Form SF-36 Health Survey
VATS	Video-assisted thoracic surgery

Introduction

Pulmonary resection is currently the most effective curative treatment for lung cancer. However, the surgery is associated with a high incidence of postoperative pulmonary complications (PPC), influencing postoperative morbidity and mortality (1,2). Following surgery, persistent respiratory problems and detriments in physical function, in particular reduced walked distance, are commonly present, contributing to an impaired health-related quality of life (HRQoL) (3,4).

Respiratory muscle weakness has been suggested as a precursor to PPC (5-7). Preoperative inspiratory muscle training (IMT) has been shown to preserve respiratory muscle function in the postoperative period and reduce the risk of pulmonary complications in patients undergoing cardiothoracic and abdominal surgery (8). However, studies evaluating the effects of postoperative IMT in the early outcomes after lung cancer surgery are scarce (9). In addition, the clinical importance of respiratory muscle dysfunction, in terms of decrease in physical performance in the postsurgical lung cancer population, has not been addressed in the literature.

The role of exercise training in the improvement of exercise capacity and HRQoL in people with chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD) (10) and different cancer types (11) is well established. But there is limited evidence supporting exercise training as an intervention following lung cancer surgery (12).

As life expectancy following lung cancer surgery increases, the ability to resume daily living activities and improve HRQoL has become increasingly important issues in health care. In this thesis, I have investigated the effect of inspiratory muscle training and exercise training following lung cancer surgery. This work will provide clinicians, patients and relatives with valuable information regarding the course of recovery of pulmonary function, respiratory muscle strength, physical performance and HRQoL in this population.

Lung cancer and surgery

With over 4000 new diagnosed cases per year, lung cancer is the second commonest type of cancer in Denmark (13). Curative pulmonary resection is the main treatment when lung cancer is of non-small cell type diagnosed in its early stages (stage I - II) (14). The surgery is performed either by an open approach (thoracotomy) or by using video-assisted thoracic surgery (VATS). Both techniques are comparable in terms of long term cancer survival, but VATS is associated with a shorter hospital stay (15) and lower incidence of complications (16). In short, the surgery consists of the removal of the lung tissue containing the tumour, together with the nearby lymph nodes. The degree of resection ranges from minor (wedge resection / segmentectomy) to major (removal of all lobes from one side of the thorax) resection (pneumonectomy). After surgery, patients are evaluated for adjuvant treatment (chemotherapy and/or radiotherapy).The post-surgery five-year survival rate is 40% (17).

Patients referred to resective surgery for lung cancer are characterized by older age (about 2 out of 3 are ≥ 65 years), and the presence of comorbidities (17). COPD is present concomitantly in 73% of men and 53% of women with newly diagnosed primary lung cancer (18). Furthermore, a smoking history predisposes these patients to other comorbid conditions, in particular atherosclerotic cardiovascular disease, which increases the risk of postoperative morbidity (19).

Pulmonary function following surgery

Lung cancer surgery affects postoperative pulmonary function in many ways. In the immediate postoperative period, there is a pronounced decrease in forced expiratory volume in 1 second (FEV_1), with partial recovery during the first six postoperative days (20). Persistent reduction in pulmonary function of 10 - 40% after surgery has been reported, depending on the extent of resection and the time elapsed from the operation (21-23). After lobectomy, the FEV_1% predicted can be reduced by ~20% one month after the surgery, with a slight recovery of ~5% after three months, when compared to preoperative values (22). On the other hand, pneumonectomy is associated with larger and long-lasting reductions in FEV_1 (40-50%) (21,22). Factors suggested as negatively influencing pulmonary function after lung cancer surgery include age > 65 years, COPD, smoking, surgery > three hours, use of general anaesthesia (24), wound pain, pleural drainage and pleural adhesions (25,26).

The reduction in pulmonary function subsequent to the resection of lung tissue adds to the common negative effects of surgery and anaesthesia

(27) on pulmonary function. In the early postoperative period, there is airway closure in the basal lung segments, resulting in reduced functional residual capacity with increased risk of atelectasis (28). Breathing occurs at lower tidal volume, and this increases respiratory frequency (26). Limitations to the chest wall motion consequent to the thoracic incision (29), together with the placement of intercostal chest drains and pain (26), may reduce the depth of breath, thereby increasing the risk of secretion retention (25). The secretion retention further impairs gas exchange and results in hypoxemia and hypercapnia (28). These mechanisms may also compromise the ventilatory demands under exercise and contribute to an increase in dyspnoea level during normal daily activities, such as walking.

Respiratory muscle strength

The respiratory muscles can be divided into those that participate mainly during inspiration and those that are predominantly expiratory in function (30). The diaphragm is the primary inspiratory muscle, accounting for two-thirds of the inspiratory work, accessed mainly by the intercostal and scalene muscles. The activation of the abdominal muscles under expiration is important during coughing manoeuvres (30). The respiratory muscles, and in particular the diaphragm, play a vital role in the breathing process, stabilising the thorax and abdomen and providing the power for the "respiratory pump". Following lung cancer surgery, the mechanical efficiency of the chest wall and thoracic compliance may be compromised by injury to the chest wall- and muscles due to the surgical procedure (6), the removal of lung tissue (6,26) and the placement of pleural drain (6,26). This may in turn change the pattern of contraction of the respiratory muscles, in particular the diaphragm, thereby limiting its capacity to generate pressure (25). Reductions in respiratory muscle strength (RMS) following pulmonary resection are documented four (31,32) and 12 weeks postoperatively (9). The decrease in RMS can also be more pronounced following pneumonectomy (9,33), when compared to lobectomy/segmentectomy (31). VATS is related to a lower decrease in RMS, compared to thoracotomy (9,31).

Respiratory muscle weakness is an additional factor that may contribute to impaired postoperative pulmonary function by worsening gas exchange secondary to ventilation/perfusion mismatch (25). As the respiratory muscles are the main contributors to ventilatory demands during exercise (34), respiratory muscle dysfunction may increase the work of breathing under physical activity (26). This is likely to reduce patient´s ability to perform daily living activities, thereby delaying postoperative recovery.

Meanwhile, the impact of respiratory muscle dysfunction on respiratory distress and functional impairments following lung cancer surgery has not yet been addressed in the literature.

In healthy persons, RMS is inversely related to age and is about 30 - 50% lower in women than in men (35). Impaired RMS is observed in patients with COPD (36,37) and cardiorespiratory disorders (34), and contributes to both reduced exercise tolerance and exertional dyspnoea (34,37). A clinically relevant decrease in respiratory muscle strength following major surgery has not yet been defined.

Postoperative pulmonary complications

PPC is defined as any pulmonary abnormality occurring in the postoperative period producing an identifiable and clinically significant disease or dysfunction (38). PPCs are a major cause of morbidity, prolonged hospital stay (1,39) and mortality, accounting for 84% of all postoperative deaths following lung cancer surgery (38). The overall incidence of PPC after pulmonary resection varies between 19 and 59%, depending on their definition, with pneumonia and atelectasis being the most common type (40). Surgical factors associated with PPC are mostly related to impaired pulmonary function as a consequence to resected lung tissue (20), residual effects of anaesthesia (24), prolonged chest drainage (41,42) and dysfunction of the respiratory muscles (25). With regard to the surgical approach, a study found that VATS was significantly associated with a lower incidence of PPC (11% reduction) than lobectomy by thoracotomy (43), while another study found no differences in the overall complication rates (15).

The occurrence of postoperative complications and long-term disability following lung cancer surgery is an independent predictor of five-year cancer-specific mortality (44). Patients with lung cancer considered for pulmonary resection undergo a preoperative physiological evaluation, due to the increased risk of both perioperative complications and long-term disabilities. The physiological evaluation comprises calculation of the expected postoperative FEV_1, measurement of diffusing capacity for carbon monoxide (D_{LCO}) and assessment of performance status. Patients with a stair-climbing altitude of < 22 m or $VO_{2\ max}$ < 20 mL/kg/min (19) or < 500 m in the six-minute walk test (6MWT) (45) are considered to be at increased risk of postoperative complications.

Physical performance

Lung cancer surgery, compounded by the presence of comorbid conditions, has a negative impact on physical performance. Low activity levels

are common throughout the cancer trajectory (46,47), leading to, or as a result of, deconditioning. Several studies have confirmed a decrease in exercise tolerance following surgery (48,49). The reasons for deconditioning are likely to be multifactorial. Daily symptoms of dyspnoea and fatigue are common among lung cancer survivors and therefore induce a more sedentary lifestyle (47,50). Daily ambulatory activity decreases following surgery (51). Increased inactivity is followed by peripheral muscle dysfunction and cardiovascular deconditioning (12), resulting in compromised exercise capacity.

Compromised exercise tolerance and reduction in exercise capacity following lung resection have been documented (22,52). These impairments are related to the extent of resection (53,54) and may be more pronounced in patients with COPD (22,55). Possible implications include ventilatory limitations with increased work of breathing at a given workload, gas exchange impairments resulting in hypoxia and subsequently increased lactic acid production (10). Chemotherapy after surgical treatment is associated with further impairments by altering the pathways involved in oxygen and metabolic transport during exercise (56,57). Finally, functional weakness of the respiratory muscles may be related to exertional breathing discomfort, a likely explanation for the interruption of exercise in cancer patients (58).

Health-related quality of life

HRQoL reflects the impact of disease and treatment on daily lifestyle and is therefore an important clinical outcome in connection with lung cancer (22). HRQoL is also a predictor of survival (59,60). Patients with lung cancer referred to pulmonary resection present with impaired HRQoL preoperatively (61) as well as after surgery, when compared to persons with other types of cancer (11) or to the general population (22). Symptom burden, mostly related to dyspnoea and fatigue, affects the physical dimensions of HRQoL for six months or longer after surgery (62-64) while the mental dimensions of HRQoL seem to return to preoperative levels (65,66). However, one study suggests that long-term adaptations to a compromised physical condition may affect a patient's perception of improvement in overall QOL over time (67).

Factors negatively associated with HRQoL following lung cancer surgery include postoperative pain (68), distressed mood (69), fatigue (70), the presence of ≥ two comorbid conditions (69) and major resection (pneumonectomy) (3,65,71). However, there is divergence on the impact

of the surgical approach on HRQoL. One study reported significant differences in physical functioning, HRQoL and thoracic pain in favour of VATS one - twelve months postoperatively (71). On the other hand, two studies reported no significant differences three - twelve months (72) and > two years post-surgery (73).

Physiotherapy interventions after surgery

Breathing exercises during hospital stay
Breathing exercises are provided by physiotherapists following thoracic surgery in order to prevent or reduce postoperative pulmonary complications (74-76). Breathing exercises are a part of the physiotherapy regime that also includes early mobilisation, the use of airway clearance techniques and shoulder and thoracic cage mobility exercises with the overall aim of accelerating the return to preoperative function (77). Breathing exercises consist of teaching patients to breathe slowly and deeply in order to induce lung re-expansion. Incentive spirometry (78) and deep breathing technique with - or without a positive expiratory pressure (PEP) device (74) are the most common physiotherapy techniques used to achieve lung re-expansion after thoracic surgery. These exercises optimize the distribution of air to the dependent lung regions and consequently improve basal ventilation of the lungs (28). Slow and deep inspiration, combined with a (2 - 5 second) inspiratory hold before expiration is recommended postoperatively (78,79).

The provision of breathing exercises following major thoracic surgery is recommended in the general belief that it is beneficial for preventing PPC (24,27,80). However, this practice is not supported by evidence, since to date no randomised controlled trial (RCT) has supported the routine provision of postoperative respiratory physiotherapy over standardised care that includes early mobilisation (81-83).

Inspiratory muscle training
Respiratory muscle training is aimed at improving the function of the respiratory muscles by applying resistance to breathing, often during inspiration (thus inspiratory muscle training (IMT)). The inspiratory muscles respond to training in the same way as other skeletal muscles (84). By strengthening the respiratory muscles with IMT, a person can increase the inspired volume, thereby enabling a better blood oxygenation (84). Patients with COPD and concomitant weakened respiratory muscles show increased exercise capacity, and physical performance and reduced dysp-

noea following IMT (10). In a surgical setting, IMT may preserve or increase RMS, consequently optimizing lung re-expansion. This, in turn, helps generate forceful expiratory manoeuvers for the clearance of secretion, consequently reducing the risk of PPC (6,8).

The effects of IMT on postoperative outcomes have been assessed by studies investigating preoperative IMT in patients undergoing cardiac or upper abdominal surgery. A systematic review with meta-analysis reported a significant reduction in the incidence of PPC, but no effect on the length of hospital stay (8). Initial training loads varied between 15 and 40% of maximal inspiratory pressure (MIP), with daily training sessions for a period of at least two weeks (8).

There is little information on the effects of IMT in patients undergoing pulmonary resection. One study reported that two weeks of preoperative IMT significantly reduced PPC (5). Moreover, in another study, IMT was combined with incentive spirometry administered two weeks preoperatively and 12 weeks postoperatively (9). It was found that MIP increased significantly two weeks after the surgery in the treated group while it was unchanged in the control group (9).

Exercise training after hospital discharge

Lung cancer patients and patients with COPD present comparable impairments and symptoms such as dyspnoea, fatigue, reduced exercise tolerance, decreased activity levels and depression. Exercise-based rehabilitation programmes in patients with COPD are well established (10) and provide the rationale for the use of exercise training in patients with lung cancer. Rehabilitation programmes improve exercise capacity and reduce exertional dyspnoea in COPD patients by enhancing the oxidative capacity of skeletal muscles at a given workload. Consequently, reduction in muscular lactic acidosis requires less pulmonary ventilation than untrained muscles. The reduction in pulmonary ventilation reduces dyspnoea and enables higher workload, even with unchanged pulmonary function (85).

Exercise-based rehabilitation programmes for patients following lung cancer surgery are based on endurance training (cycling or walking) and resistance/strength training for large muscular groups of the upper/lower limbs and trunk. The training period should last for at least three months (10). Endurance training for the elderly population should consist of training loads of > 60% of maximal work rate (somewhat hard on the rating of perceived exertion (RPE) scale), with 20 to 60 minutes per session, 3 to 5 times a week. In the case of strength training, 1 to 3 sets of 8 to 12 repeti-

tions, undertaken 2 to 3 days weekly on initial training load equivalent to 60 to 70% of the one repetition maximum (86).

Results from case series and cohort studies, based on an inpatient setting, have shown significant benefits of four – eight weeks of exercise training on physical performance, HRQoL and pain (87-89). Although these interventions were considered safe, even in the case of patients receiving adjuvant chemotherapy, rehabilitation provided in an inpatient setting may be difficult to implement due to considerable economic costs. Meanwhile, results from RCTs administered in an outpatient setting suggest that postoperative exercise interventions may confer gains in terms of an increase in 6MWT, but have no effect on HRQoL (90-92). Thus, robust evidence of the efficacy of exercise-based interventions for patients following lung cancer surgery is still lacking.

Rationale of this thesis

Persistent respiratory problems and detriments in physical performance and activity levels are common following lung cancer surgery, contributing to an impaired health-related quality of life. Exercise training is widely recommended to patients with impaired respiratory conditions to enhance physical performance and reduce symptoms, but evidence of the effects of exercise training following lung cancer surgery is inconclusive and needs further research.

Pulmonary resection for lung cancer is associated with a high incidence of postoperative pulmonary complications, influencing the outcome of the surgery. Respiratory muscle weakness following the surgery may be a precursor to postoperative pulmonary complications. Inspiratory muscle training has the potential to improve pulmonary function, but the effects of postoperative inspiratory muscle training in the early postoperative period need to be verified. The presence of respiratory muscle weakness and its impact on outcome after hospital discharge has not been addressed in the literature.

Resuming daily living activities and improving health-related quality of life following lung cancer surgery become increasingly important issues for clinicians, patients and relatives. Inspiratory muscle training and exercise training have the potential to reduce postoperative morbidity and restore physical function following lung cancer surgery.

Therefore, the hypotheses of the present thesis were:

- Supervised exercise training improves health- related quality of life and physical performance following lung cancer surgery
- The improvements in physical performance, pulmonary function and health-related quality of life are sustained over time
- There is a positive association between physical performance and health-related quality of life postoperatively
- There is an impairment in respiratory muscle strength, pulmonary function and physical performance following surgery
- Postoperative inspiratory muscle training in addition to breathing exercises and early mobilisation preserves respiratory muscle strength and reduces the incidence of postoperative pulmonary complications

Aims

The aim of this thesis was to evaluate the effect of exercise training and inspiratory muscle training and to describe pulmonary function, respiratory muscle strength, physical performance and health-related quality of life following lung cancer surgery.

The specific aims were to:

Study I
Evaluate the effects of a physiotherapist-supervised, outpatient, group-based exercise programme on health-related quality of life and functional outcome in patients radically operated on for lung cancer.

Study II
Evaluate the course of recovery of physical performance, pulmonary function and health-related quality of life from the early postoperative period up to one year after pulmonary resection for primary or secondary lung cancer. Secondarily, to evaluate the potential association between physical performance and health-related quality of life during the follow-up period.

Study III
Describe respiratory muscle strength, pulmonary function and physical performance preoperatively, and two weeks and six months postoperatively in patients undergoing pulmonary resection on suspicion of or confirmed lung cancer. Secondarily, to evaluate the influence of the surgical approach on respiratory muscle strength.

Study IV
Investigate the effect of two weeks of postoperative inspiratory muscle training on respiratory muscle strength in high-risk patients referred for pulmonary resection on suspicion of or confirmed lung cancer. Secondarily, to evaluate the effect of the intervention on the incidence of postoperative pulmonary complications.

Materials and Methods

Design, setting and ethics

Study I and **Study IV** were randomised controlled trials, 1:1 parallel-group, with assessor blinding. **Study II** and **Study III** were cohort studies with a prospective descriptive design. The studies design, sample size, main outcomes and time-points for assessment are outlined in Table 1.

Patients were recruited from the Department of Cardiothoracic Surgery, Aalborg University Hospital, Aalborg, Denmark.

The Research Ethics Committee in Denmark – Region North approved the studies (**Studies I - II** registration VN/2004/72; **Studies III - IV** registration N-20120027). Data for all studies were handled according to the requirements from the Danish Data Protection Agency (Reg. Study I-II: 2005-53-1184; **Study III - IV**: N-2008-58-0028). **Studies I** and **IV** were registered at Clinical Trials.gov, identification NCT01048762 and NCT01793155, respectively. Patients were given verbal and written information about the study and informed consent was obtained from each participant before the baseline assessments took place.

Table 1: Overview of study design, sample size, main outcome measurements and time-points for assessments for **Studies I - IV**

	Study I *	Study II *	Study III	Study IV **
Design	RCT, assessor- blinded	Descriptive	Descriptive	RCT, assessor-blinded
Sample size (n)	n = 78		n = 81	n = 68
Target population	Patients radically operated on for lung cancer		Patients scheduled for pulmonary resection on suspicion of or confirmed lung cancer	Patients from study III at high-risk of PPC
Main outcome measurements	Spirometry (FVC, FEV₁, FVC/FEV₁) 6MWT Exertional dyspnoea SF-36	Spirometry (FVC, FEV₁, FVC/FEV₁) 6MWT Exertional dyspnoea SF-36 PPC	Spirometry (FVC, FEV₁, FVC/FEV₁) 6MWT Exertional dyspnoea Exertional SpO₂ Respiratory muscle strength (MIP/MEP) Pain (incisional, cough)	Spirometry (FVC, FEV₁, FVC/FEV₁) 6MWT Exertional dyspnoea Exertional SpO₂ Respiratory muscle strength (MIP/MEP) PPC
Assessment time-points	Postoperatively: 3 weeks, 4 months and 1 year after surgery		Before surgery, 2 weeks and 6 months after surgery	Before surgery, postoperative day 3 - 5 and 2 weeks after surgery

* **Studies I – II:** same study population; ** **Study IV** includes patients from **Study III**

Abbreviations: FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 second; 6MWT, six-minute walk test; SF-36, Short Form SF-36 Health Survey; PPC, postoperative pulmonary complication; SpO₂, peripheral oxygen saturation; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure

Patients

Patients (age > 18 years) were consecutively assessed and enrolled between February 2006 and September 2009 (**Studies I - II**) and November 2012 - April 2014 (**Studies III - IV**). **Studies I – II** included patients radically operated on for lung cancer, living within a radius of 80 km from the hospital. Both studies had the same cohort. **Study III** included patients scheduled for pulmonary resection on suspicion of or a confirmed lung tumour, regardless of the surgical approach (thoracotomy or VATS). **Study IV** included patients deemed to be at high PPC risk, scheduled for pulmonary resection on suspicion of or a confirmed lung tumour, regardless of the surgical approach. High-risk criteria were defined as one or more of the following: age ≥ 70 years (31,93), FEV_1 ≤ 70 % predicted (94,95), D_{LCO} ≤ 70% predicted (1,93) or planned pneumonectomy (96).

The exclusion criteria for all studies were: inability to understand written and spoken Danish, and physical or mental deficits adversely influencing physical performance. Additionally, in **Studies I - II** patients were also excluded if they were transferred to other medical centres for further treatment. The additional exclusion criteria in **Studies III - IV** were: previous ipsilateral lung resection, preoperative tumour activity in other sites or organs, pancoast tumour and major surgery within one year.

Randomisation procedure (Studies I and IV)

For **Study I,** we used a computer-generated block randomisation list with blocks of four, stratified for pneumonectomy. For **Study IV,** we used a computer-generated block randomisation list with permuted blocks of four-six. Group allocations were placed by an independent person in sequentially numbered sealed opaque envelopes. For **Study IV,** envelopes with group allocations were kept by an external person and released individually and in sequential order to the main researcher. In both studies, randomisation allocations were disclosed by the main researcher. Patients were allocated to either intervention (IG) or control (CG) groups after the baseline assessments had taken place. For **Study I,** this took place 3 weeks after the surgery; for **Study IV,** one working-day prior to the surgery.

The recruitment process for **Studies I** and **IV** is illustrated in Figures 1 and 2 respectively. The flow charts also provide details on the exclusion criteria and dropouts throughout the follow-up period. Table 2 provides demographic information about the participants in the four studies.

Enrollment

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┌─────────────────────────────────────────┐
│   Screened for eligibility (n=294)       │
└─────────────────────────────────────────┘
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Did not meet inclusion criteria (n=123)
- not radically operated/cancer other sites n=51
- living > 50 km from the unit n=35
- transferred to other facilities n=7
- not speaking Danish n=2
- cognitive/physical deficits n=10
- other reasons n=18

Excluded (n=93)
- failed to perform 6MWT n=1
- did not wish to participate n= 92
 (Reasons: too tired to participate n=28;
  distance n=41; too fit/work n=15; chemo-
  therapy n=5; not interested n=3)

Randomised n=78

IG (n=41)
Received intervention n=39

CG (n=37)
Received intervention n=36

Follow up 4 months

Lost to follow up (n=9)
(Deceased n=2; withdrew consent)

Lost to follow up (n=2)
(Deceased n=1; withdrew consent n=1)

Analysis 4 months

IG (n=32)
Lung volumes n=28
6MWT n=32
SF-36 n=32

CG (n=35)
Lung volumes n=34
6MWT n=34
SF-36 n=35

Follow-up 1 year

Lost to follow up (n=4)
(Deceased n=1; withdrew consent n=3)

Lost to follow up (n=4)
(Deceased n=1; withdrew consent n=3)

Analysis 1 year

IG (n=28)
Lung volumes n=28
6MWT n=27
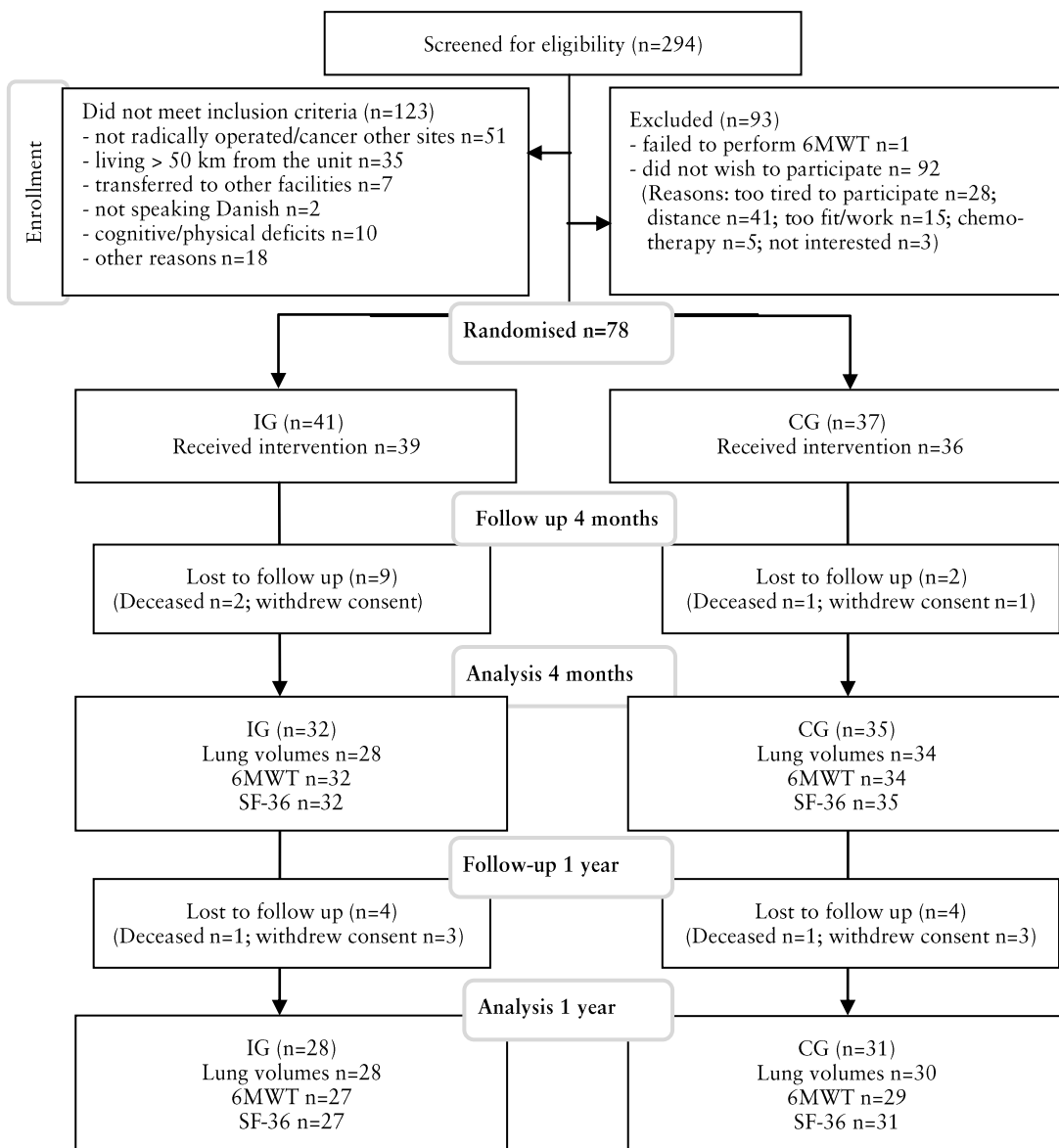SF-36 n=27

CG (n=31)
Lung volumes n=30
6MWT n=29
SF-36 n=31

Figure 1: Flow chart for **Study I.**
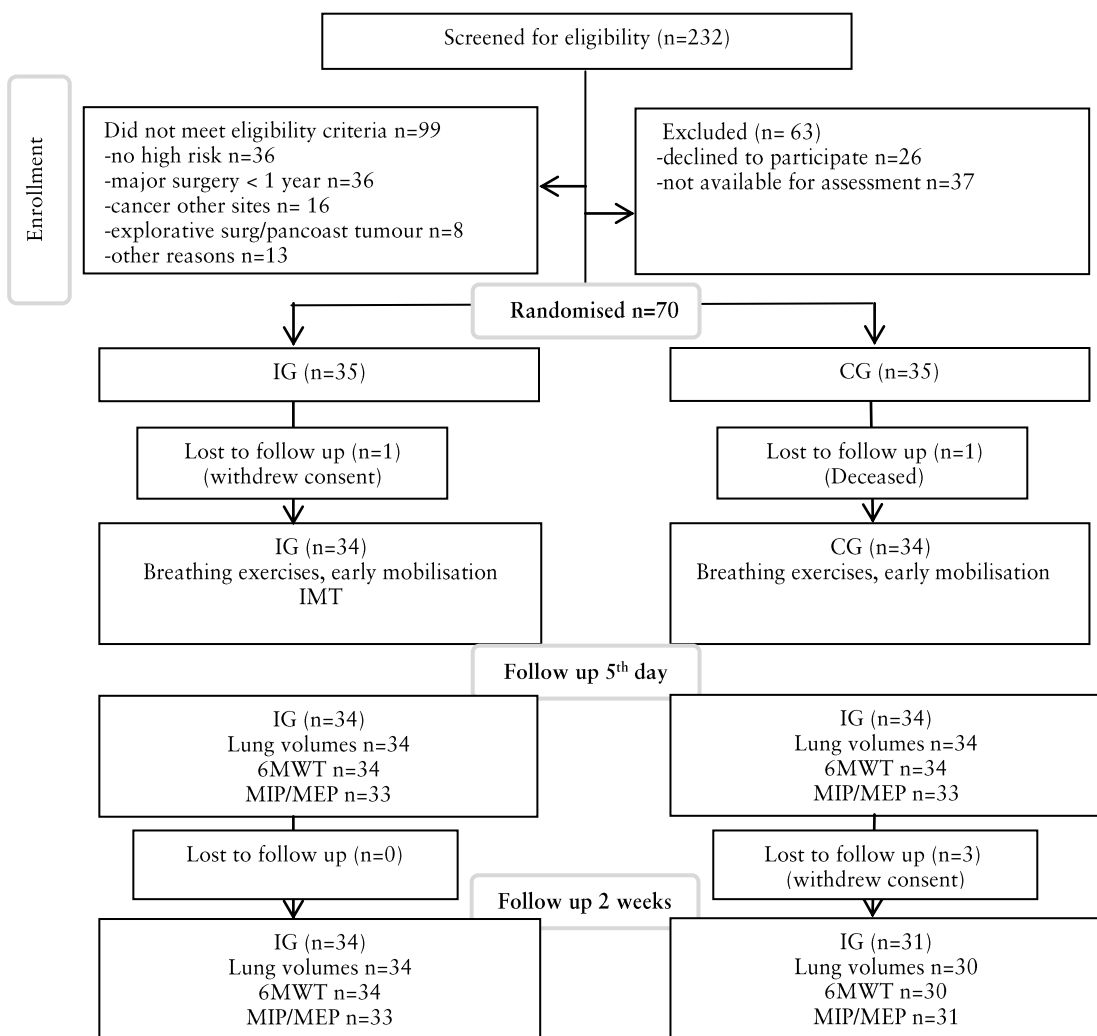IG, Intervention group; CG, control group; SF-36, Short Form SF-36 Health Survey; 6MWT, six-minute walk test.

Screened for eligibility (n=232)

Did not meet eligibility criteria n=99
-no high risk n=36
-major surgery < 1 year n=36
-cancer other sites n= 16
-explorative surg/pancoast tumour n=8
-other reasons n=13

Excluded (n= 63)
-declined to participate n=26
-not available for assessment n=37

Randomised n=70

IG (n=35)

CG (n=35)

Lost to follow up (n=1)
(withdrew consent)

Lost to follow up (n=1)
(Deceased)

IG (n=34)
Breathing exercises, early mobilisation
IMT

CG (n=34)
Breathing exercises, early mobilisation

Follow up 5th day

IG (n=34)
Lung volumes n=34
6MWT n=34
MIP/MEP n=33

IG (n=34)
Lung volumes n=34
6MWT n=34
MIP/MEP n=33

Lost to follow up (n=0)

Lost to follow up (n=3)
(withdrew consent)

Follow up 2 weeks

IG (n=34)
Lung volumes n=34
6MWT n=34
MIP/MEP n=33

IG (n=31)
Lung volumes n=30
6MWT n=30
MIP/MEP n=31

Figure 2: Flow chart for **Study IV.**
IG, Intervention group; CG, control group; IMT, inspiratory muscle training; 6MWT, six-minute walk test; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

Table 2 - Demographic and surgical characteristics of participants in **Studies I - IV.**
Mean ± SD, median [min;max] or numbers (%)

	Studies I - II (n=78)	**Study III** (n=81)	**Study IV** (n=68)
Age (years)	65 ± 9	68 ± 9	70 ± 8
	65 [42;83]	69 [46;82]	71 [51;82]
Gender (male/female), n (%)	46/32 (59/41)	47/34 (58/42)	39/29 (57/43)
Preoperative FEV$_1$% predicted	83 ± 19	101 ± 21	79 ± 22
(n=75 for **Studies I - II**)	82 [41;148]	98 [59;170]	80 [28;134]
VATS/thoracotomy, n (%)	18/60 (23/77)	47/34 (58/42)	35(51)/33(49)
Resection degree			
Wedge/segmentectomy, n (%)	12 (15)	27 (33)	21 (31)
Lobectomy, n (%)	54 (70)	45 (55)	38 (56)
Bilob/pneumonectomy, n (%)	7/5 (9/6)	4/7 (5/8)	3/6 (4/9)
Length of hospital stay (days)	10 ± 5	8 ± 5.3	8 ± 5.5
	8 [4;30]	6 [3;30]	6 [3;30]
Cancer characteristics			
NSCLC, n (%)	65 (83)	55 (68)	52 (78)
Metastatic tumour, n (%)	10 (13)	11 (14)	8 (11)
Other type, n (%)	3 (4)	15 (18)	8 (11)
Adjuvant treatment, n (%)	34 (43)	20 (25)	n.a.

Abbreviations: FEV$_1$%, forced expiratory volume in 1 second expressed as % of predicted values; VATS, video-assisted thoracic surgery; NSCLC, non-small cell lung cancer: n.a., not applicable.

Surgery and postoperative care

All patients received premedication and general anaesthesia (Propofol, Ultiva). Pulmonary resections were performed either by VATS or by the open technique using a muscle-sparing lateral or postero-lateral thoracotomy (preserving m. latissimus dorsi and m. serratus anterior). The choice of surgical approach was up to the surgeon. At the end of the surgery, two chest tubes on water seal (**Studies I - II**) or a single chest tube connected to a suction system with negative pressure of minus 5 – 10 cmH$_2$O column (Thopaz chest drainage system®, Medela Switzerland) (**Studies III - IV**) were placed in the pleural space. No drainage was used after pneumonectomy. Pain management was primarily achieved by continuous thoracic epidural infusion of bupivacaine 2,5mg and morphine, supplied by per-oral non steroid anti inflammation drugs and paracetamol over a period of two - five days. A routine chest X - ray was performed within 24 hours after removal of the chest tube (for **Studies III - IV** [range 1 - 15 days]) and again at the medical follow-up two weeks after surgery. All patients were treated by the nursing staff according to standard postoperative routines, including mobilisation.

All patients received standard physiotherapy consisting of a preoperative instruction in breathing exercises with a PEP device. Patients performed 3 x 10 breaths every waking hour after surgery, coughing and huffing technique according to institutional practice guidelines (97). The ward physiotherapist assessed the patient twice daily for the first three postoperative days (**Studies I - II**). For **Studies III - IV** patients were assessed once daily for the first two postoperative days. Patients were mobilised to sitting in a chair on the morning after the surgery and ambulation in the afternoon of postoperative day 1 (**Studies I - II**), while for **Studies III - IV**, patients sat at the bedside on the day of the surgery and ambulated 15 metres or more on the first day after the surgery.

Interventions for studies I and IV

Study I
Both the intervention (IG) and control (CG) groups were instructed on home-based strength training exercises for the major muscle groups (arms, legs and trunk) at least twice a week. Both groups were also instructed to take a daily walk or a bicycle ride for 30 minutes with an intensity of 11-

12 on the Borg Scale (98). A training diary was used to record compliance with home training. All patients were also offered three individual one-hour counselling sessions with a nurse within three weeks to four months postoperatively. Additional sessions were however provided, if necessary.

In addition to the interventions described above, the IG received 10 supervised exercise training sessions, provided at Aalborg University Hospital. The sessions were group-based and provided once weekly, starting three weeks after surgery. Details of the intervention are provided in Table 3. The exercise programme was tailored according to physical capability and based on a sub maximal exercise test (99) performed at the first training session and repeated in sessions 6 - 7. The physiotherapist in charge registered patients´ training intensity on a training diary.

Table 3: **Study I** - Supervised exercise training

Type of exercise	Duration (min)	Intensity	Progression
Warm – up Aerobic-, combined with upper/lower limb/ thoracic cage stretches	5 - 15	RPE 7 - 12	Commenced walking normal speed; ↑ walking speed, intercalated with arm swings, stretching-, knee lifts
Aerobic Stationary bike	10 - 20	RPE 11 - 12 (session 1- 4) ↑ RPE 13 - 16 (session 5 - 10)	Warm-up 4 min target RPE 10 Interv 20s RPE 12/40s RPE 10 ↑ nb intervals; ↑20s RPE 13-16
Strength training arms (Thera-band®) trunk (abdomen, back) legs (step-ups, heel raises, sit to stands)	10 - 15	6 - 10 reps 1 - 2 sets	Commenced 6 reps x 1 set ↑ reps per set ↑ sets 10 reps
Cooling down/relaxation	10	RPE 6	

Abbreviations: RPE, Borg Rating of Perceived Exertion (range 6-20); s, seconds; reps, repetitions; nb, number ® Thera-band (PROcare, Denmark), green colour

After the four- month follow-up, all patients were advised on being physically active at moderate intensity for at least 30 minutes daily and no further active intervention was given.

Study IV

The intervention consisted of IMT twice daily using a POWERbreathe K3® (HaB Ltd, UK) (Figure 3), starting one working day before surgery and continuing for two weeks after surgery; no sessions were performed on the day of surgery. Each session consisted of two cycles of 30 breaths with a two-minute rest between each cycle. The resistive breathing during every cycle was of approximately 3.5 minutes. Patients were instructed to breathe in as strongly and deeply as possible and then breathe out as slowly and deeply as possible. Patients performed breathing exercises sitting in a chair and using a nose clip.

The target training load before surgery was 30% of maximal inspiratory pressure (MIP). This training session was aimed at patients getting acquainted with the training device. After surgery, the training load started with 15% of preoperative MIP. Subsequently, during hospital stay, the training load was incremented daily in two ways: either by an increase of 2 cm H_2O or at exertion level 3 on the modified Borg 0 - 10 exertion scale. The training load after hospital discharge was either 30% of MIP measured at discharge or Borg exertion level 3. Patients graded their perceived exertion, pain level (0 – 10 Numeric rating scale, NRS) and symptoms, such as muscle soreness, in a training diary after each training session.

For safety reasons, the thoracic surgeon was contacted in the case of persistent air leak in the pleural drainage. IMT was continued if the registered air leak in the Thopaz drain did not exceed the leak produced during a coughing manoeuvre.

Most training sessions were supervised during hospital stay. The training sessions were not supervised after hospital discharge; however, patients were coached by telephone at least once after discharge. Compliance with training, measured as the number of performed training sets and the targeted training intensity, was stored electronically in the training device.

Figure 3: POWERbreathe K3 training device used for IMT.

Measurements

Assessment of pulmonary function, 6MWT and RMS was performed by skilled physiotherapists. For **Studies I** and **IV,** they were blinded as to each patient´s individual randomization results. PPC (**Study IV**) was evaluated by a thoracic surgeon who was blinded as to the randomization results, although the collection of data for peripheral oxygen saturation for the first five postoperative days was performed by the nurse in charge of the patient, who was not blinded.

Spirometry (Studies I - IV)

Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), were assessed according to current guidelines (100), the best of three measurements was recorded and the FEV_1/FVC ratio calculated. Values were related to sex, age and height according to the reference values reported by Quanjer et al. (101). Measurements were performed with a portable spirometer, the Spirovit SP-2® (Schiller, Switzerland), which was calibrated daily (Figure 4).

6MWT (Studies I – IV)

The 6MWT was used to assess functional performance. The 6MWT is a valid and reliable tool for assessing physical performance in patients with chronic respiratory diseases (102). The test was performed according to current guidelines (103). Patients were instructed to walk along a 20 m corridor at their fastest pace and cover the longest distance possible in six minutes. No encouragement was given during the test. Values were related to sex, age and height according to reference values (104).

Dyspnoea (Studies I-IV)

For **Studies I** and **II**, patients rated their post-6MWT dyspnoea level on a Borg scale (ratings 6 - 20) (98); for **Studies III** and **IV** dyspnoea before and immediately after the 6MWT was rated on a Borg CR-10 scale (rating 1 - 10) (105). Higher rates indicate a higher dyspnoea level.

Exertion (Studies III and IV)

The perceived exertion is a measure of the subjective degree of heaviness and strain during physical work (98,106). Patients rated their perceived exertion during the 6MWT immediately after the test on the modified 1 - 10 Borg scale (105). Higher rates indicate a higher perceived exertion.

Peripheral oxygen saturation (Studies III and IV)

SpO_2 was measured before and immediately after the 6MWT using a pulse oximeter (Riester ri-fox N®, Germany).

Respiratory muscle strength (Studies III – IV)

RMS was measured at the mouth while the patient was seated in a chair and using a nose clip, according to guidelines (107). We used a hand-held electronic transducer (Micro RPM®; MicroMedical/CareFusion, Kent, UK) (Figure 5) with a flanged mouth piece. Measurements were performed from total lung capacity for maximal expiratory pressure (MEP) and from residual volume for maximal inspiratory pressure (MIP). At least five attempts for each measurement were performed. The highest one-second value from three consecutive attempts lying within 10 cmH_2O of each other was used, and the percentage of predicted values was reported (35). An inter-rater reliability test with 10 healthy individuals aged 55 – 75 years performed prior to the study showed an intraclass correlation coeffi-

cient (ICC) of 0.87, 95% CI [0.49;0.96], p = 0.03 for MIP and of 0.98, 95% CI [0.91;0.99], $p < 0.001$ for MEP.

Pain (Studies III and IV)

Patients were asked to rate their pain in the chest (at the incision site) at rest, while performing a voluntary cough manouvre and during the assessment of RMS. The rating was on a 0 – 10 NRS scale, with 0 corresponding to no pain and 10 as the worst experienced pain.

Health- related quality of life (Studies I - II)

The Short Form Health Survey (SF-36) version 2 is a generic questionnaire for measuring functional health and well-being (108,109), that has been validated for pulmonary diseases (110). It comprises eight domains with a total of 36 questions related to physical functioning, physical role functioning, bodily pain, general health, vitality, social functioning, emotional role functioning, and mental health. Two summary components, each derived from four domain scores, are also calculated; the physical component summary (PCS) and the mental component summary (MCS). Raw data was transformed into a score from 0 to 100, with higher scores indicating better HRQoL. A minimally important difference of 3 units in the SF-36´s subscales (111) or 10% in the summary scores has been described as clinically relevant in lung cancer patients (112).

Figure 4:
Spirovit SP- 2 used for spirometry.

Figure 5:
Micro RPM used for measurement of respiratory muscle strength.

Postoperative pulmonary complications (studies II and IV)

PPC data was collected retrospectively from journal files. For **Study II,** the PPC was retrieved if the physician stated that particular PPC in the journal files. For **Study IV,** a cardiothoracic surgeon, who was unaware of the patients' randomisation allocation, assessed PPC two weeks after surgery according to pre-specified criteria illustrated in Table 4. These criteria were modified from Kroenke et al. (113) and Hulzebos et al. (114). PPC was classified from 1 (minor PPC) to 3 (severe PPC). A clinically relevant PPC was defined as two or more items in the grade 1 complication or one item in the grade 2 or 3 complication. SpO_2 was measured each morning up to five days postoperatively by the nurse in charge of the patient. The nurse was not blinded as to the patients' randomisation allocation. SpO_2 was measured ten minutes after the removal of the supplementary oxygen supply and hypoxemia was defined as $SpO_2 < 90\%$ for two consecutive days.

Table 4: Operational definition of PPC – **Study IV**

Grade 1
- new onset of purulent sputum or change in character of chronic sputum
- fever $\geq 38^\circ$ C with no focus outside the lungs
- a new rise in C-reactive protein value or white blood cell count
- positive blood cultures
- atelectasis: radiological confirmation or abnormal lung findings requiring non-invasive intervention e.g. continuous positive pressure breathing
- hypoxemia defined as $SpO_2 < 90\%$ for two consecutive days
- administration of postoperative antibiotics (in addition to those administered routinely postoperatively)
- trans-tracheal aspirate or bronchial washing

Grade 2
- pleural effusion resulting in drainage
- pneumonia suspected through radiological evidence without bacteriological confirmation or confirmed pneumonia with radiological evidence and documentation of pathogens from sputum
- visible pneumothorax apical and/or lateral > 2 cm detected by a surgeon on a chest radiograph with or without requirement of invasive treatment
- postoperative re-intubation, period of ventilator dependence < 48 hours
- clinically significant atelectasis requiring tracheo-bronchial suction

Grade 3
- ventilatory failure with postoperative ventilator dependence > 8 hours
- reintubation with subsequent period of ventilator > 48 hours

Statistical analyses

Statistical analyses for **Studies I - II** were performed using Stata 11 (Stata Corp LP, Texas, USA), and for **Studies III - IV** with SAS 9 (SAS Institute, Cary, NC, USA). All tests were two- sided and considered statistically significant if $p < 0.05$ with a power of 0.80. For **Studies I - II**, data were presented as means (± standard deviation), whereas for **Studies III - IV**, data were presented as means (± standard deviation) and medians (min; max) for the same variable, or as counts (%). Information on confidence intervals is available in respective papers I – IV.

Analyses for **Studies I** and **IV** were made on an intention-to treat-approach. Normality was verified by visual inspection of histograms (**Studies I, III and IV**), and by inspection of qq-plots of the residuals (**Study II**).

Statistical analyses for **Studies I - II** were performed within the frames of repeated-measures generalized estimating equations (GEE) linear regression models, using an exchangeable (**Study I**) or symmetric (**Study II**) working correlation. The model included baseline measurements, time, baseline-time interaction, the effect of treatment and gender - the latter for efficiency reasons, since women´s SF-36 values are generally lower than men´s (109). To assess the robustness of findings to missingness, we performed two sensitivity analyses for each outcome. The first was based on a worst-case-for-the-intervention/best-case-for-the-control approach. The second sensitivity analysis was based on a best-case-for-the-intervention/worse-case-for-the-control approach.

For **Study II**, the response variables used to assess the association with 6MWT were: PCS, MCS and SF-36´s domains. The GEE model was adjusted for gender and intervention. For analysis of the influence of baseline variables in PCS at baseline and after one year, we fitted an unadjusted GEE model with PCS as response variable; the independent continuous variables were age, postoperative FEV_1 and BMI. Length of hospital stay was dichotomized with a cut-off value of ≥ 8 days. Nominal variables were dichotomized and consisted of: surgery type, resection degree, adjuvant treatment, previous cancer diagnosis, ≥ 1 complications, ASA and primary cancer. The paired Student´s t-test was used to assess changes over time and for comparisons between the study sample and a weighted age- and gender- matched reference population. Kazis effect size was used to quantify the size of change over time (115).

For **Study III**, we used the Wilcoxon Signed rank test for analysis of changes over time in continuous variables. The Mann-Whitney U-test was used to assess differences between surgical approach in RMS and in pain.

For comparison between groups in **Study IV**, we used the Mann–Whitney U-test for continuous variables; for nominal or ordered categorical variables we used the Mantel–Haenszel Chi-square test and for dichotomous variables we used the Fisher's exact test or Chi-squared test. For analysis of within-group changes over time we used the Wilcoxon signed rank test. To assess the influence of surgical approach on RMS and incidence of PPC, a univariate linear regression was used. A sensitivity analysis of isolated missing values at the two-week follow-up (n = 1 – 4 missing values) was performed to confirm the main results. The sensitivity analysis was based on the last-value-carried-forward approach. For efficacy reasons, we performed a supplementary per-protocol analysis that included participants from both the IG and the CG who were available for assessment two weeks after surgery. Furthermore, we only included participants from the IG who had ≥ 65% compliance with the IMT protocol.

Sample size calculations were performed for **Studies I - II** and **IV**. For **Study I**, a sample size of 30 patients in each group was necessary to detect a mean difference between groups of 20 ± 12 points in the SF-36 domain for physical functioning (109) and 78 patients were included to accommodate dropouts. For **Study II**, considering a sample of 78 participants, we could detect a moderate association of 0.34 points between SF-36´s PCS and 6MWT, adjusted for intervention and gender. For **Study IV**, 29 patients in each group were needed to detect a mean difference in MIP between groups of 15 ± 20 cmH$_2$O (116). We included 70 patients to compensate for a 15% dropout. Sample size calculations were made based on 80% power and 0.05 as significance level.

The study data was double-entered using Epidata software (http://www.epidata.dk/). The files were compared to ensure consistency and corrected if needed.

Results

Studies I – II

The IG and the CG were comparable at baseline (3 weeks postoperatively) for all outcome variables. Of the 78 patients initially included in the study, 67 (86%) completed assessments four months postoperatively and 58 (74%) after one-year (Figure 1). The most common reasons for withdrawal of consent were cancer recurrence (n = 6, 43%) and side-effects of chemotherapy (n = 2, 14%).

In **Study I** we found a minor improvement in lung function four months postoperatively, compared to baseline values. No significant differences between groups were found in lung function four months and one year postoperatively. In **Study II** we found that FVC increased significantly four months and one year postoperatively (0.37 l, p <0.00 and 0.43 l, p < 0.00 respectively), compared to baseline values. One year postoperatively, 37 patients had FEV_1/FVC < 0.70.

No significant differences between groups were found four months and one year after the surgery, respectively, in 6MWT (p = 0.57; p = 0.93) and dyspnoea (p = 0.93; p = 0.77) (**Study I**). In **Study II,** we found that 6MWT reached 97% of the expected values one year after surgery. Compared to baseline values, this increase was significant and of moderate effect size (p < 0.00, effect size (ES) 0.6).

Baseline values for SF-36 domains and summary scores for the IG and CG, together with changes from baseline at both follow-ups, are provided in Table 5. In **Study I** we found that patients in the IG had significant improvement in the SF-36 domain for bodily pain (p = 0.01) four months after the surgery, when compared to the CG. After one year, the CG had significant improvement in the domains of general health and vitality (mean difference 10.34 units, p = 0.01, and 8.48 units, p = 0.04), when compared to the IG. In **Study II** we found that the overall PCS and MCS were significantly improved one year after the surgery, compared to values three weeks after the surgery (PCS p < 0.00; MCS p < 0.00), reaching values comparable to the healthy reference population (Figure 6). This improvement was of large effect size (PCS ES 0.8; MCS ES 0.9). The 6MWT was positively associated with the SF-36 domain for role emotional after four months (β 0.06, p = 0.03) and with the physical functioning domain (β 0.06, p = 0.03) after one year.

Table 5: SF-36 values for the intervention and control groups 3 weeks, 4 months and 1 year postoperatively. Confidence intervals and differences between groups are reported in the manuscript

| | Intervention group | | | Control group | | | P-values for the difference between groups | |
	3 weeks n = 41	Change from baseline 4 months n = 32	1 year n = 27	3 weeks n = 37	Change from baseline 4 months n = 35	1 year n = 31	4 months	1 year
PF	60.4 ± 25	8.4 ± 21	4.8 ± 24	59.1 ± 23	6.4 ± 20	14.5 ± 20	0.3	0.28
RP	31.2 ± 29	28.1 ± 34	26.4 ± 42	36.7 ± 24	15.0 ± 27	34.9 ± 26	0.07	0.33
BP	45.8 ± 28	30.3 ± 29	28.4 ± 25	45.5 ± 24	15.3 ± 34	30.8 ± 34	0.01	0.49
GH	68.3 ± 21	31.2 ± 25	-2.8 ± 19	66.4 ± 19	1.1 ± 13	7.7 ± 15	0.49	0.01
VT	46.5 ± 18	-1.8 ± 19	12.0 ± 24	73.7 ± 30	14.1 ± 15	22.2 ± 15	0.23	0.04
SF	73.4 ± 27	13.3 ± 24	14.8 ± 28	53.6 ± 33	9.3 ± 32	19.4 ± 27	0.44	0.67
RE	56.9 ± 36	12.5 ± 43	21 ± 41	61.0 ± 17	20.7 ± 32	36.8 ± 35	0.75	0.61
MH	60.8 ± 18	9.0 ± 19	7.6 ± 13	31.2 ± 29	6.6 ± 19	14.8 ± 16	0.25	0.3
PCS	38.9 ± 10	6.7 ± 8.0	5.1 ± 11.1	39.0 ± 7	3.1 ± 9.2	7.7 ± 8.5	0.06	0.46
MCS	45.6 ± 10	4.4 ± 10.4	5.3 ± 8.7	44.9 ± 9	5.4 ± 9.4	9.6 ± 9	0.99	0.27

Abbreviations: PF, physical performance; RP, role of physical limitations; BP, bodily pain; GH, general heath; VT, vitality; SF, social functioning; RE, role emotional problems; MH, mental health; PCS, physical component summary; MCS, mental component summary
Statistics: generalized estimating equations linear regression model adjusted for baseline values, time interaction and gender
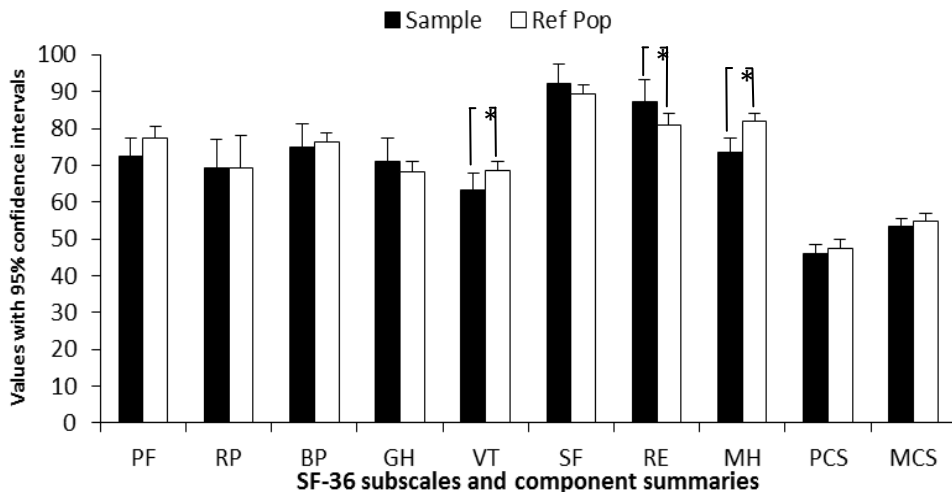
* Significant difference between groups, p < 0.05, based on a weighted mean calculation

Figure 6: SF-36 subscales and component summaries. Comparison between values for the study population and a gender and age-matched reference healthy population at one year.
Abbreviations: PF, physical performance; RP, role of physical limitations; BP, bodily pain; GH, general heath; VT, vitality; SF, social functioning; RE, role emotional problems; MH, mental health; PCS, physical summary component; MCS, mental summary component.

The occurrence of pneumonia was 16.6% (n = 13); pleural drainage ≥ 7 days was required in 1 patient while another needed ventilator assistance due to respiratory failure (**Study II**).

Compliance with the intervention (Study I)
The number of supervised exercise training sessions in the 32 patients (IG) who completed the assessment at four months was: 10 sessions (n = 17), 8 - 9 sessions (n = 13) and 6 - 7 sessions (n = 2); five patients finished the 10 supervised sessions after the four-month assessments, due to side effects of chemotherapy. Home exercising at least twice weekly, registered in the training diary, was performed by the IG (n = 14) and the CG (n = 5) respectively, while a further 10 patients in the CG reported that they joined regular exercise training at community level. From all the patients enrolled in the study, 34 accepted the invitation for individual counselling sessions with a nurse. The number of conducted sessions per patient ranged from one (n = 16) to nine (n = 1).

Study III

Of the 81 patients enrolled in the study, 65 were available for assessments six months after the surgery. The most common reason for dropout was non-malignancy (n = 8). $FEV_1/FVC < 0.70$ was present preoperatively in 55% of the patients.

Lung function was significantly reduced two weeks and six months after surgery (mean drop in FEV_1 respectively 19% and 9%, p < 0.001), compared to preoperative values. Six months postoperatively $FEV_1/FVC < 0.70$ was present in 62% of the patients.

Compared to baseline values, 6MWT was reduced by 7% two weeks postoperatively (mean decrease 37 ± 75m, $p < 0.001$). SpO_2 after the 6MWT decreased significantly at both follow-up times (baseline 95 ± 4%, 2 weeks 92± 5%, 6 months 93 ± 4%, $p < 0.001$), followed by a significant increase in dyspnoea and exertion (both ~1 unit, $p < 0.001$).

MIP and MEP were not reduced two weeks after the surgery, when compared to the preoperative values (Table 6). MIP increased significantly by 9% at the six-month follow-up ($p < 0.001$), while MEP remained unchanged.

Table 6: Respiratory muscle strength (mean ± SD and median [min;max]).

	Bef. surgery	Postoperatively		p-value for the difference	
		2 weeks n = 81	6 mths n= 65	Bef-2 wks	Bef-6 mths
MIP, cmH$_2$0	84 ± 30 86[23;152]	83 ± 33 78[18;181]	94 ± 31 86[23;152]	0.97	< 0.001
MIP % pre	104 ± 30 106[40;165]		114 ± 31 117[32;196]		
MEP,cmH$_2$0	103 ± 33 101[37;152]	99±34 95[36;203]	108 ± 37 108[37;247]	0.22	0.14
MEP % pre	106 ± 30 103[49;168]		109 ± 30 103[46;207]		

MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure

The surgical approach did not result in differences in MIP or MEP (Figure 7), NRS pain rating at rest or NRS pain while performing a voluntary cough throughout the follow-up period.

Figure 7: Box plots illustrating MIP values before surgery, and two weeks and six months postoperatively, stratified by the surgical approach.
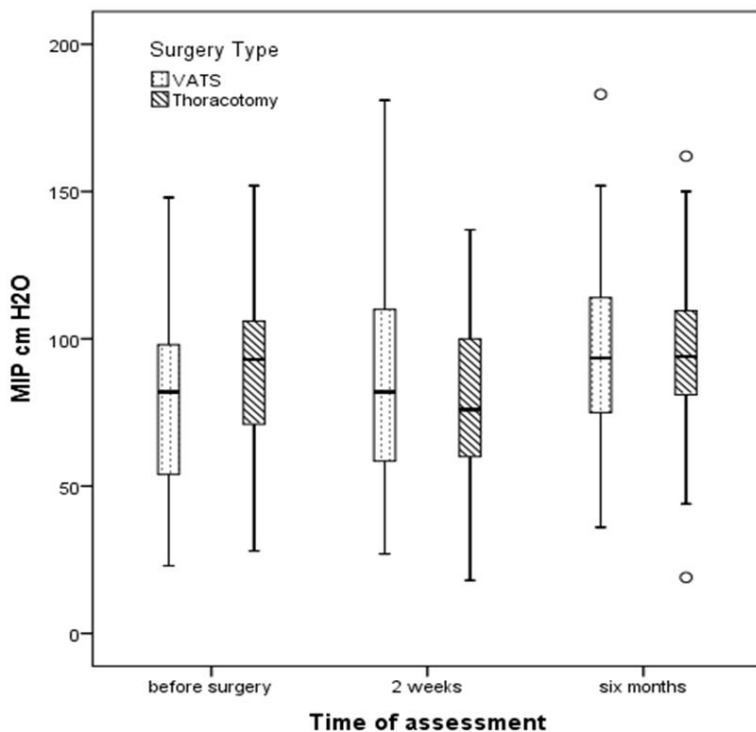
The median NRS pain at rest, while coughing and during MIP measurements was 0 - 1 (Table 7). NRS pain $\geq$ 5 during MIP measurements was reported by 6% of patients two weeks postoperatively and by 3% of patients at the six-month follow-up. These patients had similar values of MIP throughout the follow-up period.

Table 7: Numeric rank score for pain (median [min;max]).

	2 weeks postoperatively n= 81	6 months n = 65
At rest	0 [0;5]	0 [0;6]
Voluntary cough	1 [0;8]	1 [0;6]
MIP measurement	0 [0;8]	0 [0;6]

MIP, maximal inspiratory pressure

Study IV

A total of 70 patients were randomized in **Study IV**; two patients were subsequently excluded (one (IG) declined immediately after the randomization and another (CG) had a cardiac arrest and died two days after the surgery). Thus, the study sample consisted of 68 patients (IG n = 34; CG n = 34). Both groups were comparable in terms of demographic and surgical characteristics and baseline outcome variables. One patient (IG) was re-operated on in the first postoperative day due to major air-leak, while another patient (CG) needed prolonged ventilator assistance due to respiratory failure. Two patients from the CG needed replacement of the pleural drain because of persistent air leak. Pleural drainage > 7 days was necessary in five patients (IG n = 3, CG n = 2). Three patients (IG n = 2, CG n = 1) were readmitted before the two-week follow-up due to pleural effusion.

No significant differences between the IG and CG were found five days or two weeks after surgery regarding RMS, lung function, 6MWT, dyspnoea, or SpO_2 at the 6MWT. MIP was significantly reduced in both groups at postoperative day five (~15%, $p < 0.001$), but had recovered two weeks postoperatively. FEV_1 and FVC dropped by ~30% in both groups by the fifth postoperative day ($p < 0.001$). Compared to preoperative values, FEV_1 was reduced two weeks postoperatively by 15% and 23% for the IG and CG, respectively ($p = 0.11$).

We found no association between surgical procedure and RMS or with incidence of PPC two weeks after surgery.

The overall incidence of pneumonia was 13% (9/68, IG n = 2, CG n = 7) and that of clinically relevant atelectasis 18% (22/68, IG n = 3, CG n = 9). Both were non-significant ($p = 0.14$ and $p = 0.11$). The incidence of hypoxemia in the IG was significantly lower (15%, 5/34) than in the CG (35%, 12/34) ($p = 0.049$). Three days postoperatively, SpO_2 was 94% ± 3 in the IG and 92% ± 4 in the CG ($p = 0.058$) and by the fourth postoperative day, 93.5% ± 3 in the IG and 91% ± 4 in the CG ($p = 0.02$) (Figure 8).

Compliance with the intervention

The IMT duration during hospital stay varied between 20 and 25 minutes per session. The training load during hospital stay varied from 15% to 41% of the preoperative MIP value. After discharge, the training load varied from 17% to 43% of the MIP value measured at the fifth postoper-

ative day. The compliance with the IMT protocol during hospital stay was as follows: 16 patients had 100% compliance, 13 patients ≥ 80%, and five patients < 80%. After hospital discharge, 17 patients had 100% compliance, 11 patients ≥ 65% and four < 65%.

Safety considerations
There were no statistically significant differences between groups in the incidence of pneumothorax (IG 53% vs. CG 35%, p = 0.14) or pleural drainage time (median [min;max] IG 45 [11;360] vs. CG 27 [8;271], p = 0.31). IMT was discontinued for 24 hours in three cases and resumed the following day, as no difference in air leak was registered in the Thopaz drain while IMT was withheld. One patient in the IG was readmitted 10 days after discharge and reoperated on due to a rupture of the intercostal suture. No adverse events occurred during the IMT sessions or assessments.
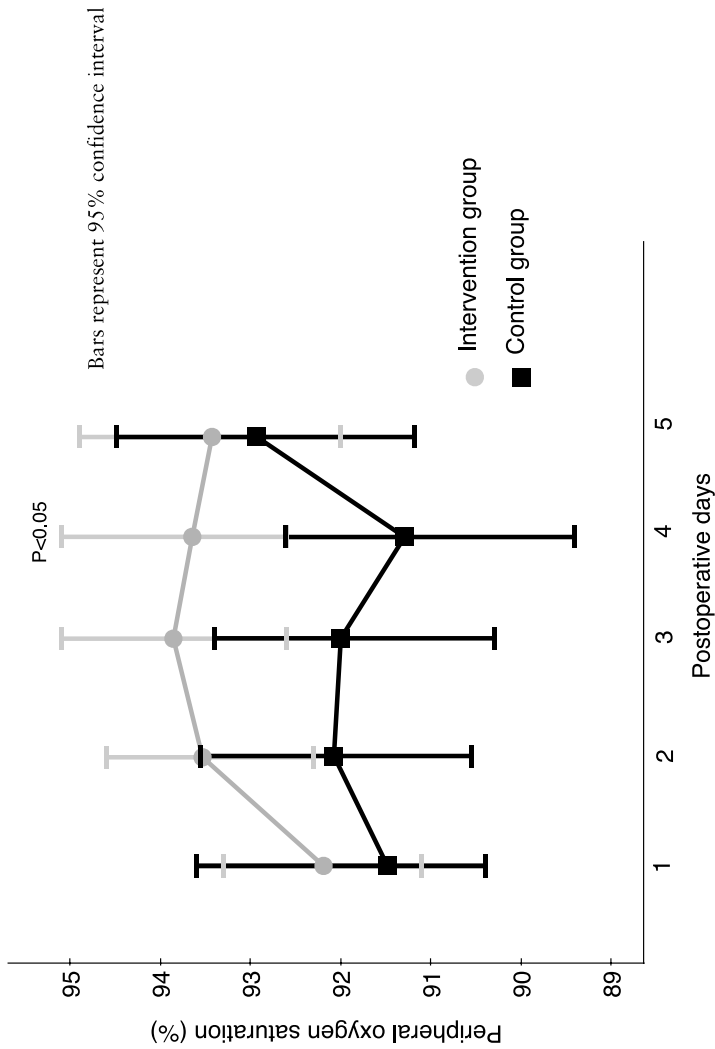
Figure 8: Peripheral oxygen saturation postoperative days 1 - 5 in both groups.
Daily number of cases for each group: Day 1 (IG n=34; CG n=33); day 2 (IG n=34; CG n=33); day 3 (IG n=31; CG n=30); day 4 (IG n=25; CG n=24); day 5 (IG n=19; CG n=20).

Discussion

In patients radically operated on for lung cancer, supervised exercise training in addition to non-supervised training did not result in significant differences in HRQoL four months after the surgery, except for the SF-36 bodily pain domain. There were no significant effects of supervised training one year after the surgery (**Study I**). Health-related quality of life in the whole study sample was similar to a healthy reference population one year after surgery. Physical performance (6MWT) was positively associated with the SF-36 domain for physical functioning (**Study II**).

In **Study III** we found that respiratory muscle strength in patients following pulmonary resection on suspicion of or confirmed lung cancer was not affected two weeks and six months following surgery, regardless of the surgical approach. In **Study IV** we found that two weeks of postoperative inspiratory muscle training, in addition to breathing exercises and early mobilisation, did not increase maximal inspiratory pressure, but significantly reduced hypoxemia in patients at high risk of developing postoperative pulmonary complications.

Effect of exercise training on health-related quality of life

Ten sessions of physiotherapy-supervised exercise training, in addition to non-supervised training, had no effect on HRQoL four months after the surgery, except for the SF-36 bodily pain domain. One year after the surgery, patients performing home exercising alone improved SF-36 domains for general health and vitality, compared to the group who received additional supervised exercise.

The low frequency, once weekly, of supervised exercise sessions might be an explanation for the lack of additional benefit. Both IG and CG performed home-exercising and 44% of the patients in the CG reported on home exercising. This may have contributed to the small differences between groups in effect of HRQoL. Secondarily, personal preferences as to when and where to exercise may explain why non-supervised training also was effective in improving HRQoL in the GC.

We chose to use the generic SF-36 for assessment of HRQoL because this questionnaire is sensitive to detect changes in physical function domains of HRQoL (111). Only one study, performed by Edvardsen et al. (117) has reported a significant increase in SF-36´s PCS in favour of exercise training, while three other studies have found no differences between groups (90,92,118). Like in our study, the SF-36 was used by (117-119),

while the disease-specific tool (EORTC- LC13, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer supplement) was used in the study performed by Arbane et al. (90). The study performed by Edvardsen et al. (117) was based on three weekly sessions with high-intensity training for a period of 20 weeks. Their study most likely provided with the optimal setting of exercise delivery, since the study was community-based and exercise training sessions were performed at fitness centres near patients´ homes. This setting may increase adherence and compliance to training by reducing travel time and should be considered in the implementation of exercise-based training programmes following lung cancer surgery.

In **Study II** we found that the whole study population showed improvement in SF-36 PCS and MCS of large effect size one year after the surgery, compared to values three weeks postoperatively. Values were comparable to those of the healthy reference population. Our findings are contradictory to reports on persisting impairments in physical functioning domains in lung cancer survivors (61) or compared to the healthy population (22). Our positive results can be used in the clinical setting to inform patients on expected outcomes after surgery.

Effect of exercise training on physical performance and lung function

In **Study I** we found that one weekly session of supervised, group-based exercise training for a period of 10 weeks, in addition to unsupervised home-based exercising, did not result in significant differences in 6MWT or spirometry four months or one year postoperatively, compared to patients performing unsupervised home-based exercise training.

To our knowledge, five randomised controlled trials investigating the effects of exercise interventions after lung cancer surgery were published between 2011 and 2014 (90-92,117,118). The active interventions varied: walking programme initiated during hospital stay (90,91,118); an individually tailored 4-week walking programme verified by an activity monitor (118); supervised out-patient endurance and strength training twice weekly for 12 weeks (91,92) and three weekly supervised sessions lasting for 20 weeks (117). The target intensity for the supervised programmes varied from moderate, rated 4 on the modified Borg scale (91) to 60 - 80% of peak cycling load (92), or high intensity (80 - 95% of the maximum heart rate) (117).

It was only in the studies providing at least two weekly supervised training sessions that an effect favouring the IG was found, either in physical performance (91,92) or in cardiorespiratory fitness (117). In our study, the supervised training sessions were individually tailored at 60 - 80% of the exercise capacity. Since they were provided only once a week, they may have been insufficient to promote larger benefits in physical performance. Given that the patients in the CG also received advice on home exercising, this has likely contributed to the small difference in 6MWT found between groups. It is worth noting that both the IG and the CG improved 6MWT four months postoperatively beyond 54 m, which is the minimal important difference for the 6MWT in chronic lung disease patients (120).

The choice of one weekly supervised exercise sessions was made to enhance adherence to the programme because of geographical issues. Another concern was that patients receiving chemotherapy might suffer from side effects to such a degree that they would not join the program and thus lowering compliance. Edvardsen et al. (117) reported similar compliance issues in patients receiving chemotherapy.

In the study performed by Stigt et al. (92), a deterioration in the 6MWT was found in the control group one year post-surgery, which is in line with reports from cohort-based studies targeting patients ½ year – two years after lung cancer surgery (61,87,121). In **Study II** we have shown that patients improved 6MWT four months postoperatively as compared to baseline values three weeks postoperatively, and that this improvement was sustained after one year, without an increase in exertional dyspnoea. This may confirm the effect of advice on home exercising in motivating patients towards a more active lifestyle in order to prevent detriments in cardiorespiratory function and HRQoL. This is supported by Philip el al. (122), who showed that the majority of early-stage lung cancer survivors reported a desire for physical activity advice and a willingness to engage in physical activity.

Postoperative respiratory muscle strength

In **Study IV** we found that MIP and MEP were significantly reduced by ~15% five days after the surgery, returning to preoperative values two weeks postoperatively. Results from **Study III** confirmed that RMS returned to preoperative values two weeks postoperatively. Our findings do not support reports on persistent decrease in RMS over time: 50% of preoperative values one week postoperatively (31,32) and 27% four weeks postoperatively (5). Impaired RMS twelve weeks postoperatively has also

been reported (9). Conversely, one study found that both MIP and MEP were recovered 10 - 15 days following thoracotomy, but 50% of the patients had not undergone any lung tissue resection (123). The resection of lung tissue has been proposed to contribute to respiratory muscle dysfunction by decreasing lung compliance (124), although that has not objectively been measured.

In **Study III** we found that thoracotomy, compared to VATS did not result in differences in MIP or MEP two weeks or six months after the surgery. This was supported by **Study IV,** since no association was found between decreased MIP and more extensive surgical approach i.e. thoracotomy. These finding are contradictory to previous reports on a faster recovery of RMS following VATS, compared to thoracotomy (31,32). The possible explanations are firstly that the muscle-sparing surgical technique performed in our study does not affect RMS, compared to a posterolateral approach without muscle preservation (32). Secondly, studies reporting impaired RMS in the early postoperative period did not address the influence of incisional pain during assessments. This is important, because pain may negatively affect the RMS measurements. Our data (**Study III**) did not indicate that pain had a negative influence on RMS, since the postoperative level of pain in the chest during MIP assessment or in a voluntary cough manoeuvre was low (medians of 0 and 1, respectively). Finally, standardised clinical pathways of postoperative care that include optimal pain relief and early mobilisation are likely to have induced recovery of pulmonary function.

The decrease in RMS by the fifth postoperative day suggests a transient respiratory muscle dysfunction, alongside restrictive impairment in pulmonary function (**Study IV**). This may be of importance in the presence of comorbid conditions. Respiratory muscle weakness in COPD patients has been defined as MIP < 60 cm H_2O (2). However, a definition of respiratory muscle weakness in the surgical context is lacking. Likewise, the clinical relevant treatment effect of improved MIP in connection with lung cancer surgery has not been established. The large standard deviation in all MIP and MEP measurements (**Study III**) suggests that impaired RMS might be present in a subgroup of patients. More research is needed to investigate patients at risk of decline in RMS as well as its correlates.

Effect of inspiratory muscle training on postoperative outcome

Two weeks of postoperative IMT, in addition to breathing exercises and early mobilisation, did not result in improved respiratory muscle strength

in high-risk patients following pulmonary resection on suspicion of- or confirmed lung cancer, when compared to the effects of breathing exercises and early mobilisation alone.

Our hypothesis was that RMS would be impaired five days and two weeks after the surgery and that postoperative IMT would reverse the negative impact of surgery on RMS. However, we found no detriments in RMS beyond the fifth postoperative day. According to the sample size calculation, a difference between groups in MIP of 15 cmH$_2$O was needed to detect an effect of the intervention. After two weeks the actual difference was of only 4.5 cmH$_2$O in favour of the IG. We are aware that more than two weeks of training is necessary to increase muscle strength (86) and that the short intervention is a limitation in **Study IV**. However, 10 days of IMT in connection with cardiac surgery (five preoperatively and five postoperatively) can increase RMS in the IG by 13 cmH$_2$O, evaluated five days after the surgery. At the same time, a 36 cmH$_2$O decrease in MIP was detected in the CG not performing IMT (125). The difference between groups in MIP in the above mentionedstudy was far larger than the 15 cmH$_2$O that our study was based on.

It is possible that a higher training load e.g. > 30% of MIP (8), might have induced a larger increase in RMS in the IG. Conversely, higher levels of inspiratory resistance could induce over distension of the lung at the end-inspiration, increasing the risk of air leak in emphysematous of fibrotic lung (26). The training intensity used in **Study IV** varied between 15 – 43% of MIP. This level was shown to be feasible, and the incidence of pneumothorax two weeks postoperative was not significantly different between the groups.

Hypoxemia, defined as peripheral oxygen saturation below 90% on room air on two consecutive days, was a secondary outcome in **Study IV**. The incidence of hypoxemia was significantly lower (by 20%) in the IG. This suggests that IMT can increase oxygenation and possibly prevent PPC in high-risk patients, when applied in the early postoperative period. Applying an inspiratory resistance is likely to facilitate lung re-expansion, consequently helping to maintain patency of the smaller airways (27,28). A higher inspiratory volume enables preferential distribution of air to the dependent lung regions (27,28), which in turn helps generate forceful expiratory manoeuvers for secretion clearance (25). Lung re-expansion aids secretion clearance via enhanced expiratory flow (80), thereby improving the cough ability but unfortunately, we did not measure that.

The occurence of both pneumonia and atelectasis in the IG was less than one-third of that of the CG. Although this difference was non-significant, it may be of clinical relevance. To date, there has been a lack of evidence on the added value of routine postoperative breathing exercises in the prevention of PPC following lung cancer surgery (76). More research is needed to evaluate the value of postoperative IMT in the prevention of PPC in patients at high risk of PPC.

Postoperative physical performance

The ability to walk is a precursor to engagement in physical activity. Seventy per cent of patients operated on for lung cancer do not engage in sufficient physical activity during the early period after hospital discharge (126), which may increase physical deconditioning and delay recovery. In **Study IV** we found a pronounced decrease in 6MWT to 76% of preoperative values by the fifth postoperative day, with a partial recovery, to 93% of preoperative values, two weeks after the surgery. This can be attributed to the negative impact of surgery on physical function, such as pain and fatigue, especially in the early postoperative period. Similar results have been reported five days (90,118,127) and two weeks postoperatively (91,127).

The overall decrease in 6MWT two weeks after the surgery was small and results from Studies **II** and **IV** showed that patients reached normal predicted values for 6MWT by 6 - 12 months. In **Study II** we also found that the 6MWT was associated with the SF-36 domains of role emotional four months postoperatively and with the physical functioning domain after one year (**Study II**). This information is useful when counselling patients on expected outcomes following surgery, since fear of physical debility may influence their decisions about surgery (128).

In spite of the relatively small drop in 6MWT two weeks postoperatively (**Study IV**), patients still had impaired peripheral oxygen saturation (SpO_2 of 92%), followed by an increase in dyspnoea and exertion (~1 unit). Similarly, while 6MWT had recovered six months postoperatively, SpO_2 did not return to preoperative values. A combination of ventilatory and gas exchange limitations is the likely explanation: the lung resection itself reduces pulmonary function (22); a restrictive as well as an obstructive airflow limitation results in breathing at lower tidal volumes (127), which in turn increases the work of breathing, resulting in a higher dyspnoea rating (10). This mechanism may in particular influence postoperative physical performance in patients with most impaired postoperative

lung function (e.g. bilobectomy or pneumonectomy) (21,22,53,54) as well as in COPD (22,55). These populations could be target of future research investigating the relationship between 6MWT, dyspnea and respiratory muscle strength.

Methodological considerations

Participants
The samples in **Studies I - III** were comparable to the Danish population undergoing lung cancer surgery regarding age and gender (14), and to similar studies investigating long-term outcomes following lung cancer surgery (121,129). Conversely, the sample in **Studies I - II** had a lower comorbidity rate compared to **Study III** (14). Considering the low accrual rate in **Studies I – II,** we cannot exclude the risk of selection bias. Results from both studies should primarily be generalised to patients who are motivated in being physical active and who have few coexisting comorbidities. None of the studies was designed to perform subgroup analyses and the sample size did not allow for further adjustments. Additional research is required to study specific patient groups.

The cohort for **Studies I - II** was enrolled three weeks after the surgery and we have no preoperative outcome data, since those were not routinely assessed in our unit prior to the surgery. This makes difficult to evaluate the degree of recovery from surgery up to three weeks postoperatively. However, Arbane et al. (118) assessed a similar population before and four weeks after the surgery and found that most participants recovered their preoperative walked distance and HRQoL.

There is no consensus in the literature regarding the definition of high-risk patients referred for lung cancer patients (**Study IV**). The single criterion used in this thesis was based on reports from different studies (age $\geq$ 70 years (31,93), $FEV_1 \leq$ 70% predicted (94,95), $D_{LCO} \leq$ 70% predicted (1,93) or planned pneumonectomy (96). Meanwhile, a combination of different risk factors or lower cut-off values for FEV_1 % and D_{LCO}% could be more sensitive to characterize high-risk patients.

Outcome measurements
The reference values used for lung function were those developed by Quantjer (101) and take in consideration gender, age and height. These values are well established and used in clinical practice (100).

Respiratory muscle strength is indirectly measured through the pressure generated at the mouth and depends on high degree of patient cooperation. Test/retest reliability is adequate, with an intraclass correlation coefficient > 0.80 in the sitting position in healthy subjects (130). The normal range in healthy subjects is very large and since the measurement is effort-dependent, number of attempts, learning effects, and degree of fatigue are important to consider (130). The measurement can also be influenced by the patients' capability to breathe in and out. Measurement of MEP is performed at total lung capacity and this may be difficult to achieve for the postoperative surgical patient. Conversely, maximal inspiration to a level close to residual volume is required for measurement of MIP. In **Study IV** we found that the lung function measured by spirometry was significantly decreased at the fifth postoperative day. As a consequence, the decrease in lung volumes at that specific time-point may have negatively influenced the possibility to perform the proper respiratory muscle function test. The median amount of attempts for assessment of MIP and MEP (**Studies III - IV**) was in accordance with the guidelines (107). We used age and gender reference values derived from a combination of several studies, as reported by Evans et al. (35). This is important, considering that MIP decreases nonlinearly when age exceeds 60 years and males exceed female MIP by 34 - 66% (35).

The 6MWT was chosen to assess physical performance, and is a self-paced test of walking capacity. The test has a good construct and criterion validity in individuals with chronic diseases, with correlation coefficients 0.4- 0.93 to maximal exercise performance and physical activity (102). Reference values are established using a 30 meter course (104). We used a 20 meter course, since a longer one was not available. The implication is that the calculation of the reference values in our study population may be underestimated (131). For **Studies III – IV,** we measured SpO_2, dyspnoea on a Borg 0 -10 scale, and perceived exertion on a modified Borg 0 - 10 scale, according with the guidelines for the 6MWT (102,103). For **Studies I – II** we only measured dyspnoea after the 6MWT and used the Borg 6 - 20 scale (102). Since the Borg 6 - 20 scale does not have the ratio properties of the 0 - 10 scale, we could not compare dyspnoea levels across the studies populations.

For definition of postoperative pulmonary complications (**Study IV**), we adapted criteria from Kroenke at al. (113) and Hulzebos el al. (114). Our initial intention was to categorise the type of PPC according to their sever-

ity: minor = grade 1, severe = grade 3. Meanwhile, the operationalisation of minor PPC (grade 1) also included criteria requiring additional clinical intervention (eg. clinically relevant atelectasis), thus not a minor PPC. Conversely, pneumothorax was a grade 2 complication, with an incidence two weeks postoperatively of 44%. Out of those, only two patients had abnormal radiological findings that required invasive treatment. Therefore, we report the incidence of each PPC variable, without grouping them according to their clinical severity.

The measurement of SpO_2 (**Study IV**) is part of the standard patient observation procedure in our unit to improve detection of hypoxemia in the early postoperative period. Whereas SpO_2 cannot substitute arterial blood gas analyses, its accuracy in the 70 - 100% saturation range is within ± 2 - 3 units from the results obtained from the blood gas analyses (132).

We chose to use the generic SF-36 to evaluate HRQoL (**Studies I - II**) because this questionnaire is widely used in clinical research and provides norm-based reference values (109), thus allowing for cross-studies comparisons. Furthermore, since the SF-36 covers many aspects of physical functioning, the questionnaire is sensitive to detect changes in physical function domains (111). This aspect was relevant in **Study II,** where we investigated associations with the 6MWT. The use of a cancer-specific questionnaire such as the EORTC-QLQ30-LC13 (133) might though have disclosed disease-specific symptoms and cancer relevant effects of supervised exercise training beyond the dimensions contained in the SF-36. This is another limitation to the study.

Clinical implications

As life expectancy following lung cancer surgery increases, patient-centered outcomes such as health-related quality of life become important, since they reflect patients ability to return to usual daily living activities after end treatment. The findings of this thesis suggest that both supervised and non-supervised physiotherapy-based counselling regarding home exercising may be considered to improve physical performance and health-related quality of life in patients following lung cancer surgery. Lung function and physical performance improve over time. One year after the surgery, patient´s health-related quality of life reach values comparable to those from healthy population. These findings are important in the clinical setting and can be used to inform patients on expected outcomes following surgery.

Our findings also show that respiratory muscle strength is not affected after the second postoperative week and that muscle-sparring thoracotomy does not deteriorate respiratory muscle strength, compared to video-assisted thoracic surgery. Furthermore, two weeks of postoperative inspiratory muscle training may enhance oxygenation in the early postoperative period and should be considered by physiotherapists as a choice of treatment in patients presenting postoperative hypoxemia. Respiratory muscle strength is not commonly assessed in this population, and thus the role and impact of respiratory muscle dysfunction in the postoperative morbidity and recovery of physical function after pulmonary resection is not fully understood. This could be the target of future research.

Conclusions

The main findings and conclusions of the present thesis can be summarized as following:

Study I: Supervised compared to non-supervised exercise training did not result in differences between groups in SF-36 health-related quality of life, except for the domain for bodily pain. No effects of supervised training were found for any outcome one year after the surgery.

Study II: Compared to values three weeks postoperatively, individuals who were radically operated for lung cancer improved health-related quality of life one year after the surgery, reaching values similar to a healthy reference population. Lung function and physical performance improved over time. The six-minute walked distance was positively associated with health-related quality of life, SF-36 domain for physical functioning.

Study III: Surgery for pulmonary resection on suspicion of or confirmed lung cancer did not alter respiratory muscle strength two weeks or six months postoperatively, regardless of the surgical approach. Physical performance was recovered, while lung volumes remained significantly impaired six months postoperatively.

Study IV: Two weeks of additional postoperative inspiratory muscle training, compared to standard physiotherapy alone, did not increase respiratory muscle strength but improved oxygenation in high-risk patients following lung cancer surgery. Respiratory muscle strength was recovered in both groups two weeks postoperatively.

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References

(1) Amar D, Munoz D, Shi W, Zhang H, Thaler HT. A clinical prediction rule for pulmonary complications after thoracic surgery for primary lung cancer. Anesth Analg 2010 05/01;110(1526-7598; 0003-2999; 5):1343-1348.

(2) Agostini P, Naidu B, Cieslik H, Rathinam S, Bishay E, Kalkat MS, et al. Comparison of recognition tools for postoperative pulmonary complications following thoracotomy. Physiotherapy 2011 12;97(1873-1465; 0031-9406; 4):278-283.

(3) Schulte T, Schniewind B, Dohrmann P, Kuchler T, Kurdow R. The extent of lung parenchyma resection significantly impacts long-term quality of life in patients with non-small cell lung cancer. Chest 2009 Feb;135(2):322-329.

(4) Voll-Aanerud M, Eagan TM, Plana E, Omenaas ER, Bakke PS, Svanes C, et al. Respiratory symptoms in adults are related to impaired Quality of Life, regardless of asthma and COPD. Results from the European Community Respiratory Health Survey. Health Qual Life Outcomes 2010 09/27;8(1477-7525; 1477-7525; 1):107.

(5) Nomori H, Kobayashi R, Fuyuno G, Morinaga S, Yashima H. Preoperative respiratory muscle training. Assessment in thoracic surgery patients with special reference to postoperative pulmonary complications. Chest 1994 06;105(0012-3692; 0012-3692; 6):1782-1788.

(6) Siafakas NM, Mitrouska I, Bouros D, Georgopoulos D. Surgery and the respiratory muscles. Thorax 1999 May;54(5):458-465.

(7) Welvaart WN, Paul MA, Stienen GJ, van Hees HW, Loer SA, Bouwman R, et al. Selective diaphragm muscle weakness after contractile inactivity during thoracic surgery. Ann Surg 2011 12;254(1528-1140; 0003-4932; 6):1044-1049.

(8) Mans CM, Reeve JC, Elkins MR. Postoperative outcomes following preoperative inspiratory muscle training in patients undergoing cardiothoracic or upper abdominal surgery: a systematic review and meta analysis. Clin Rehabil 2014 Aug 26.

(9) Weiner P, Man A, Weiner M, Rabner M, Waizman J, Magadle R, et al. The effect of incentive spirometry and inspiratory muscle training on pulmonary function after lung resection. J Thorac Cardiovasc Surg 1997 03;113(0022-5223; 0022-5223; 3):552-557.

(10) Spruit MA, Singh SJ, Garvey C, Zuwallack R, Nici L, Rochester C, et al. An official american thoracic society/european respiratory society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med 2013 Oct 15;188(8):e13-64.

(11) Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, et al. American College of Sports Medicine

roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc 2010 Jul;42(7):1409-1426.

(12) Cavalheri V, Tahirah F, Nonoyama M, Jenkins S, Hill K. Exercise training undertaken by people within 12 months of lung resection for non-small cell lung cancer. Cochrane Database Syst Rev 2013 Jul 31;7:CD009955.

(13) Engholm G, Ferlay J, Christensen N, Kejs A, Johannesen T, Khan S, et al. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 7.1 (09.07.2015). Association of the Nordic Cancer Registries. Danish Cancer Society. Available from http://www.ancr.nu, accessed on 11/september/2015.

(14) The Danish Lung Cancer Register http://www.lungecancer.dk/00037/. Acessed April, 15 2013.

(15) Kuritzky AM, Aswad BI, Jones RN, Ng T. Lobectomy by Video-Assisted Thoracic Surgery vs Muscle-Sparing Thoracotomy for Stage I Lung Cancer: A Critical Evaluation of Short- and Long-Term Outcomes. J Am Coll Surg 2015 Jan 21.

(16) Chen FF, Zhang D, Wang YL, Xiong B. Video-assisted thoracoscopic surgery lobectomy versus open lobectomy in patients with clinical stage non-small cell lung cancer: a meta-analysis. Eur J Surg Oncol 2013 Sep;39(9):957-963.

(17) Danish Lung Cancer Group. Report 2013. http://www.lungecancer.dk

(18) Loganathan RS, Stover DE, Shi W, Venkatraman E. Prevalence of COPD in women compared to men around the time of diagnosis of primary lung cancer. Chest 2006 05;129(0012-3692; 0012-3692; 5):1305-1312.

(19) Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013 May;143(5 Suppl):e166S-90S.

(20) Varela G, Ballesteros E, Jimenez MF, Novoa N, Aranda JL. Cost-effectiveness analysis of prophylactic respiratory physiotherapy in pulmonary lobectomy. Eur J Cardiothorac Surg 2006 02;29(1010-7940; 1010-7940; 2):216-220.

(21) Bolliger CT, Jordan P, Soler M, Stulz P, Tamm M, Wyser C, et al. Pulmonary function and exercise capacity after lung resection. Eur Respir J 1996 03;9(0903-1936; 0903-1936; 3):415-421.

(22) Brunelli A, Socci L, Refai M, Salati M, Xiume F, Sabbatini A. Quality of life before and after major lung resection for lung cancer: a prospective follow-up analysis. Ann Thorac Surg 2007 Aug;84(2):410-416.

(23) Cukic V. Reduction of pulmonary function after surgical lung resections of different volume. Med Arch 2014 Aug;68(4):231-235.

(24) Smetana GW. Postoperative pulmonary complications: an update on risk assessment and reduction. Cleve Clin J Med 2009 Nov;76 Suppl 4:S60-5.

(25) Siafakas NM, Mitrouska I, Argiana E, Bouros D. Effects of surgery on the function of the respiratory muscles. Monaldi Arch Chest Dis 1999 12;54(1122-0643; 1122-0643; 6):526-531.

(26) Miserocchi G, Beretta E, Rivolta I. Respiratory mechanics and fluid dynamics after lung resection surgery. Thorac Surg Clin 2010 08;20(1547-4127; 3):345-357.

(27) Tusman G, Bohm SH, Warner DO, Sprung J. Atelectasis and perioperative pulmonary complications in high-risk patients. Curr Opin Anaesthesiol 2012 Feb;25(1):1-10.

(28) Lumb A. Nunn´s applied respiratory physiology. 5th ed. Oxford: Butterworth-Heinemann; 2000.

(29) Massard G, Wihlm JM. Postoperative atelectasis. Chest Surg Clin N Am 1998 Aug;8(3):503-28, viii.

(30) Flaminiano LE, Celli BR. Respiratory muscle testing. Clin Chest Med 2001 Dec;22(4):661-677.

(31) Nomori H, Horio H, Fuyuno G, Kobayashi R, Yashima H. Respiratory muscle strength after lung resection with special reference to age and procedures of thoracotomy. Eur J Cardiothorac Surg 1996;10(1010-7940; 1010-7940; 5):352-358.

(32) Bernard A, Brondel L, Arnal E, Favre JP. Evaluation of respiratory muscle strength by randomized controlled trial comparing thoracoscopy, transaxillary thoracotomy, and posterolateral thoracotomy for lung biopsy. Eur J Cardiothorac Surg 2006 04;29(1010-7940; 1010-7940; 4):596-600.

(33) Hsia CC, Peshock RM, Estrera AS, Mcintire DD, Ramanathan M. Respiratory muscle limitation in patients after pneumonectomy. Am Rev Respir Dis 1993 03;147(0003-0805; 0003-0805; 3):744-752.

(34) Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med 1995 Dec;152(6 Pt 1):2021-2031.

(35) Evans JA, Whitelaw WA. The assessment of maximal respiratory mouth pressures in adults. Respir Care 2009 Oct;54(10):1348-1359.

(36) Gosselink R, Troosters T, Decramer M. Distribution of muscle weakness in patients with stable chronic obstructive pulmonary disease. J Cardiopulm Rehabil 2000 Nov-Dec;20(6):353-360.

(37) Gosselink R, De VJ, van den Heuvel SP, Segers J, Decramer M, Kwakkel G. Impact of inspiratory muscle training in patients with COPD: what is the evidence? Eur Respir J 2011 02;37(1399-3003; 0903-1936; 2):416-425.

(38) Ploeg AJ, Kappetein AP, van Tongeren RB, Pahlplatz PV, Kastelein GW, Breslau PJ. Factors associated with perioperative complications and long-term results after pulmonary resection for primary carcinoma of the lung. Eur J Cardiothorac Surg 2003 Jan;23(1):26-29.

(39) Warner DO. Preventing postoperative pulmonary complications: the role of the anesthesiologist. Anesthesiology 2000 May;92(5):1467-1472.

(40) Garcia-Miguel FJ, Serrano-Aguilar PG, Lopez-Bastida J. Preoperative assessment. Lancet 2003 Nov 22;362(9397):1749-1757.

(41) Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy--video-assisted thoracic surgery versus muscle-sparing thoracotomy. A randomized trial. J Thorac Cardiovasc Surg 1995 May;109(5):997-1001; discussion 1001-2.

(42) Whitson BA, Andrade RS, Boettcher A, Bardales R, Kratzke RA, Dahlberg PS, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. Ann Thorac Surg 2007 Jun;83(6):1965-1970.

(43) Jeon JH, Kang CH, Kim HS, Seong YW, Park IK, Kim YT, et al. Video-assisted thoracoscopic lobectomy in non-small-cell lung cancer patients with chronic obstructive pulmonary disease is associated with lower pulmonary complications than open lobectomy: a propensity score-matched analysis. Eur J Cardiothorac Surg 2014 Apr;45(4):640-645.

(44) Rueth NM, Parsons HM, Habermann EB, Groth SS, Virnig BA, Tuttle TM, et al. The long-term impact of surgical complications after resection of stage I nonsmall cell lung cancer: a population-based survival analysis. Ann Surg 2011 08;254(1528-1140; 0003-4932; 2):368-374.

(45) Marjanski T, Wnuk D, Bosakowski D, Szmuda T, Sawicka W, Rzyman W. Patients who do not reach a distance of 500 m during the 6-min walk test have an increased risk of postoperative complications and prolonged hospital stay after lobectomy. Eur J Cardiothorac Surg 2015 May;47(5):e213-9.

(46) Coups EJ, Park BJ, Feinstein MB, Steingart RM, Egleston BL, Wilson DJ, et al. Correlates of physical activity among lung cancer survivors. Psychooncology 2009 04;18(1099-1611; 1057-9249; 4):395-404.

(47) Coups EJ, Park BJ, Feinstein MB, Steingart RM, Egleston BL, Wilson DJ, et al. Physical activity among lung cancer survivors: changes across the cancer trajectory and associations with quality of life. Cancer Epidemiol Biomarkers Prev 2009 02;18(1055-9965; 1055-9965; 2):664-672.

(48) Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS, Mackey JR, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. Cancer 2007 Aug 1;110(3):590-598.

(49) Benzo R, Kelley GA, Recchi L, Hofman A, Sciurba F. Complications of lung resection and exercise capacity: a meta-analysis. Respir Med 2007 Aug;101(8):1790-1797.

(50) Feinstein MB, Krebs P, Coups EJ, Park BJ, Steingart RM, Burkhalter J, et al. Current dyspnea among long-term survivors of early-stage non-small cell lung cancer. J Thorac Oncol 2010 08;5(1556-1380; 1556-0864; 8):1221-1226.

(51) Novoa N, Varela G, Jimenez MF, Aranda JL. Influence of major pulmonary resection on postoperative daily ambulatory activity of the patients. Interact Cardiovasc Thorac Surg 2009 Dec;9(6):934-938.

(52) Jones LW, Eves ND, Waner E, Joy AA. Exercise therapy across the lung cancer continuum. Curr Oncol Rep 2009 07;11(1534-6269; 1523-3790; 4):255-262.

(53) Wang JS, Abboud RT, Wang LM. Effect of lung resection on exercise capacity and on carbon monoxide diffusing capacity during exercise. Chest 2006 Apr;129(4):863-872.

(54) Nagamatsu Y, Maeshiro K, Kimura NY, Nishi T, Shima I, Yamana H, et al. Long-term recovery of exercise capacity and pulmonary function after lobectomy. J Thorac Cardiovasc Surg 2007 Nov;134(5):1273-1278.

(55) Bobbio A, Chetta A, Carbognani P, Internullo E, Verduri A, Sansebastiano G, et al. Changes in pulmonary function test and cardio-pulmonary exercise capacity in COPD patients after lobar pulmonary resection. Eur J Cardiothorac Surg 2005 11;28(1010-7940; 1010-7940; 5):754-758.

(56) Jones LW, Eves ND, Haykowsky M, Joy AA, Douglas PS. Cardiorespiratory exercise testing in clinical oncology research: systematic review and practice recommendations. Lancet Oncol 2008 Aug;9(8):757-765.

(57) Curigliano G, Mayer EL, Burstein HJ, Winer EP, Goldhirsch A. Cardiac toxicity from systemic cancer therapy: a comprehensive review. Prog Cardiovasc Dis 2010 Sep-Oct;53(2):94-104.

(58) Travers J, Dudgeon DJ, Amjadi K, McBride I, Dillon K, Laveneziana P, et al. Mechanisms of exertional dyspnea in patients with cancer. J Appl Physiol (1985) 2008 Jan;104(1):57-66.

(59) Braun DP, Gupta D, Staren ED. Quality of life assessment as a predictor of survival in non-small cell lung cancer. BMC Cancer 2011 Aug 15;11:353-2407-11-353.

(60) Moller AF, Sartipy U. Quality of life six months after lung cancer surgery is associated with long-term survival. Acta oncologica (Stockholm, Sweden) JID - 8709065 1226(1651-226; 0284-186).

(61) Handy JR,Jr., Asaph JW, Skokan L, Reed CE, Koh S, Brooks G, et al. What happens to patients undergoing lung cancer surgery? Outcomes and

quality of life before and after surgery. Chest 2002 07;122(0012-3692; 0012-3692; 1):21-30.

(62) Kenny PM, King MT, Viney RC, Boyer MJ, Pollicino CA, McLean JM, et al. Quality of life and survival in the 2 years after surgery for non small-cell lung cancer. J Clin Oncol 2008 01/10;26(1527-7755; 0732-183; 2):233-241.

(63) Sarna L, Evangelista L, Tashkin D, Padilla G, Holmes C, Brecht ML, et al. Impact of respiratory symptoms and pulmonary function on quality of life of long-term survivors of non-small cell lung cancer. Chest 2004 02;125(0012-3692; 0012-3692; 2):439-445.

(64) Myrdal G, Valtysdottir S, Lambe M, Stahle E. Quality of life following lung cancer surgery. Thorax 2003 Mar;58(3):194-197.

(65) Brunelli A, Pompili C, Koller M. Changes in quality of life after pulmonary resection. Thorac Surg Clin 2012 Nov;22(4):471-485.

(66) Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: A systematic review. Lung Cancer 2013 Apr 4.

(67) Yang P, Cheville AL, Wampfler JA, Garces YI, Jatoi A, Clark MM, et al. Quality of life and symptom burden among long-term lung cancer survivors. J Thorac Oncol 2012 Jan;7(1):64-70.

(68) Kinney MA, Hooten WM, Cassivi SD, Allen MS, Passe MA, Hanson AC, et al. Chronic postthoracotomy pain and health-related quality of life. Ann Thorac Surg 2012 Apr;93(4):1242-1247.

(69) Ostroff JS, Krebs P, Coups EJ, Burkhalter JE, Feinstein MB, Steingart RM, et al. Health-related quality of life among early-stage, non-small cell, lung cancer survivors. Lung Cancer 2011 Jan;71(1):103-108.

(70) Ferguson MK, Parma CM, Celauro AD, Vigneswaran WT. Quality of life and mood in older patients after major lung resection. Ann Thorac Surg 2009 Apr;87(4):1007-12; discussion 1012-3.

(71) Balduyck B, Hendriks J, Lauwers P, Van Schil P. Quality of life evolution after lung cancer surgery: a prospective study in 100 patients. Lung Cancer 2007 Jun;56(3):423-431.

(72) Aoki T, Tsuchida M, Hashimoto T, Saito M, Koike T, Hayashi J. Quality of life after lung cancer surgery: video-assisted thoracic surgery versus thoracotomy. Heart Lung Circ 2007 Aug;16(4):285-289.

(73) Li WW, Lee TW, Lam SS, Ng CS, Sihoe AD, Wan IY, et al. Quality of life following lung cancer resection: video-assisted thoracic surgery vs thoracotomy. Chest 2002 Aug;122(2):584-589.

(74) Orman J, Westerdahl E. Chest physiotherapy with positive expiratory pressure breathing after abdominal and thoracic surgery: a systematic review. Acta Anaesthesiol Scand 2010 Mar;54(3):261-267.

(75) Agostini P, Reeve J, Dromard S, Singh S, Steyn RS, Naidu B. A survey of physiotherapeutic provision for patients undergoing thoracic surgery in the U.K. Physiotherapy 2013 Mar;99(1):56-62.

(76) Rodriguez-Larrad A, Lascurain-Aguirrebena I, Abecia-Inchaurregui LC, Seco J. Perioperative physiotherapy in patients undergoing lung cancer resection. Interact Cardiovasc Thorac Surg 2014 Aug;19(2):269-281.

(77) Hough A. Physiotherapy in respiratory care. An evidence-based approach to respiratory and cardiac management. 3rd ed. Cheltenham: Nelson Thornes Ltd; 2003.

(78) Agostini P, Singh S. Incentive spirometry following thoracic surgery: what should we be doing? Physiotherapy 2009 Jun;95(2):76-82.

(79) Westerdahl E. Optimal technique for deep breathing exercises after cardiac surgery. Minerva Anestesiol 2015 Jun;81(6):678-683.

(80) Varela G, Novoa NM, Agostini P, Ballesteros E. Chest physiotherapy in lung resection patients: state of the art. Semin Thorac Cardiovasc Surg 2011 Winter;23(4):297-306.

(81) Gosselink R, Schrever K, Cops P, Witvrouwen H, De Leyn P, Troosters T, et al. Incentive spirometry does not enhance recovery after thoracic surgery. Crit Care Med 2000 Mar;28(3):679-683.

(82) Reeve JC, Nicol K, Stiller K, McPherson KM, Denehy L. Does physiotherapy reduce the incidence of postoperative complications in patients following pulmonary resection via thoracotomy? a protocol for a randomised controlled trial. J Cardiothorac Surg 2008;3(1749-8090; 1749-8090):48.

(83) Agostini P, Naidu B, Cieslik H, Steyn R, Rajesh PB, Bishay E, et al. Effectiveness of incentive spirometry in patients following thoracotomy and lung resection including those at high risk for developing pulmonary complications. Thorax 2013 Jun;68(6):580-585.

(84) McConnell AK, Romer LM. Dyspnoea in health and obstructive pulmonary disease : the role of respiratory muscle function and training. Sports Med 2004;34(2):117-132.

(85) Wagner PD. Skeletal muscles in chronic obstructive pulmonary disease: deconditioning, or myopathy? Respirology 2006 Nov;11(6):681-686.

(86) American College of Sports Medicine, Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, Minson CT, Nigg CR, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. Med Sci Sports Exerc 2009 Jul;41(7):1510-1530.

(87) Spruit MA, Janssen PP, Willemsen SC, Hochstenbag MM, Wouters EF. Exercise capacity before and after an 8-week multidisciplinary inpatient rehabilitation program in lung cancer patients: a pilot study. Lung Cancer 2006 05;52(0169-5002; 0169-5002; 2):257-260.

(88) Cesario A, Ferri L, Galetta D, Pasqua F, Bonassi S, Clini E, et al. Post-operative respiratory rehabilitation after lung resection for non-small

cell lung cancer. Lung Cancer 2007 08;57(0169-5002; 0169-5002; 2):175-180.

(89) Riesenberg H, Lubbe AS. In-patient rehabilitation of lung cancer patients--a prospective study. Support Care Cancer 2010 Jul;18(7):877-882.

(90) Arbane G, Tropman D, Jackson D, Garrod R. Evaluation of an early exercise intervention after thoracotomy for non-small cell lung cancer (NSCLC), effects on quality of life, muscle strength and exercise tolerance: randomised controlled trial. Lung Cancer 2011 02;71(1872-8332; 0169-5002; 2):229-234.

(91) Granger CL, Chao C, McDonald CF, Berney S, Denehy L. Safety and Feasibility of an Exercise Intervention for Patients Following Lung Resection: A Pilot Randomized Controlled Trial. Integr Cancer Ther 2012 Jul 16.

(92) Stigt JA, Uil SM, van Riesen SJ, Simons FJ, Denekamp M, Shahin GM, et al. A randomized controlled trial of postthoracotomy pulmonary rehabilitation in patients with resectable lung cancer. J Thorac Oncol 2013 Feb;8(2):214-221.

(93) Lee JY, Jin SM, Lee CH, Lee BJ, Kang CH, Yim JJ, et al. Risk factors of postoperative pneumonia after lung cancer surgery. J Korean Med Sci 2011 Aug;26(8):979-984.

(94) Bernard A, Ferrand L, Hagry O, Benoit L, Cheynel N, Favre JP. Identification of prognostic factors determining risk groups for lung resection. Ann Thorac Surg 2000 Oct;70(4):1161-1167.

(95) Lee JH, Song EM, Sim YS, Ryu YJ, Chang JH. Forced expiratory volume in one second as a prognostic factor in advanced non-small cell lung cancer. J Thorac Oncol 2011 02;6(1556-1380; 1556-0864; 2):305-309.

(96) Marret E, Miled F, Bazelly B, El MS, de MJ, Quesnel C, et al. Risk and protective factors for major complications after pneumonectomy for lung cancer. Interact Cardiovasc Thorac Surg 2010 06;10(1569-9285; 1569-9285; 6):936-939.

(97) Brocki BC. Fysioterapi til patienter der får foretaget åben eller torakoskopisk lungeoperation. 2014; Available at: https://pri.rn.dk/Sider/10171.aspx, 2015/09/15.

(98) Borg GA. Perceived exertion. Exerc Sport Sci Rev 1974;2(0091-6331; 0091-6331):131-153.

(99) Åstrand PO, K R, H D, S S. Textbook of work physiology. : Mc Graw Hill; 2003.

(100) Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J 2005 Aug;26(2):319-338.

(101) Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993 03;16(0904-1850; 0904-1850):5-40.

(102) Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J 2014 Dec;44(6):1428-1446.

(103) American Thoracic Society. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002 07/01;166(1073-449; 1073-449; 1):111-117.

(104) Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. Am J Respir Crit Care Med 1998 11;158(1073-449; 1073-449; 5):1384-1387.

(105) Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;14(5):377-381.

(106) Turner SE, Eastwood PR, Cecins NM, Hillman DR, Jenkins SC. Physiologic responses to incremental and self-paced exercise in COPD: a comparison of three tests. Chest 2004 Sep;126(3):766-773.

(107) ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med 2002 08/15;166(1073-449; 1073-449; 4):518-624.

(108) Ware JE,Jr., Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. Med Care 1995 04;33(0025-7079; 0025-7079; 4):AS264-AS279.

(109) Bj¢rner JB, MT D, T W, P B, NK R, TS K, et al. Dansk Manual til SF-36. Copenhagen: Lif Lægemiddelindustriforeningen; 1997.

(110) Mahler DA, Mackowiak JI. Evaluation of the short-form 36-item questionnaire to measure health-related quality of life in patients with COPD. Chest 1995 06;107(0012-3692; 0012-3692; 6):1585-1589.

(111) Swigris JJ, Brown KK, Behr J, du Bois RM, King TE, Raghu G, et al. The SF-36 and SGRQ: validity and first look at minimum important differences in IPF. Respir Med 2010 Feb;104(2):296-304.

(112) Moller A, Sartipy U. Predictors of postoperative quality of life after surgery for lung cancer. J Thorac Oncol 2012 Feb;7(2):406-411.

(113) Kroenke K, Lawrence VA, Theroux JF, Tuley MR, Hilsenbeck S. Postoperative complications after thoracic and major abdominal surgery in patients with and without obstructive lung disease. Chest 1993 11;104(0012-3692; 0012-3692; 5):1445-1451.

(114) Hulzebos EH, Helders PJ, Favie NJ, De Bie RA, Brutel de la Riviere A, Van Meeteren NL. Preoperative intensive inspiratory muscle training to

prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. JAMA 2006 Oct 18;296(15):1851-1857.

(115) Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989 Mar;27(3 Suppl):S178-89.

(116) Dronkers J, Veldman A, Hoberg E, van der WC, van MN. Prevention of pulmonary complications after upper abdominal surgery by preoperative intensive inspiratory muscle training: a randomized controlled pilot study. Clin Rehabil 2008 02;22(0269-2155; 0269-2155; 2):134-142.

(117) Edvardsen E, Skjonsberg OH, Holme I, Nordsletten L, Borchsenius F, Anderssen SA. High-intensity training following lung cancer surgery: a randomised controlled trial. Thorax 2015 Mar;70(3):244-250.

(118) Arbane G, Douiri A, Hart N, Hopkinson NS, Singh S, Speed C, et al. Effect of postoperative physical training on activity after curative surgery for non-small cell lung cancer: a multicentre randomised controlled trial. Physiotherapy 2014 Jun;100(2):100-107.

(119) Stigt JA, Uil SM, van Riesen SJ, Simons FJNA, Denekamp M, Shahin, GM et al. A randomized controlled trial of postthoracotomy pulmonary rehabilitation in patients with resectable lung cancer. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer JID - 101274235 0118.

(120) Redelmeier DA, Bayoumi AM, Goldstein RS, Guyatt GH. Interpreting small differences in functional status: the Six Minute Walk test in chronic lung disease patients. Am J Respir Crit Care Med 1997 Apr;155(4):1278-1282.

(121) Schulte T, Schniewind B, Walter J, Dohrmann P, Kuchler T, Kurdow R. Age-related impairment of quality of life after lung resection for non-small cell lung cancer. Lung Cancer 2010 Apr;68(1):115-120.

(122) Philip EJ, Coups EJ, Feinstein MB, Park BJ, Wilson DJ, Ostroff JS. Physical activity preferences of early-stage lung cancer survivors. Support Care Cancer 2014 Feb;22(2):495-502.

(123) Borges-Santos E, Genz IC, Longo AF, Hayahsi D, Goncalves CG, Bellinetti LM, et al. Pulmonary function, respiratory muscle strength and quality of life in patients submitted to elective thoracotomies. Rev Col Bras Cir 2012;39(1):4-9.

(124) Bolton JW, Weiman DS. Physiology of lung resection. Clin Chest Med 1993 Jun;14(2):293-303.

(125) Savci S, Degirmenci B, Saglam M, Arikan H, Inal-Ince D, Turan HN, et al. Short-term effects of inspiratory muscle training in coronary artery bypass graft surgery: a randomized controlled trial. Scand Cardiovasc J 2011 Oct;45(5):286-293.

(126) Solberg Nes L, Liu H, Patten CA, Rausch SM, Sloan JA, Garces YI, et al. Physical activity level and quality of life in long term lung cancer survivors. Lung Cancer 2012 Sep;77(3):611-616.

(127) Nomori H, Ohtsuka T, Horio H, Naruke T, Suemasu K. Difference in the impairment of vital capacity and 6-minute walking after a lobectomy performed by thoracoscopic surgery, an anterior limited thoracotomy, an anteroaxillary thoracotomy, and a posterolateral thoracotomy. Surg Today 2003;33(1):7-12.

(128) Cykert S, Kissling G, Hansen CJ. Patient preferences regarding possible outcomes of lung resection: what outcomes should preoperative evaluations target? Chest 2000 Jun;117(6):1551-1559.

(129) Rauma V, Sintonen H, Rasanen JV, Salo JA, Ilonen IK. Long-term lung cancer survivors have permanently decreased quality of life after surgery. Clin Lung Cancer 2015 Jan;16(1):40-45.

(130) Dimitriadis Z, Kapreli E, Konstantinidou I, Oldham J, Strimpakos N. Test/retest reliability of maximum mouth pressure measurements with the MicroRPM in healthy volunteers. Respir Care 2011 Jun;56(6):776-782.

(131) Beekman E, Mesters I, Hendriks EJ, Klaassen MP, Gosselink R, van Schayck OC, et al. Course length of 30 metres versus 10 metres has a significant influence on six-minute walk distance in patients with COPD: an experimental crossover study. J Physiother 2013 Sep;59(3):169-176.

(132) Pretto JJ, Roebuck T, Beckert L, Hamilton G. Clinical use of pulse oximetry: official guidelines from the Thoracic Society of Australia and New Zealand. Respirology 2014 Jan;19(1):38-46.

(133) Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. Eur J Cancer 1994;30A(5):635-642.

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