Physiotherapy interventions and outcomes following lung cancer surgery
To Lars, Cristina and Mads

with love
Physiotherapy interventions and outcomes following lung cancer surgery
Abstract


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 health-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
Accepted for publication at the Eur J Cardiothorac Surg
DOI: 10.1093/ejcts/ezv359

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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 (FEV₁), 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 FEV₁% 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 FEV₁ (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 FEV₁, measurement of diffusing capacity for carbon monoxide (D_L,CO) and assessment of performance status. Patients with a stair-climbing altitude of < 22 m or VO₂ 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 manoeuvres 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 (8,5).

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

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

* 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.
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.
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>
<thead>
<tr>
<th></th>
<th>Studies I - II (n=78)</th>
<th>Study III (n=81)</th>
<th>Study IV (n=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 9</td>
<td>68 ± 9</td>
<td>70 ± 8</td>
</tr>
<tr>
<td></td>
<td>65 [42;83]</td>
<td>69 [46;82]</td>
<td>71 [51;82]</td>
</tr>
<tr>
<td>Gender (male/female), n (%)</td>
<td>46/32 (59/41)</td>
<td>47/34 (58/42)</td>
<td>39/29 (57/43)</td>
</tr>
<tr>
<td>Preoperative FEV₁% predicted</td>
<td>83 ± 19</td>
<td>101 ± 21</td>
<td>79 ± 22</td>
</tr>
<tr>
<td>(n=75 for Studies I - II)</td>
<td>82 [41;148]</td>
<td>98 [59;170]</td>
<td>80 [28;134]</td>
</tr>
<tr>
<td>VATS/thoracotomy, n (%)</td>
<td>18/60 (23/77)</td>
<td>47/34 (58/42)</td>
<td>35(51)/33(49)</td>
</tr>
<tr>
<td>Resection degree</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wedge/segmentectomy, n (%)</td>
<td>12 (15)</td>
<td>27 (33)</td>
<td>21 (31)</td>
</tr>
<tr>
<td>Lobectomy, n (%)</td>
<td>54 (70)</td>
<td>45 (55)</td>
<td>38 (56)</td>
</tr>
<tr>
<td>Bilob/pneumonectomy, n (%)</td>
<td>7/5 (9/6)</td>
<td>4/7 (5/8)</td>
<td>3/6 (4/9)</td>
</tr>
<tr>
<td>Length of hospital stay (days)</td>
<td>10 ± 5</td>
<td>8 ± 5.3</td>
<td>8 ± 5.5</td>
</tr>
<tr>
<td>Cancer characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSCLC, n (%)</td>
<td>65 (83)</td>
<td>55 (68)</td>
<td>52 (78)</td>
</tr>
<tr>
<td>Metastatic tumour, n (%)</td>
<td>10 (13)</td>
<td>11 (14)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Other type, n (%)</td>
<td>3 (4)</td>
<td>15 (18)</td>
<td>8 (11)</td>
</tr>
<tr>
<td>Adjuvant treatment, n (%)</td>
<td>34 (43)</td>
<td>20 (25)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

Abbreviations: FEV₁%, 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 posterolateral 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 cmH2O 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 peroral 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>
<thead>
<tr>
<th>Type of exercise</th>
<th>Duration (min)</th>
<th>Intensity</th>
<th>Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warm-up</td>
<td>5 - 15</td>
<td>RPE 7 - 12</td>
<td>Commenced walking normal speed; ↑ walking speed, intercalated with arm swings, stretching; knee lifts</td>
</tr>
<tr>
<td>Aerobic, combined with upper/lower limb thoracic cage stretches</td>
<td>10 - 20 (session 1-4)</td>
<td>RPE 11 - 12 (↑ RPE 13 - 16 (session 5 - 10))</td>
<td>Warm-up 4 min target RPE 10 Interv 20s RPE 12/40s RPE 10 ↑ nb intervals; ↑20s RPE 13-16</td>
</tr>
<tr>
<td>Stationary bike</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strength training</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>arms (Thera-band®)</td>
<td>10 - 15</td>
<td>6 - 10 reps</td>
<td>Commenced 6 reps x 1 set</td>
</tr>
<tr>
<td>trunk (abdomen, back)</td>
<td></td>
<td>1 - 2 sets</td>
<td>↑ reps per set</td>
</tr>
<tr>
<td>legs (step-ups, heel raises, sit to stands)</td>
<td></td>
<td></td>
<td>↑ sets 10 reps</td>
</tr>
<tr>
<td>Cooling down/relaxation</td>
<td>10</td>
<td>RPE 6</td>
<td></td>
</tr>
</tbody>
</table>

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 H₂O 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 зарегистриed 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)
SpO2 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 cmH2O 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 manoeuvre 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. SpO₂ 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. SpO₂ was measured ten minutes after the removal of the supplementary oxygen supply and hypoxemia was defined as SpO₂ < 90% for two consecutive days.

Table 4: Operational definition of PPC – Study IV

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>new onset of purulent sputum or change in character of chronic sputum</td>
<td>pleural effusion resulting in drainage</td>
<td>ventilatory failure with postoperative ventilator dependence &gt; 8 hours</td>
</tr>
<tr>
<td>fever ≥ 38°C with no focus outside the lungs</td>
<td>pneumonia suspected through radiological evidence without bacteriological confirmation or confirmed pneumonia with radiological evidence and documentation of pathogens from sputum</td>
<td>reintubation with subsequent period of ventilator &gt; 48 hours</td>
</tr>
<tr>
<td>a new rise in C-reactive protein value or white blood cell count</td>
<td>visible pneumothorax apical and/or lateral &gt; 2 cm detected by a surgeon on a chest radiograph with or without requirement of invasive treatment</td>
<td></td>
</tr>
<tr>
<td>positive blood cultures</td>
<td>postoperative re-intubation, period of ventilator dependence &lt; 48 hours</td>
<td></td>
</tr>
<tr>
<td>atelectasis: radiological confirmation or abnormal lung findings requiring non-invasive intervention e.g. continuous positive pressure breathing</td>
<td>clinically significant atelectasis requiring tracheo-bronchial suction</td>
<td></td>
</tr>
<tr>
<td>hypoxemia defined as SpO₂ &lt; 90% for two consecutive days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>administration of postoperative antibiotics (in addition to those administered routinely postoperatively)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-tracheal aspirate or bronchial washing</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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. Kazi’s 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 cmH2O (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 FEV1/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 dyspnœa (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.

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

Abbreviations: PF, physical performance; RP, role of physical limitations; BP, bodily pain; GH, general health; 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.
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 health; 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). FEV₁/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 FEV₁ respectively 19% and 9%, p < 0.001), compared to preoperative values. Six months postoperatively FEV₁/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). SpO₂ 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]).

<table>
<thead>
<tr>
<th></th>
<th>Bef. surgery</th>
<th>Postoperatively</th>
<th>p-value for the difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 weeks n = 81</td>
<td>6 mths n = 65</td>
<td>Bef-2 wks Bef-6 mths</td>
</tr>
<tr>
<td>MIP, cmH₂O</td>
<td>84 ± 30</td>
<td>83 ± 33</td>
<td>94 ± 31</td>
</tr>
<tr>
<td></td>
<td>86[23;152]</td>
<td>78[18;181]</td>
<td>86[23;152]</td>
</tr>
<tr>
<td>MIP % pre</td>
<td>104 ± 30</td>
<td>78 ± 33</td>
<td>114 ± 31</td>
</tr>
<tr>
<td></td>
<td>106[40;165]</td>
<td>114[30;165]</td>
<td>117[32;196]</td>
</tr>
<tr>
<td>MEP, cmH₂O</td>
<td>103 ± 33</td>
<td>99±34</td>
<td>108 ± 37</td>
</tr>
<tr>
<td></td>
<td>101[37;152]</td>
<td>95[36;203]</td>
<td>108[37;247]</td>
</tr>
<tr>
<td>MEP % pre</td>
<td>106 ± 30</td>
<td>109 ± 30</td>
<td>109 ± 30</td>
</tr>
<tr>
<td></td>
<td>103[49;168]</td>
<td>103[46;207]</td>
<td></td>
</tr>
</tbody>
</table>

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 ≥ 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]).

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<th></th>
<th>2 weeks postoperatively n= 81</th>
<th>6 months n = 65</th>
</tr>
</thead>
<tbody>
<tr>
<td>At rest</td>
<td>0 [0;5]</td>
<td>0 [0;6]</td>
</tr>
<tr>
<td>Voluntary cough</td>
<td>1 [0;8]</td>
<td>1 [0;6]</td>
</tr>
<tr>
<td>MIP measurement</td>
<td>0 [0;8]</td>
<td>0 [0;6]</td>
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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 SpO₂ at the 6MWT. MIP was significantly reduced in both groups at postoperative day five (~15%, \( p < 0.001 \)), but had recovered two weeks postoperatively. FEV₁ and FVC dropped by ~30% in both groups by the fifth postoperative day (\( p < 0.001 \)). Compared to preoperative values, FEV₁ 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, SpO₂ 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 \( \frac{1}{2} \) 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 et 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-sparring 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 H2O (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\textsubscript{2}O was needed to detect an effect of the intervention. After two weeks the actual difference was of only 4.5 cmH\textsubscript{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\textsubscript{2}O, evaluated five days after the surgery. At the same time, a 36 cmH\textsubscript{2}O decrease in MIP was detected in the CG not performing IMT (125). The difference between groups in MIP in the above mentioned study was far larger than the 15 cmH\textsubscript{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 manoeuvres 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 occurrence 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 (SpO₂ of 92%), followed by an increase in dyspnoea and exertion (~1 unit). Similarly, while 6MWT had recovered six months postoperatively, SpO₂ 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 ≥ 70 years (31,93), FEV₁ ≤ 70% predicted (94,95), Dlco ≤ 70% predicted (1,93) or planned pneumonectomy (96). Meanwhile, a combination of different risk factors or lower cut-off values for FEV₁ % and Dlco% 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 SpO2, 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 SpO₂ (Study IV) is part of the standard patient observation procedure in our unit to improve detection of hypoxemia in the early postoperative period. Whereas SpO₂ 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.
Acknowledgments

I would like to express my most sincere gratitude to all who, in one way or another, have contributed to this thesis. In particular I’d like to thank:

All patients who participated in the studies.

My three supervisors who made this journey possible:
Elisabeth Westerdahl, my main supervisor. It has been a privilege to be her doctoral student and be able to share her extensive knowledge of respiratory physiotherapy within the thoracic surgery field. Thanks for the professional supervision, support, and friendship.
Jan Jesper Andreasen, my supervisor, for inspiration and support. Especially, thanks for motivating me to getting started into the research field.
Domingos Savio R Souza, my supervisor, for valuable collaboration and support.

Jane Andreasen, co-author and dear friend. Thanks for shared knowledge, support, frustrations and laughter.

Hans Erik Madsen, for providing the circumstances that made it possible for me to complete my doctoral studies.

Vytautas Nekrasas and Lene Rodkjær, co-authors for the first study for valuable collaboration.

My colleagues PhD-students at Aalborg University Hospital for inspiration, support and for sharing with me the daily joy and challenges that come with research work.

My colleagues at Team Rehab at Aalborg University Hospital for their help, concern with my well-being and inspiration through many years of clinical work. In particular, I’d like to thank Ruth Bliksted and Thomas W. Asp who performed the assessments for the two RCTs.

My colleagues at the Department of Physiotherapy and Occupational Therapy at Alborg University Hospital. Thanks for the many times you had to walk the other way around, so you did not “disturb” the patients performing the 6MWT.

Nils-Gunnar Perhson, for attentive and very patient help with statistics.
The staff at the Department of Cardiothoracic Surgery, Aalborg University Hospital: The nurses, for helping me with the data collection for studies III and IV, and the surgeons for sharing their clinical knowledge with me. I’d also like to thank the secretaries at the department, and in particular Helle Hald, for helping me to keep track of the patients who were target for my studies.

My friends: Irene Longmuir and Anderson Oliveira, for valuable help and suggestions with my papers and thesis regarding the English language; Bärbel Witt, for concern, encouragement and many years friendship.

My father (in memorium) and mother – thanks for teaching me the value of working hard to achieve my goals and never, ever to lose hope.

And last but definitely not least to my family: Lars, my very patient husband, who is very skilled with software and helped me a lot with that; my daughter Cristina and my son, Mads. I couldn’t have reached so far without your endless support and encouragement.

This work was supported by grants from the Danish Cancer Society, the Danish Cancer Research Foundation, the Danish Lung Foundation, the Danish Physiotherapists Association, Dagmar Marshals Foundation, Tømrermester Jørgen Holm og Hustru Elise f. Hansens Mindelegat, Örebro University and Aalborg University Hospital.
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