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Short-term preoperative high-intensity interval training in patients awaiting lung cancer surgery: a randomized controlled trial

Running head: Preoperative physical training and lung cancer surgery

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Abstract (Word count = 270)

Background: Impairment in aerobic fitness is a potential modifiable risk factor for postoperative complications. In this randomized controlled trial, we hypothesized that a high-intensity interval training (HIIT) program enhances cardiorespiratory fitness before lung cancer surgery and therefore reduces the risk of postoperative complications.

Methods: Patients with operable lung cancer were randomly assigned to usual care (UC, N=77) or preoperative rehabilitation based on HIIT (Rehab, N=74). Maximal cardiopulmonary exercise testing and the six-minute walk test were performed twice before surgery. The primary outcome measure was a composite of death and in-hospital postoperative complications. .

Results: Groups were well balanced in terms of patient characteristics. During the preoperative waiting period (median 25 days), the peak oxygen consumption (peakVO_2) and the six-minute walking distance increased (respectively, median +15 % [IQ 25-75%, +9 to +22%] P=0.003 and +15% [IQ25-75, +8 to +28%], P<0.001) in the Rehab group whereas VO_{2peak} declined in the UC group (median -8% [IQ25-75, -16 to 0%], P=0.005). The primary endpoint did not differ significantly between the two groups: 27 of the 74 patients (35.5%) in the Rehab group and 39 of 77 patients (50.6%) in the UC group developed at least one postoperative complication (P=0.080). Noteworthy, the incidence of pulmonary complications was lower in the Rehab compared with the UC group (23% vs 44%, P=0.018), owing to a significant reduction in atelectasis (12.2% vs 36.4%, P<0.001) and this was accompanied by a shorter length of stay in the postanesthesia care unit (median -7 hours, IQ25-75% -4 to -10).

Conclusions: In this RCT, preoperative HIIT resulted in significant improvement in aerobic performances but failed to reduce early complications after lung cancer resection.

TRIAL REGISTRY: ClinicalTrials.gov; No. NCT01258478; URL: www.clinicaltrials.gov

Introduction

Currently, surgical resection remains the best treatment in the early stages of non-small cell lung cancer (NSCLC).[1] Advanced age, cancer stage, associated illnesses and impaired cardiorespiratory fitness (CRF) are predictive factors of major postoperative complications and long term survival.[2,3]

Cardiopulmonary exercise testing (CPET) represents the gold standard for evaluating CRF and the response to rehabilitation program.[4] Peak oxygen uptake (peakVO_2) reflects the integrative ability of the pulmonary, circulatory and autonomic neural systems to maximally deliver oxygen towards the working skeletal muscles. Cut-off values around 16 $ml.kg^{-1}.min^{-1}$ peak$VO_{2\ peak}$ and 10-12 ml/kg/min anaerobic threshold (AT) have been shown helpful to discriminate patients at low risk from those at higher risk of major postoperative complications.[2,5]

In patients with lung cancer, peakVO_2 is on average 25% to 30% lower than in age-and gender matched non-cancer individuals.[2,6,7] Although implementation of exercise-based rehabilitation programs has been shown effective in improving CRF and quality of life of these patients, rehabilitation is largely underutilized because of scarce scientific evidence and uncertainties regarding the modalities on how to implement physical therapy over the limited preoperative time period.[8-11] Recent evidence has highlighted the potential of low-volume, high-intensity interval training (HIIT) for inducing a protective cardiopulmonary phenotype while enhancing oxygen extraction in skeletal muscle by increasing capillary density and mitochondrial oxidative capacity.[12,13]

In this trial, we aimed to evaluate and compare short-term preoperative HIIT to usual care in patients undergoing NSCLC resection by assessing CRF parameters and the incidence of postoperative complications. We hypothesized that exercise-induced improvement in CRF would enhance protective defense mechanisms among surgical candidates making them more resistant to physiological alterations consequent to surgical stress.

Methods

Study Design

The Lung Cancer Rehabilitation Study was a prospective randomized open blinded end point controlled trial (PROBE) using assessor blinding and intention-to-treat analysis. It was registered at the National Institutes of Health ClinicalTrials.Gov (NCT01258478).and conducted at the University Hospital of Geneva and the Hospital of Valais.

Patients

After approval by the Local Ethics Committees (protocol n° 06-225), written informed consent was obtained from all eligible adult patients with proven or suspected NSCLC, stage IIIA or less. The criteria of resectability were based on the recommendations of the European Respiratory Society and the European Society of Thoracic Surgery (ERS and ESTS).[4] Exclusion criteria were any contraindication to perform CPET (e.g., uncontrolled cardiac disease, severe pulmonary hypertension), limitations impeding cycling or the inability to adhere to a rehabilitation program.

Randomization

Consenting patients were randomized on a 1:1 basis into a Rehabilitation arm (Rehab) and a Usual Care arm (UC) using permuted block of 4. The randomization sequence was developed before the initiation of the trial and concealed until after enrollment.

Interventions

Adapted from previous published data,[14] the HIIT program was designed in cooperation with experienced physical therapists specialized in rehabilitation. Participants in the Rehab group exercised on a cycling ergometer in the outpatient clinic, two to three times a week under the supervision of physiotherapists. After a 5 min warm-up period at 50% of peak work rate (WR) the patients completed two 10 min long series of 15 sec sprint intervals (at 80-100% peakWR) interspersed by 15 sec pauses and a 4 min rest between the two series. The patients then cooled down with a 5 min active recovery period at 30% peakWR. The work rate was adjusted by the physiotherapist on each session to target near maximal heart rates towards the end of each series of sprints based on the individual's exercise response. Additional exercises were proposed on an individual basis, such as leg press, leg extension, back extension, seat row, biceps curls or chest-and-shoulder press.

Patients in the two groups were given advices regarding active mobilization (at least four 30-min walk per week) and risk factor management (e.g., healthy nutrition, smoking and alcohol cessation).

Lung resections were performed by open thoracotomy or video-assisted thoracic surgery and, standardized perioperative interventions included antibiotic prophylaxis, restrictive fluid management, thoracic epidural analgesia and protective lung ventilation.[15] After surgery, patients were managed in a postanesthesia care unit (PACU) and were transferred to the surgical ward when the discharge criteria were met.[16] Routine postoperative physiotherapy consisted in deep breathing using an incentive spirometer, coughing exercise and assistance with ambulation.

Measurements and Outcomes

The Six Minute Walk Test (6MWT) was conducted by physiotherapists according to the ERS and American Thoracic Society (ATS) guidelines.[17] A symptom-limited CPET was performed on an upright electronically braked cycle ergometer with breath-by-breath expired gas analysis (SensorMedics Model 2200 SP; Yorba Linda, CA); peakHR and peakVO_2 were determined as the highest average values over 30 sec and peakWR was identified at the highest exercise level or, interpolated if the last stage was not maintained for two minutes.[18] Peak oxygen pulse (peakO_2pulse) was calculated by dividing peak$\dot{V}O_2$ by the peakHR. The AT was determined using the V-slope method as primary criterion and the first rise in the ventilatory equivalent for oxygen (V_E/VO_2) as a secondary criterion.[19]

All respiratory function tests and physiologic measurements were performed according to the ATS and ERS standards, and expressed as absolute and predicted values (%) based on age, sex, and weight of the patients.[20] Age and sex-specific predicted distances during the 6MWT were calculated from the Enright's equation.[21]

On the day of enrollment, collected data included demographic and clinical information as well as the results of lung functional and blood laboratory tests. The Revised Cardiac Risk Index was computed for each patient.[22] Two to four days before surgery (after the rehabilitation or control period), the CPET and the 6MWT were repeated and a multi-axis accelerometer (ActiSmile SA, Baar, Switzerland) was used to estimate daily physical activity (average value of the last three days prior to surgery).

Surgical and anesthetic data were extracted from the electronic Patient Data Management System. Postoperatively, patients were followed until hospital discharge to report any adverse events according to a modified version of the Thoracic Mortality and Morbidity (TMM) classification system (see supplemental material).[23]

The primary outcome was a composite endpoint of postoperative morbidity (30-day mortality or any complications TMM grades $\geq$ 2). Secondary outcomes were the preoperative changes in CPET parameters (peakVO_2, AT, peakHR) and in 6MWT (in meters, m), the incidence of postoperative complications TMM grades $\geq$ 2, the length of stay in PACU and the admission rate in the Intensive Care Unit (ICU). A positive response to rehabilitation was defined by meaningful changes in VO_{2peak} ($\geq$10%) or in 6MWT ($\geq$30 m) occurring between the first and the second preoperative measurements.[17,24] Adherence to the HIIT program was defined as the ratio of the number of attended-to-prescribed sessions. All serious adverse events (SAE) during the HIIT were reported to the study coordinator and the data monitoring and safety committee (DMSC)

Sample size

Based on a previous cohort study, we assumed an incidence of 22% complications and expected a 50% reduction of postoperative morbidity after implementing preoperative rehabilitation.[15] A sample of 178 patients per group was required (80% power; 2-sided test; type I error of 0.05) and to allow for dropouts, we intended to randomize 400 patients (200 per group). Given concerns regarding the occurrence of SAE and a possible changing pattern of clinical outcome, two interim analyses were planned after the inclusion of 120 and 240 patients as recommended by the DMSC. Stopping/continuing rules were based on the followings: SAE related to the HIIT, changes in the rate of postoperative complications and between-group difference in primary endpoint or in at least 2 secondary endpoints. The first interim showed an overall incidence of 46% complications, therefore 44 additional patients were deemed necessary to complete the study.

Statistical Analysis

All data were analyzed using statistical software SPSS version 11.5 (SPSS Inc., Chicago, IL, USA) and tested with the Kolmogorov-Smirnov for normality. Summary descriptive statistics were expressed as frequencies (and percentages, %), medians (and interquartile range, IQ25-75%), or means (and standard deviations, SD). Intergroup differences were analyzed by two-sided unpaired *t* test, Mann-Whitney test, or $\chi 2$ test with Yates corrections where appropriate. Physiologically important changes were estimated as effect sizes (ES) using Cohen's guidelines,[25] whereby a value of 0.2 denotes a small, 0.5 a medium, and 0.8 a large effect size.

The ES induced by the intervention was calculated by subtracting the mean changes in the UC group from the mean change in the Rehab group divided by the pooled standard deviation. Prespecified analyses using a generalized linear model were conducted to explore modification of HIIT response by patient's characteristics and cancer stages as well as the impact of these variables on the occurrence of postoperative complications. All statistical tests were 2-sided and conducted at the 5% significance level.

Results

Study population

Between October 2011 and October 2014, 189 patients were screened, 164 provided consent and 13 were excluded (Figure 1). Therefore, 151 patients were analyzed, 77 in the UC group and 74 in the Rehab group. The time delay from the date of enrollment to surgery was similar in the two groups (median of 26 days [IQ25-75, 21-33] in the Rehab group and median of 25 days [IQ25-75, 20-40] in the UC group).

The two groups did not differ regarding preoperative demographic, clinical and functional data (Tables 1 and 2). Surgical characteristics and anesthetic management were also similar in the two groups: more than 80% of patients underwent major lung resection through open thoracotomy and received thoracic epidural analgesia (Table 3). In the Rehab group, adherence to the prescribed training sessions was 87±18% (median 8 sessions, IQ25-75 [7-10]) and no serious adverse event was reported during the HIIT sessions. The daily step count tended to be higher in the Rehab group (7’243±3’934 steps versus 6’315±3’690 steps in the UC group, P=0.082).

Primary Outcome

In-hospital clinical outcome data were available in all participants. As shown in Table 4, a total of 66 patients reached the composite postoperative mortality-morbidity endpoint including 27 of the 74 patients (35.5%) in the Rehab group and 39 of 77 patients (50.6%) in the UC group (Relative Risk 0.70, 95% confidence interval 0.48 – 1.02).

Secondary outcomes

Compared with baseline measurements, significant changes in CPET and 6MWT parameters occurred at the end of the preoperative waiting period (table 5). In the UC group, the peakVO_2 declined during the preoperative waiting period (median -8% [IQ25-75, -16 to 0%], P=0.005).

In contrast, in the Rehab group, there were significant increases in peakVO_2 (median +15 % [IQ25-75%, +9 to +22%], P=0.004), in peakWR (median +6% [IQ25-75, 0 to +17%]; P=0.003), and in walking distance at the 6MWT (median +15% [IQ25-75, +8 to +28%], P<0.001) with a non-significant increase in AT (median +8 % [IQ25-75, -7 to + 20%, P=0.083)]. The effect size of the Rehab intervention was significant regarding peakVO_2 (0.46, 95%CI 0.26 to 0.66) and walking distance (0.49, 0.24 to 0.74), and non-significant regarding the AT (0.20, -0.95 to 0.45), peak O_2 pulse (0.29, -0.99 to 0.59), peakHR (0.15, -0.94 to 0.36) and peakWR (0.28, -0.98 to 0.58). The target physiological endpoints were achieved in 75.7% of rehabilitated patients and this functional improvement was consistent regardless of patient characteristics and cancer stages (Figure 2). Attendance to the prescribed training sessions did not differ between responders and non-responders (89% vs 81%).

The incidence of cardiovascular and surgical complications as well as the rate of admission in the ICU and the hospital length of stay did not differ between the two groups. In contrast, the incidence of postoperative pulmonary complications was lower in the Rehab group (23% vs 44% in the UC group P=0.018), owing to a reduced rate of atelectasis (12.2% vs 36.4%, P<0.001) and this was accompanied by a shorter stay in the PACU (median -7 hours, IQ25-75% -4 to -10) compared with the UC group. Subgroup analysis revealed that the beneficial effect of Rehab on postoperative pulmonary complications was larger among “responders” than in “non-responders” (RR 0.25, 95%CI [0.12-0.53]) and consistent among men, elderly, overweight subjects, patients with cardiac risks factors, those with preserved aerobic capacity and regardless of the presence or absence of COPD (Figure 3).

Regression analysis showed that independent predictors of postoperative pulmonary complications were: preoperative peakVO_2, rehabilitation intervention, and COPD (Wald = 10.0, 7.5, and 4.1; P= 0.002, 0.006 and, 0.043, respectively).

Discussion

This study demonstrates that preparing patients before lung cancer resection with a HIIT program enhances their physical fitness but fails to improve postoperative clinical outcome.

At patient enrollment, the mean peakVO_2 (20 ml/kg/min) and the mean 6MWT distance (383 m) were on average, respectively 18% and 42% below values expected for age- and sex-matched sedentary individuals. In a multicenter trial including 346 patients with NSLC, Loewen et al. reported even greater preoperative impairment in aerobic capacity (mean VO_{2peak} of 15.8 ml/kg/min) and a larger proportion of patients with low preoperative VO_{2peak} that has been shown to be predictive of major cardiopulmonary complications.[2,26] In contrast to chronic conditions such as COPD and cardiovascular disease, poor aerobic fitness, as well as heavy smoking and alcohol absorption are amenable to targeted risk-reducing strategies.

Therefore, our short-term HIIT program was intended to augment preoperative physiological reserves and to facilitate postoperative functional recovery. The delay from “decision-to-treat” to surgery was within the maximal waiting time of 28 days recommended by the British Thoracic Society.[27] During the three to four weeks waiting period, patients receiving usual care exhibited a mild decline in CPET parameters and walking capacity that could be attributed to the inflammatory component associated with lung cancer, COPD and other chronic illnesses.[28] This impairment in aerobic functional capacity was successfully offset in 76% patients who were enrolled in a HIIT program. After attending 7 to 13 supervised training sessions, both peakVO_2 and walking capacity improved by a median value of 15%, regardless of patient preoperative characteristics. Baseline physiological values as well as the intensity, the type and the duration of exercise training are key factors determining CRF changes. Endurance training classically entails moderate intensity efforts during daily sessions lasting 60 to 120 min and scheduled over a prolonged period of 6 to 12 weeks. Such “high volume” training has been shown to improve aerobic performances as a result of blood volume expansion, higher cardiac output and enhanced muscle oxygen extraction.[28] In contrast, the "low-volume" HIIT (40 min, 2-3 times a week, 3-4 weeks) has been shown to produce similar or larger gains in peakVO_2 owing to enhanced skeletal muscle oxidative capacity, independent of any changes in cardiac performances and in blood-oxygen carrying capacity.[29,30] Even a few sessions of HIIT appear sufficient to stimulate transcriptional mitochondrial biogenesis, inducing aerobic phenotypic changes characterized by increased mitochondrial expression/activity of proteins involved in fat oxidation, tricarboxylic acid cycle and electron transport chain.[31]

In the current trial, we reported all TMM complications graded II to IV. Hence, the incidence of postoperative complications (overall 37%) was higher than expected from our previous work and higher than reported by others.[15,32] The TMM classification has been derived from the Dindo-Clavien scoring system in order to standardize the reporting of adverse outcome and to overcome the limitations of considering each complication separately.[33] This composite measure is well validated and widely applied in perioperative medicine to grade the severity of postoperative complications, considering the intensity of therapeutics and resources. In a study involving a majority of video-assisted thoracoscopic lung resection, Beck-Schimmer et al recently reported a 15% incidence of postoperative complications graded III to IV.[34] Besides the different threshold to capture postoperative morbidity, our study population was also at greater risk of postoperative complications given the more invasive surgical approach (81% thoracotomies) and a higher proportion of extended resection (e.g., 20% pneumonectomy/bilobectomy).

Although peakVO_2, peakWR and walking distance were all increased after 5 to 10 HIIT sessions, this enhanced aerobic condition did not translate into better clinical outcome, except a lower rate of atelectasis coupled with a shorter length of stay in the PACU.

Several arguments can be given to explain these findings and, at the same time, to highlight the limitations of this trial. One may argue that the relative risk reduction in primary outcome (approximately -30%) would have been statistically significant if the study had been continued to enroll a total of 362 patients. Down-sizing the study sample was justified by the interim analysis showing a higher than expected incidence of postoperative complications (46% instead of 22% initially estimated). Noteworthy, the majority of patients enrolled after the interim analysis underwent lung resection via VATS instead of open thoracotomy. This lesser invasive surgical approach contributed to reduce the rate of postoperative complications over the last 6 month of this study, regardless of group allocation.

Cardiovascular complications did not differ between the two groups. The standard risk reducing strategies that were applied (e.g., preoperative patient assessment, thoracic epidural analgesia and fluid restriction) resulted in a low rate of myocardial infarct and heart failure (< 5%). Not surprisingly, tachy-arrhythmias, the most frequent cardiac adverse event, were not responsive to the effects of rehabilitation as they are mainly related to surgical inflammation, autonomic nerve injuries and cardiac overload.[35] Moreover, concerns have been raised about the pro-arrhythmic effects of HIIT although the effectiveness of long term endurance training has been clearly established in improving endothelial dysfunction, myocardial remodeling, cardiac autonomic control and β-adrenoceptor balance.[36,37]

Interestingly, pulmonary complications were reduced by 45% in the Rehab group, the greatest impact being on atelectasis and particularly among patients who exhibited a positive response to HIIT. Even if atelectasis graded II are often considered benign, the initiation of corrective therapy with CPAP or NIV in the PACU is justified in order to correct oxygenation disturbances and to prevent further extension and the development of infection. In the Rehab group, the lesser incidence of atelectasis was associated with a slight reduction in PACU length of stay (median -7h), compared with the usual care group.

Reversal of respiratory muscle dysfunction is an attractive mechanism underlying the protective effects of HIIT in thoracic surgical patients. Indeed, weakness of the respiratory muscles has been consistently reported in patients with low preoperative peakVO_2 and COPD.[38] two features that were identified as independent predictors of pulmonary complications in the current trial. Using similar short-term total-body aerobic reconditioning programs, Dunham et al reported up to 40% increase in maximal inspiratory pressure, the HIIT modality providing a time-efficient alternative to endurance training in increasing both CRF and respiratory muscle function.[39]

Recent systematic reviews suggest that preoperative, -but not postoperative-, interventions including moderate-intense aerobic exercise may contribute to improve functional capacity and to reduce postoperative pulmonary morbidity.[40,41] However, no firm conclusions could be drawn given the heterogeneity of patient populations, the variety of interventional approaches, the lack of standardized criteria defining morbidity outcomes and the small numbers of enrolled patients. To date, only 5 randomized controlled trials including a total of 196 patients have been published and none was powered to detect meaningful clinical differences.[41] The current study including 151 patients is the largest trial conducted so far.

Even though this trial presents negative results regarding the primary outcome, the positive impact on the development of atelectasis should not be ignored nor overemphasized. Our results are consistent with the hypothesis that HIIT-induced CRF improvement enables patients to better withstand respiratory derangements, namely muscular weakness resulting from surgical stress and the residual effects of anesthetic agents while facilitating lung reexpansion postoperatively. The study was underpowered to detect meaningful difference in major pulmonary complications such as pneumonia or ARDS. Moreover, 25 % of rehabilitated patients failed to experience any benefit in terms of aerobic fitness or walking capacity despite attending the prescribed training sessions. Non-response to specialized rehabilitative interventions has been attributed to genetic factors, physical disabilities, adjunctive chemotherapy and low volume/low intensity of exercise.[42,43] Psycho-social interventions, inspiratory muscle training and nutritional support could favorably complement the rehabilitation programs.[44]

In conclusion, we demonstrated the safety and effectiveness of a short-term exercise training program in improving aerobic performances in patients awaiting lung cancer surgery. However, this HIIT rehabilitation modality failed to produce significant difference in composite morbidity-mortality index, compared with usual care. Adequately powered randomized studies including high-risk patients and focusing on clinical outcome endpoints should question the benefits of preoperative rehabilitation interventions.

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Legends

Figure 1: CONSORT Flow Diagram

Figure 2: Distribution of patients (number) according to physiological changes observed in the preoperative period. Responders (dark bar) experienced at least 10% increase in peak oxygen uptake or an increase of at least 30 m at the six-minute walk test. Non-responders (grey bars) experienced lesser changes or decreases in peak oxygen uptake or six-minute walking distance. BMI, Body Mass Index; COPD, Chronic Obstructive Lung Disease; VO_{2peak}, peak oxygen uptake.

Figure 3: Effect of Rehabilitation intervention on postoperative pulmonary complications in prespecified subgroups. COPD, Chronic Obstructive Lung Disease; VO_{2peak}, peak oxygen uptake

Table 1: Demographic and clinical characteristics of the study population

Variables	**Usual Care (N = 77)**	**Rehabilitation (N = 74)**	**P value**
Age, y	64 (10)	64 (13)	0.737
Body Mass Index, kg/m^2	24.4 (4.1)	25.0 (4.5)	0.365
Gender Male	50 (65)	41 (55)	0.637
ASA classes 3 & 4	28 (36)	22 (30)	0.394
Chronic Obstructive Lung Disease	27 (35)	30 (41)	0.506
Hypertension	32 (42)	33 (45)	0.744
Diabetes mellitus	11 (14.3)	10 (13.5)	0.890
Coronary Artery Disease	8 (10.4)	10 (13.5)	0.621
Heart Failure	8 (10.4)	8 (10.8)	0.989
Cardiac Arrhythmias	5 (6.5)	3 (4.1)	0.719
History of Stroke	1 (1.3)	6 (8.1)	0.060
Renal dysfunction (eGFR < 60 ml/min)	6 (7.8)	4 (5.4)	0.746
Peripheral Arterial disease	13 (16.9)	16 (21.6)	0.537
Revised Cardiac Risk Index	1 (1-2)	1 (1-2)	0.342
Alcohol	25 (32.5)	15 (20.3)	0.820
Smoking			0.451
Current	39 (51)	28 (39)	
Past	31 (40)	43 (58)	
No	7 (9.1)	4 (5.4)	
Chronic drug treatment			
Beta-blockers	13 (16.9)	11 (14.9)	0.825
ACE inhibitors or AII blockers	11 (14.3)	18 (24.3)	0.149
Statins	8 (10.4)	13 (17.6)	0.243
Steroids	7 (9.1)	10 (13.5)	0.447
Antiplatelets	13 (16.9)	19 (25.7)	0.233
Neoadjuvant chemotherapy	9 (11.7)	6 (8.1)	0.589

Data presented as numbers (%), means (SD) or medians (interquartile 25%-75%).
Data are analyzed by unpaired Student t test, Man-Whitney U test or Chi-square test.
ASA, American Society Association physical status classification; eGFR, estimated glomerular filtration rate. .

Table 2: Laboratory and functional characteristics of the study population

Variables	N	Usual Care (N = 77)	Rehabilitation (N = 74)	P value
Laboratory values				
Hemoglobin, g/L	151	135 (34)	131 (31)	0.567
Creatinine, μm/L	151	80 (27)	76 (22)	0.550
NT-pro BNP, ng/L	121	35 (19-68)	31 (17-80)	0.703
hsCRP, mg/L	121	4.1 (1.7-14.9)	4.8 (2.3-11.5)	0.466
Pulmonary function				
FVC, % predicted	151	104 (21)	102 (18)	0.441
FEV_1, % predicted	151	88 (19)	86 (22)	0.588
$ppoFEV_1$, % predicted	151	65 (14)	63 (17)	0.658
D_LCO, % predicted	151	76 (19)	75 (21)	0.900
$ppoD_LCO$, % predicted	151	64 (17)	62 (19)	0.832
Cardiopulmonary exercise test				
$peakVO_2$, ml/kg/min	151	20.4 (5.7)	19.9 (5.7)	0.557
$peakVO_2$, % pred	151	82 (19)	83 (22)	0.833
Anaerobic threshold, %	136	48 (12)	50 (16)	0.314
V_E/VO_2, L/ml	136	36.6 (5.8)	35.6 (5.2)	0.245
V_E/VCO_2, L/min	136	36.4 (5.2)	36.6 (4.7)	0.731
peakWork Rate, Watts	150	101 (39)	96 (39)	0.421
Heart Rate at rest, beats/min	149	73 (14)	72 (12)	0.757
peakHeart Rate, beats/min	149	138 (21)	136 (20)	0.537
$peakO_2$ pulse, ml/beat	146	10.3 (2.7)	10.3 (3.0)	0.903
$peakPaO_2$, kPa	126	11.3 (3.7)	10.3 (4.1)	0.343
Distance 6MWT,m	151	368 (143)	398 (167)	0.072
peakHeart Rate, beats/min	121	112 (42)	111 (41)	0.604

Data presented as means (SD) or median (interquartile 25%-75%) and analyzed by unpaired Student t test or Man-Whitney U test.
FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in one second; DLCO, Diffusion Capacity for monoxide; ppo, predicted postoperative; NT-proBNP, N-terminal pro B-type natriuretic peptide; hsCRP, High-sensitivity C-reactive Protein; V_E/VCO_2, ventilatory equivalents of expired carbon dioxide; V_E/VO_2, ventilatory equivalents of consumed oxygen; $peakVO_2$ peak, maximum oxygen uptake.

Table 3: Surgical characteristics and perioperative data

Variables	**Usual Care (N = 77)**	**Rehabilitation (N = 74)**	**P value**
Type of Surgery			0.715
Pneumonectomy or bi-lobectomy	17 (22.1)	13 (17.6)	
Lobectomy	46 (59.7)	49 (66.2)	
Segmentectomy	15 (19.5)	12 (16.2)	
Video-Assisted Thoracic Surgery	14 (18.2)	12 (16.2)	0.199
TNM Cancer Stage			0.729
Stage I	40 (52)	33 (44)	
Stage II	27 (35)	28 (38)	
Stage III	10 (12)	13 (18)	
Thoracic Epidural Analgesia	70 (91)	70 (95)	0.534
Duration of surgery, min	161 (54)	160 (63)	0.918
Duration of anesthesia,min	245 (68)	234 (76)	0.347
V_T during TLV, ml/kg PBW	8.0 (1.8)	8.4 (1.9)	0.222
PEEP during TLV, cmH_20	5 (2)	5 (1)	0.589
$P_{Plateau}$ (cmH_20) during TLV	19 (7)	18 (7)	0.376
FIO_2during TLV, %	55 (12)	56 (13)	0.423
V_T during OLV, ml/kg PBW	6.2 (1.4)	6.4 (1.4)	0.348
PEEP during OLV, cmH_20	6 (1)	6 (2)	0.759
$P_{Plateau}$ during OLV, cmH_20	21 (8	22 (8)	0.595
FIO_2 during OLV, %	60 (13)	66 (21)	0.609
Intraoperative Fluids, ml/kg/h	4.7 (1.5)	5.2 (3.5)	0.285
IV fluids on POD1, ml	1187 (682)	1279 (1036)	0.526
Patients requiring NE infusion	14 (18.2)	18 (24.3)	0.427
Patients requiring blood transfusion	2 (2.6)	9 (12.2)	0.126
Hemoglobin, on POD1, g/L	118 (26)	120 (33)	0.614

Data presented as numbers (%) or mean (SD). Analyzed by unpaired by Student t test Chi-square test.

FIO_2, fraction of inspiratory oxygen; NE, Norpinephrine; PaO_2/FIO_2, ratio of partial oxygen pressure to inspiratory fraction of oxygen; PEEP, Positive End-Expiratory pressure; PBW, Predicted Body Weight; POD1, first postoperative day; V_T, tidal volume; OLV, One Lung Ventilation; TLV, two Lung Ventilation.

Table 4: Primary and Secondary Outcomes after lung resection

Outcomes	**Usual Care (N = 77)**	**Rehabilitation (N = 74)**	**P value**
Primary Composite Endpoint	39 (50.6)	27 (36.5)	0.080
30-day mortality	2 (2.6)	2 (2.7)	0.640
Respiratory complications	33 (43)	17 (23)	0.009
ARDS[§]	1 (1.3)	2 (2.79)	0.972
Ventilation (>6h)	5 (6.5)	8 (10.8)	0.512
Pneumonia	15 (19.5)	8 (10.8)	0.209
Atelectasis	28 (36.4)	9 (12.2)	<0.001
Cardiovascular complications	10 (13)	13 (17.6)	0.578
Acute Coronary Syndrome	1 (1.3)	2 (2.7)	0.972
Acute Heart Failure	0 (0.0)	2 (2.7)	0.460
Pulmonary Embolism	1 (1.3)	2 (2.79	0.972
Stroke	0 (0.0)	1 (1.4)	0.984
Arrhythmias	8 (10.4)	11 (14.9)	0.560
Surgical complications			
Re-operation	2 (2.6)	8 (10.8)	0.089
Broncho-Pleural Fistula	3 (3.9)	3 (4.1)	0.714
Wound Infections	4 (5.2)	3 (4.1)	0.957
Renal dysfunction*	4 (5.2)	2 (2.7)	0.731
Length of stay in PACU, hours	25 (10)	17 (7)	<0.001
Unplanned ICU admission	14 (18.2)	10 (13.5)	0.574
Length of stay in hospital, days	9 (7-13)	10 (8-12)	0.223

Data presented as N (%),or median (interquartile 25-75%); Analyzed Chi-square test or Man-Whitney test.

[§]ARDS, Acute Respiratory Distress Syndrome

*Renal dysfunction, postoperative decrease in estimated glomerular filtration rate >25%

Table 5: Changes in Cardio-Pulmonary Exercise test and Six-Minute Walk parameters before and after usual care or rehabilitation

Variables	N	Usual Care (N = 77)	Rehabilitation (N = 74)	P value
ΔpeakVO$_2$ at CPET, ml/kg/min	151	-1.5 (-3.2 to 0.5)	+2.9 (1.1 to +4.2)	0.004
ΔAT at CPET, %	136	-2.5 (- 6.9 to 3.1)	+3 (-2.1 to +8.3)	0.183
ΔV$_E$/VO$_2$ at CPET, L/ml	136	-1.8 (-7.2 to +4.1)	-1.1 (-6.8 to +3.7)	0.845
ΔV$_E$/VCO$_2$ at CPET, L/min	136	-0.6 (-4.8 to +4.2)	-0.7 (-5.9 to +5.2	0.731
ΔpeakWR at CPET,Watts	150	-4 (-9 to + 1)	+8 (+1 to +15)	0.021
ΔpeakHR at CPET, beats/min	149	-9 (-16 to 0)	-5 (-11 to +1)	0.237
Δpeak O$_2$ pulse at CPET, ml/beat	146	+0.1 (-1.9 to +2.3)	+0.9 (-0.9 to +2.5)	0.303
ΔDistance 6MWT, m	148	-2 (-9 to +5)	+66 (+8 to + 125)	0.001
ΔpeakHR 6MWT,beats/min	120	-1 (-10 to + 8)	0 (- 12 to +9)	0.804

Data presented as median (interquartile 25% - 75%) and analyzed by Mann-Whitney U test. CPET, cardiopulmonary exercise testing; 6MWT, six minute walk test; V$_E$/VCO$_2$, ventilatory equivalents of expired carbon dioxide; V$_E$/VO$_2$, ventilatory equivalents of consumed oxygen; peakVO$_2$, peak oxygen uptake; peakWR, peak work rate.

Figure 1

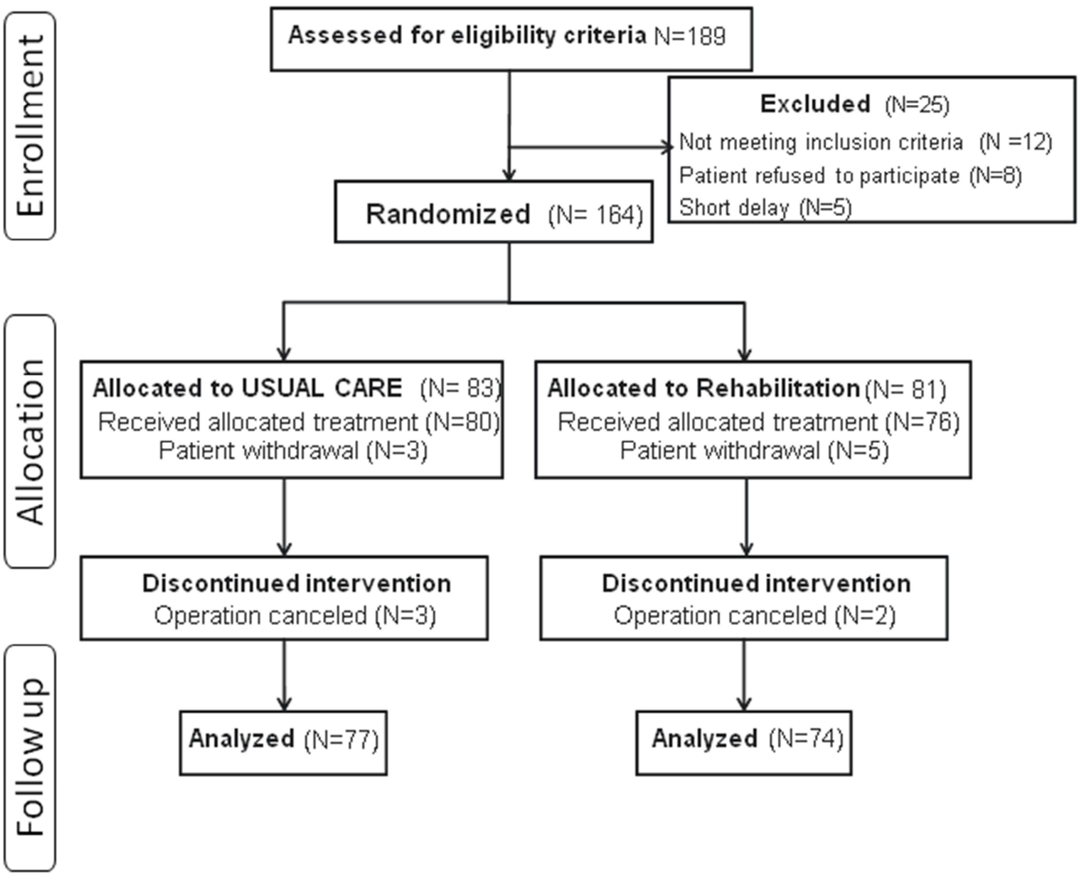

Enrollment
Allocation
Follow up
Assessed for eligibility criteria N=189
Excluded (N=25)
Not meeting inclusion criteria (N =12)
Patient refused to participate (N=8)
Short delay (N=5)
Randomized (N= 164)
Allocated to USUAL CARE (N= 83)
Received allocated treatment (N=80)
Patient withdrawal (N=3)
Allocated to Rehabilitation (N= 81)
Received allocated treatment (N=76)
Patient withdrawal (N=5)
Discontinued intervention
Operation canceled (N=3)
Discontinued intervention
Operation canceled (N=2)
Analyzed (N=77)
Analyzed (N=74)

Figure 2

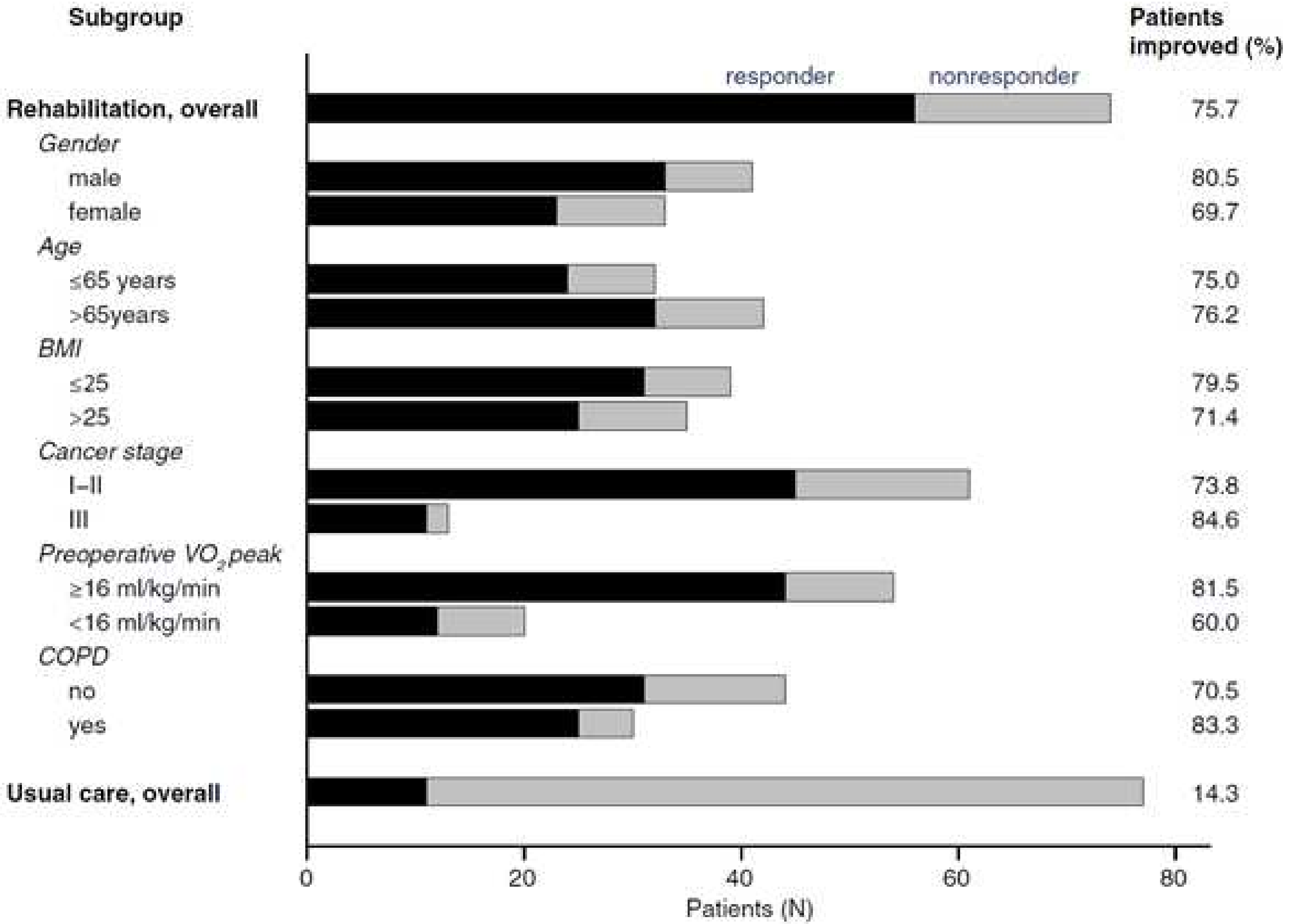
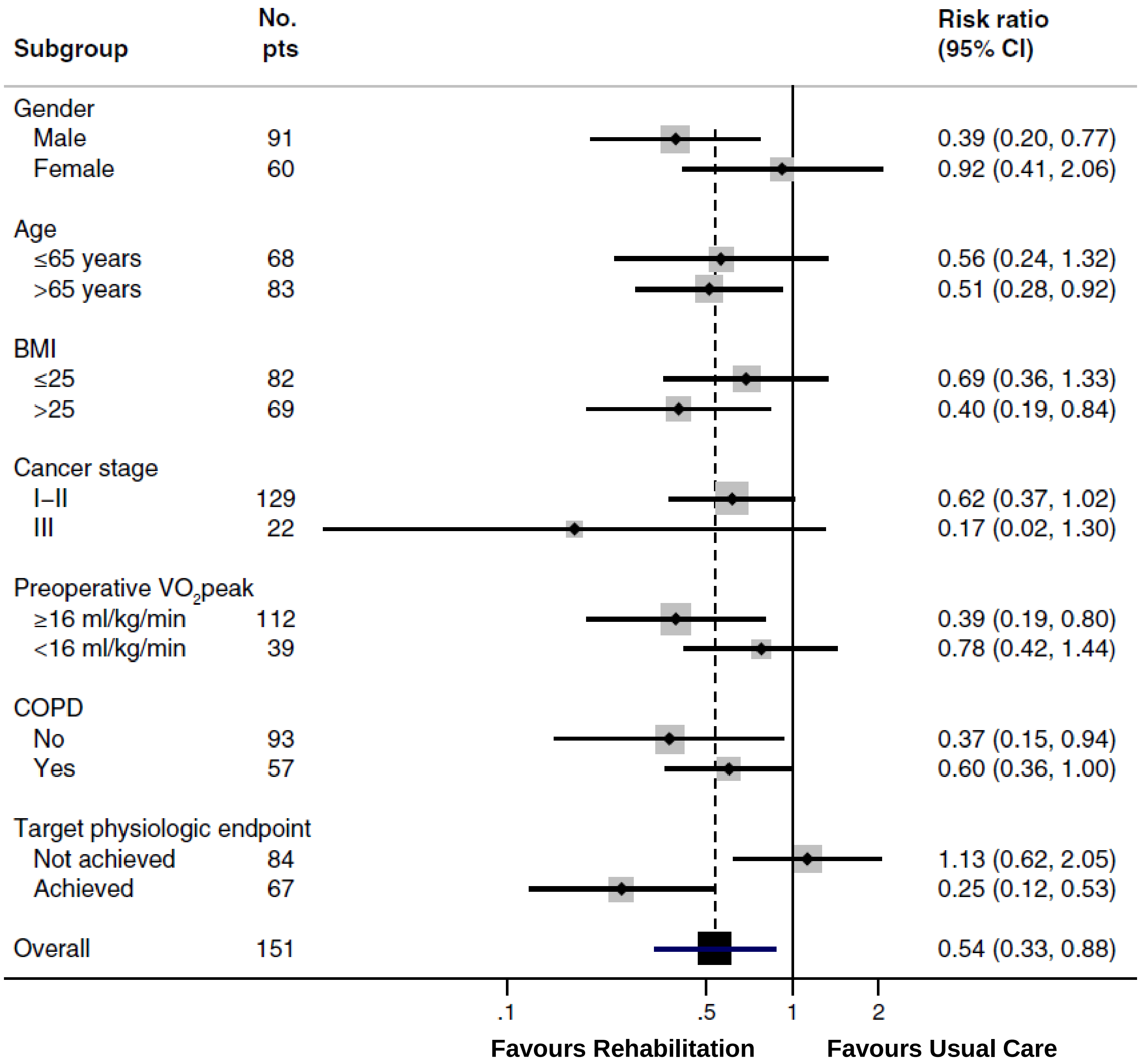

Subgroup
Patients improved (%)
responder
nonresponder
Rehabilitation, overall
75.7
Gender
male
80.5
female
69.7
Age
≤65 years
75.0
>65years
76.2
BMI
≤25
79.5
>25
71.4
Cancer stage
I–II
73.8
III
84.6
Preoperative VO_2peak
≥16 ml/kg/min
81.5
<16 ml/kg/min
60.0
COPD
no
70.5
yes
83.3
Usual care, overall
14.3
0
20
40
60
80
Patients (N)

Figure 3


Subgroup
No. pts
Risk ratio (95% CI)
Gender
Male 91 0.39 (0.20, 0.77)
Female 60 0.92 (0.41, 2.06)
Age
≤65 years 68 0.56 (0.24, 1.32)
>65 years 83 0.51 (0.28, 0.92)
BMI
≤25 82 0.69 (0.36, 1.33)
>25 69 0.40 (0.19, 0.84)
Cancer stage
I–II 129 0.62 (0.37, 1.02)
III 22 0.17 (0.02, 1.30)
Preoperative VO_2peak
≥16 ml/kg/min 112 0.39 (0.19, 0.80)
<16 ml/kg/min 39 0.78 (0.42, 1.44)
COPD
No 93 0.37 (0.15, 0.94)
Yes 57 0.60 (0.36, 1.00)
Target physiologic endpoint
Not achieved 84 1.13 (0.62, 2.05)
Achieved 67 0.25 (0.12, 0.53)
Overall 151 0.54 (0.33, 0.88)
.1
.5
1
2
Favours Rehabilitation
Favours Usual Care