

## Rehabilitation in patients with radically treated respiratory cancer: A randomised controlled trial comparing two training modalities

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### ABSTRACT

**Introduction:** The evidence on the effectiveness of rehabilitation in lung cancer patients is limited. Whole body vibration (WBV) has been proposed as an alternative to conventional resistance training (CRT). **Methods:** We investigated the effect of radical treatment (RT) and of two rehabilitation programmes in lung cancer patients. The primary endpoint was a change in 6-min walking distance (6MWD) after rehabilitation. Patients were randomised after RT to either CRT, WBVT or standard follow-up (CON). Patients were evaluated before, after RT and after 12 weeks of intervention.

**Results:** Of 121 included patients, 70 were randomised to either CON (24), CRT (24) or WBVT (22). After RT, 6MWD decreased with a mean of 38m (95% CI 22-54) and increased with a mean of 95 m (95% CI 58-132) in CRT ( $p < 0.0001$ ), 37m (95% CI -1-76) in WBVT ( $p = 0.06$ ) and 1 m (95% CI -34-36) in CON ( $p = 0.95$ ), respectively. Surgical treatment, magnitude of decrease in 6MWD by RT and allocation to either CRT or WBVT were prognostic for reaching the minimally clinically important difference of 54 m increase in 6MWD after intervention.

**Conclusions:** RT of lung cancer significantly impairs patients' exercise capacity. CRT significantly improves and restores functional exercise capacity, whereas WBVT does not fully substitute for CRT.

**Keywords:** Lung cancer Radical treatment Pulmonary rehabilitation Resistance training Whole body vibration Exercise

### 1. INTRODUCTION

A minority of patients with lung cancer receives a treatment with curative intent, consisting of either radical surgery or definitive radiotherapy, administered either as single modality or combined with platinum-based chemotherapy [11,33,34].

These treatments lead to a decrease in QoL, physical activity and enhance their morbidity [10]. Cancer-related fatigue (CRF), which is frequently reported by cancer patients, is defined as an unusual and persistent sense of tiredness, affecting both physical and mental capacity and is unrelieved by rest [35]. The underlying mechanisms are biological (anaemia, pro-inflammatory cytokines, nutritional and fluid imbalances, muscle wasting), functional (reduced aerobic capacity and decreased activity of daily living) and psycho-behavioural (sleep disorders, anxiety, depression, reduced self-efficacy, sleep disorders, distress and difficulty coping). This may lead to a further muscle deconditioning and disuse atrophy [35], which in turn may aggravate the feeling of fatigue [1].

Oncological rehabilitation has most been extensively studied in breast cancer patients [28]. The beneficial effects of rehabilitation in lung cancer patients, were currently limited to a few randomised trials. These trials showed that patients with lung cancer can improve their exercise capacity, muscle strength and QoL, however the results were not consistent [2,9,29].

Whole body vibration training (WBVT) has been proposed as an alternative training modality for resistance training on multi-gym equipment. WBVT generates vertical sinusoidal vibrations and elicits in short periods reflectory neuromuscular training without much effort [26]. It is assumed that these vibrations evoke muscle contractions via a tonic vibration reflex [32]. In elderly subjects, WBVT improved both aerobic fitness and muscle strength [4].

The present multi-centre trial, acronamed "REINFORCE" (Randomized Exercise trainINg FOr patients with Radically treated respiratory CancEr), was designed to assess the potential beneficial effect of rehabilitation in

lung cancer patients. More specifically, we wanted to address the following questions: (1) does lung cancer therapy affect exercise capacity, muscle strength and QpL; (2) does a 12-week rehabilitation programme improve 6MWD (the primary outcome), maximal exercise capacity, muscle strength and QpL; and (3) are both training methods, WBVT and conventional resistance training (CRT), equally effective in improving 6MWD and other outcome variables?"

## 2. MATERIALS AND METHODS

Sequential patients with stages I—III lung cancer or mesothelioma, candidate for a treatment with curative intent, were solicited by their attending physician of four departments of Respiratory Medicine to participate in the present study. Radical treatment was defined as either radical resection with or without a perioperative platinum-based chemo-(radio) therapy, or definitive thoracic radiotherapy with or without concurrent or sequential platinum-based induction chemotherapy. Patients were between 18 and 80 years and had a baseline haemoglobin level of at least 8 g/dl. Patients with severe cachexia (a decrease of at least 35% pre-morbid weight), co-morbidities interfering with exercise training and contra-indications for WBVT, such as a pacemaker, joint prostheses or recently introduced osteosynthetic material and osteoporotic fractures were excluded. All patients provided written informed consent at inclusion. The study was approved by the Ethics Committee of each participating hospital.

This open multi-centre trial consisted of a prospective observational part I, describing the effect of radical treatment and a randomised part II, analysing the effect of the intervention in those patients who were radically treated. In part I, patients were evaluated before (M1) and after (M2) radical treatment. M2 was assessed within 8 weeks of resection or within 2 weeks after the end of the non-surgical treatment. Patients proceeded only to part II, if their treatment was considered radical and if their post-treatment quadriceps force (QF) was either equal or less than 70% of the predicted normal value or showed a decrease of at least 10% from the baseline value [8]. The randomisation procedure was conducted directly after the M2 evaluation.

Patient randomisation was conducted by a blinded, web-based platform using a minimisation technique with surgery, COPD and centre as stratification variables and with random allocation to either a control group (CON), a CRT-group and a WBVT-group. Patients allocated to CON were discouraged to improve their exercise tolerance with professional help. Patients allocated to either CRT and WBVT received 20 min of aerobic training on the bicycle and treadmill at 70% of the respective maximal workload ( $W_{max}$ ) and speed, observed at M2. Thereafter, CRT-group received resistance training on multigym equipment starting with three sets of eight repetitions for each exercise at 50% one-repetition-maximum (1RM) (Appendix 1). WBVT-group performed exercises on the vibration platform (FITVIBE, Gymna, Belgium), starting with three sets of 30 s for each exercise at 27 Hz. Rehabilitation started within 8 days after randomisation. Patients trained three times a week for 12 weeks, whereafter they were re-evaluated (M3). The investigator was unblinded for the intervention and its evaluation.

The Charlson comorbidity index was used to reflect comorbidities [7]. Spirometry, diffusion capacity (DL,CO) and 6MWD with continuous oxygen saturation monitoring were measured according to existing guidelines and expressed as percentage predicted [5,19,23,30]. A change of at least 54m in 6MWD was considered as the minimally clinically important difference (MCID) [24]. Maximal exercise capacity was assessed by  $W_{max}$  and  $VO_2$  peak using an incremental symptom-limited cycle ergometer test and compared with normal values [18]. A change exceeding 10 W was considered as MCID [25]. QF was assessed using an isometric handheld dynamometer (Microfet; Biometrics, Almere, the Netherlands) attached to a knee perpendicular bank. Extension peak torque was evaluated at 60° of knee flexion, by performing a 5 s maximal isometric contraction. The best out of three attempts was retained. Health-related QoL was measured by the European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire (EORTC QLQ-C30) and more specifically the item physical functioning (PF) [14]. Fatigue was assessed by the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) [6,37]. Pain and dyspnoea were scored with visual analogue scales (VAS) [13].

The adherence of the trial was defined as the percentage of patients completing the intervention. It was calculated as ratio between the number of patients, who did not drop out and the total number of patients who were randomised to the active intervention. The attendance was defined as the percentage of attended sessions of the proposed 36 sessions. At each supervised training session, the study-intervention-related adverse events were recorded.

### Statistical analysis

Baseline patient characteristics are expressed as medians with ranges. The effect of radical treatment was analysed in all participants completing part I (sample 1). The primary endpoint of the trial is the change in 6MWD (m) in those patients who proceeded to part II (sample 2). The null hypothesis is that neither CRT nor WBVT would result in an increase of at least 54 m in 6MWD, the proposed MCID [24]. To refute this, a sample

size of 57 patients (19 patients in each group) is needed ( $\alpha$ : 0.05; power: 0.80) [3]. Assuming a dropout rate of 50% of patients after part I, 114 participants had to be included in the study.

The primary endpoint was analysed by performing an intention-to-treat (ITT)-analysis on sample 2. A per protocol (PP)-analysis on patients who completed part II, defined as sample 3, was also conducted. For the ITT-analysis, missing observations at M3 were predicted by applying multiple imputations using monotone linear regression (Proc MI in SAS 9.3). Linear regression was applied on 50 imputed datasets and the results were combined using SAS Proc Mianalyse to calculate means with 95% confidence intervals (CI) [38]. Bonferroni corrections were applied to correct for multiple pairwise comparisons.

The effect of radical treatment and the combined effect of radical treatment and intervention, both expressed as changes in exercise capacity, muscle strength and QoL, were analysed with the paired- $\Gamma$  test for differences within, and by one-way ANOVA for differences in-between groups. These results were expressed as means with 95%CI (SPSS version 20, Chicago IL). In order to analyse variables predictive for reaching the MCID in 6MWD, the allocation to either CRT or WBVT, together with relevant clinical factors, were combined in a multiple logistic regression model on sample 3. All comparisons were done with the use of a two-sided  $\alpha$  level of 0.05.

### 3. RESULTS

#### 3.1. Patient population

Between January 2009 and February 2012, 121 consecutive patients were recruited (Fig. 1). Eighty-six patients completed part I and constitute sample 1. Before randomisation, 16 additional patients dropped out. Seventy radically treated patients were randomly assigned to either CON ( $n = 24$ ), CRT ( $n = 24$ ) or WBVT ( $n = 22$ ) (sample 2). Of these patients, 21, 20 and 17, respectively, completed the intervention (sample 3). Eighty percent of patients completed the rehabilitation programme. Twelve patients dropped out before M3 because of loss of motivation ( $n = 6$ ), progression of disease ( $n = 3$ ), an acute COPD exacerbation ( $n = 1$ ), an ankle injury unrelated to the intervention ( $n = 1$ ) and worsening of pre-existing low back pain, probably not related to the training ( $n = 1$ ). No study-intervention-related adverse events were observed during part II.

The baseline clinical features of sample 1 and the three intervention groups were well balanced (Table 1a) with 6MWD averaging 75% of the predicted value (Table 1b). Significant differences in patient characteristics between the randomised patients ( $N = 70$ ) and the non-randomised patients ( $N = 51$ ) were not observed, except for median  $\text{VO}_2$  peak (1.40 L/min (0.8-1.8) vs. 1.24 L/min (0.4-2.4) (Supplementary appendix 1).

#### 3.2. Effect of radical treatment ( $\Delta M2 - M1$ ) in sample 1 ( $N = 86$ )

The median interval between M1 and M2 was 13 weeks (6-35). Radical treatment decreased the  $\text{FEV}_1$  with a mean of 0.4 L (95% CI 0.3-0.5) ( $p < 0.001$ ), the  $\text{DL}_{\text{CO}}$  expressed as a % of the predicted value decreased with 16% (95% CI 13-20) ( $p < 0.001$ ) and the 6MWD with a mean of 38 m (95% CI 22-54) ( $p < 0.001$ ) (Table 2). Maximal exercise capacity, QF and QoL were also significantly affected.

#### 3.3. Effect of rehabilitation ( $\Delta M3 - M2$ ) in sample 2 ( $N = 70$ )

The median interval between M2 and M3 was 13 (5-30), 14 (7-36) and 13 weeks (6-37) for CON, CRT and WBVT, respectively. Of the proposed 36 sessions, CRT-patients attended a median of 28 (10-36) and WBVT-patients a median of 23 sessions (0-36) ( $p = 0.09$ ).

With respect to the primary endpoint, 6MWD increased with a mean of 1 m (95% CI -34-36;  $pp = 0.95$ ) in CON, 95 m (95% CI 58-132;  $p < 0.0001$ ) in CRT and 37m (95% CI -1-76;  $pp = 0.06$ ) in WBVT (Table 3, Fig. 2). Fifteen (75%) of the CRT, 5 (29%) of the WBVT and 5 of the CON (24%) patients reached the MCID for 6MWD. The mean change in 6MWD between CRT and CON was the only significant observation ( $p = 0.002$ ). The PP-analysis showed similar results (Supplementary appendix 2).

The mean change in  $W_{\text{max}}$  was significantly increased in both CRT and WBVT (15W (95%CI 6-24);  $pp = 0.002$  in both groups). Seventy-four percent of CRT, 63% of WBVT and 50% of CON reached the MCID for  $W_{\text{max}}$ .

QF significantly increased with a mean of 23 Nm (95% CI 10-36) ( $p = 0.0009$ ) in CRT only.

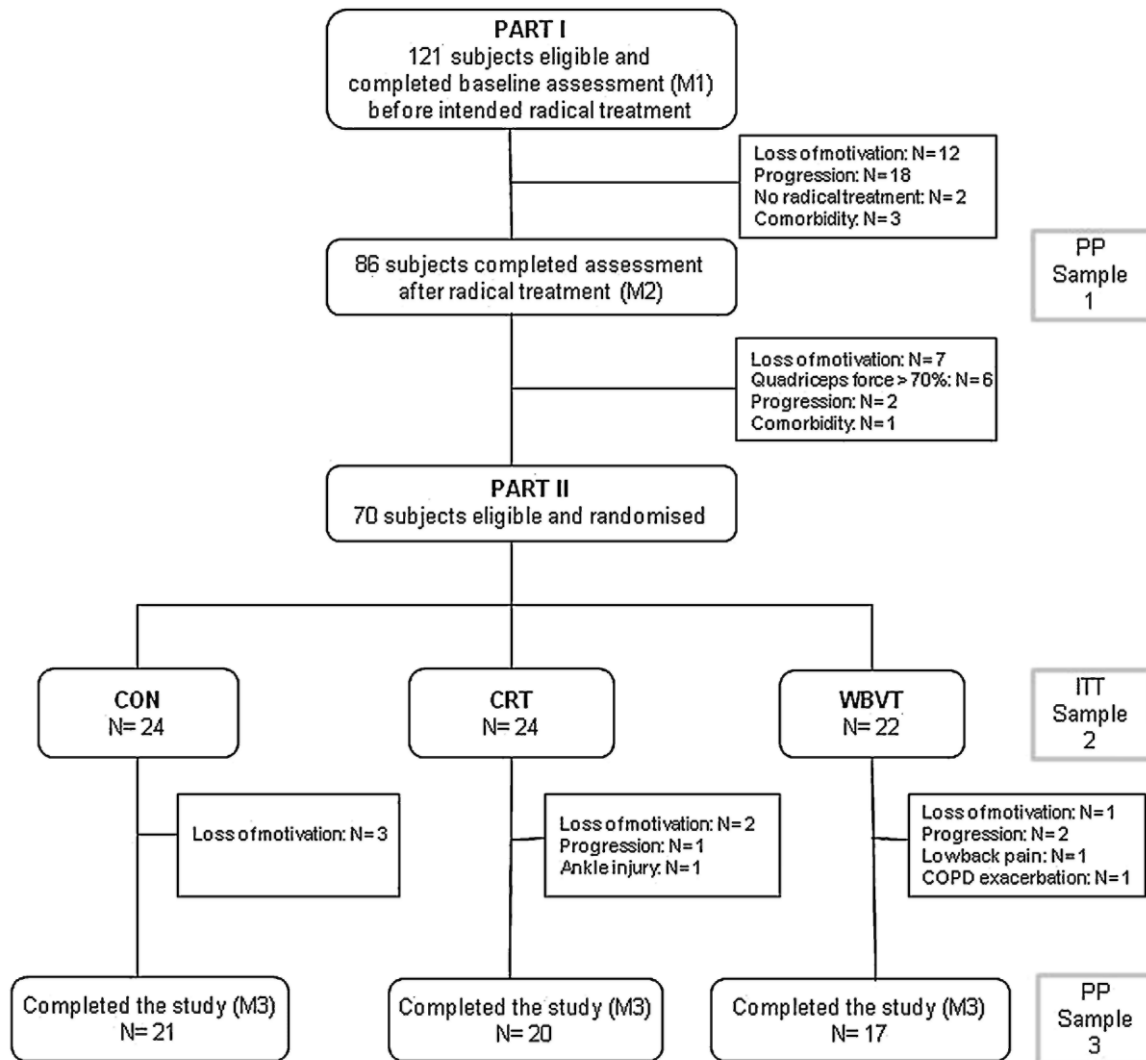
For none of the groups, the score of QLQ-C30 Global and FACT-F changed significantly. However by combining the active intervention groups (CRT and WBVT) a significant increase was observed for both QLQ-C30 Global (+7 points (95% CI 0-14),  $p = 0.04$ ) and FACT-F (-3 points (95% CI -5-0),  $p = 0.04$ ). No differences were observed between the active intervention groups and the control group (Table 4). The score for PF and dyspnoea improved only significantly in WBVT (PF:  $p = 0.04$ ; dyspnoea:  $p = 0.009$ ). The scores for pain did not significantly change after 12 weeks of intervention.

3.4. Overall-effect ( $\Delta M3 - M1$ ) and multiple logistic regression in sample 3 (N = 58)

The 6MWD did not recover in CON-patients, the mean difference between M1 and M3 remaining -46m (95%CI -105-13) ( $p = 0.12$ ). The 6MWD increased with 36 m (95% CI 1-71) in CRT-patients ( $p = 0.048$ ) and 16 m (95% CI -20-52) in WBVT-patients ( $p = 0.35$ ).

Forty percent of COPD patients reached the MCID in 6MWD vs. 45% of patients without COPD ( $p = 0.524$ ). Multiple logistic regression showed that surgical treatment, allocation to either CRT or WBVT and the magnitude of decrease in 6MWD by the radical treatment, were independently associated with reaching the MCID of 6MWD (Fig.3).

Fig. 1. CONSORT flow diagram.



PP: Per Protocol; CON: Control; CRT: Conventional Resistance Training; WBVT: Whole Body Vibration Training; ITT: Intention To Treat  
 PP Sample 1: 86 radically treated patients evaluated at M2; ITT Sample 2: 70 randomised patients; PP Sample 3: 58 patients completed the trial and evaluated at M3.

**Table 1a :** Baseline clinical characteristics of sample 1 and the three intervention groups.

	<b>PART I (N = 86)</b>	<b>CON (N = 24)</b>	<b>CRT (N = 24)</b>	<b>WBVT (N = 22)</b>
Male (N)	64(74.4)	18(75.0)	18(75.0)	15(68.2)
Median age (years)	63 [29-84]	64 [51-79]	63 [29-76]	60 [38-77]
Median BMI (kg/m <sup>2</sup> )	25 [16-45]	26 [18-35]	26 [17-45]	23 [16-29]
Median Charlson Comorbidity Index (points)	3 [0-11]	3 [1-7]	3 [0-10]	3 [0-7]
COPD (N)	36(41.9)	9(37.5)	11(45.8)	9(40.9)
Smoking status (N)				
Never smoker	5(5.8)	1(4.2)	2(8.3)	2(9.1)
Ex-smokers	48(55.8)	12(50)	14(58.3)	12(54.5)
Current smoker	33(38.4)	11(45.8)	8(33.3)	8(36.4)
Pack years (N)	40 [0-100]	40 [0-80]	40 [0-100]	35 [0-70]
Diagnosis (N)				
NSCLC	79(91.9)	23(95.8)	22(91.7)	19(86.4)
SCLC	4(4.7)	1(4.2)	0	3(13.6)
Mesothelioma	3(3.5)	0	2(8.3)	0
Clinical stage (N)				
NSCLC I	44(52.2)	15(62.5)	10(41.6)	12(54.5)
NSCLC II	16(18.6)	2(8.3)	7(29.2)	4(18.1)
NSCLC III	17(22.1)	6(25)	5(20.9)	3(13.6)
NSCLC IV	0	0	0	0
SCLC limited	4(4.7)	1(4.2)	0	3(13.6)
Mesothelioma I-III	3(3.5)	0	2(8.3)	0
Treatment (N)				
Any surgery	45(52.4)	15(62.5)	10(41.6)	13 (59)
Surgery with chemotherapy and/or radiotherapy	21 (24.4)	3(12.5)	8(33.4)	5(22.8)
Lobectomy	50(58)	15(83.5)	12(66.5)	14(77.7)
Pneumonectomy	16(16.6)	3(16.5)	6(33.5)	4(22.3)
Radiotherapy	5(5.8)	1(4.2)	3(12.5)	0
Radiotherapy and chemotherapy	15(17.4)	5(208)	3(12.5)	4(18.2)

**Table 1b :** Baseline assessment of sample 1 and the three intervention groups.

	<b>PART I (N=86)</b>	<b>CON (N=24)</b>	<b>CRT (N=24)</b>	<b>WBVT (N=22)</b>
Median FEV <sub>1</sub> (L)	2.50 [0.79-4.651]	2.40 [1.28-4.181]	2.55 [0.79-4.651]	2.68 [1.39-3.611]
Median DL <sub>CO</sub> (% predicted)	72 [36-1541]	81 [43-154]	70 [36-1071]	64 [42-1011]
Median 6MWD(m)	510 [232-671]	525 [232-671]	490[385-625]	522 [375-645]
Median 6MWD (% predicted)	75 [40-100]	77 [40-100]	73 [60-891]	76 [56-951]
Median VO <sub>2</sub> peak (L/min)	1.4 [0.3-2.5]	1.35 [0.79-2.48]	1.39 [0.69-2.4]	1.34 [0.84-2.23]
Median Wmax (W)	99 [36-226]	90 [36-220]	100[50-226]	100 [56-1781]
Median QF (Nm)	96 [28-227]	97 [28-227]	90[48-1861]	102 [50-184]
Median EORTC QLQ-C 30, PF (points)	87 [13-100]	93 [13-100]	87[20-100]	87 [13-1001]
Median FACT-F (points)	9 [0-421]	7 [4-421]	10 [3-401]	11 [4-291]
Median VAS pain (points)	0 [0-91]	1 [0-9]	010-71	1 [0-9]
Median VAS dyspnoea (points)	0 [0-9]	1 [0-9]	1[0-7]	3 [0-9]

MI: at inclusion: sample 1: subjects assessed at M1 and M2.

CON: Control; CRT: Conventional Resistance Training; WBVT: Whole Body Vibration Training; FEV<sub>1</sub> : Forced Expiratory Volume in 1 s; DL<sub>CO</sub>: Diffusion Capacity; 6MWD: 6 Minute Walking Distance; VO<sub>2</sub> peak: Peak Oxygen Consumption; Wmax: Maximal Workload; QF: Quadriceps Force; EORTC-C30, PF: European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire, Physical Functioning; FACT-F: Functional Assessment of Cancer Therapy-Scale Fatigue; VAS: Visual Analogue Scale. N: Number; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; NSCLC: Non Small Cell Lung Cancer; SCLC: Small Cell Lung Cancer. Numbers between ( ) are percentages; Numbers between [ ] are ranges.

**Table 2 :** Effect of radical treatment (sample 1).

	<b>M1 Mean (95%CI)</b>	<b>M2 Mean (95%CI)</b>	<b>ΔM2-M1 Mean (95%CI)</b>	<b>P value<sup>a</sup></b>
MeanFEV <sub>1</sub> (L)	2.49 [2.31-2.66]	2.09 [1.94-2.24]	-0.4 [0.3-0.5]	0< 0.0001
Mean DL,CO (% predicted)	75 [70-80]	59 [54-63]	-16 [13-20]	0< 0.0001
Mean6MWD(m)	508 [491-525]	471 [451-490]	-38 [22-54]	0< 0.0001
Mean 6MWD (% predicted)	77 [74-79]	71 [68-74]	-5[3-8]	0< 0.0001
MeanVO <sub>2</sub> peak(L/min)	1.39 [1.31-1.48]	1.16 [1.07-1.25]	-0.6 [0.2-0.3]	0< 0.0001
Wmax (W)	105 [96-114]	85 [78-93]	-20[15-25]	0< 0.0001
Mean QF(Nm)	102 [93-111]	90 [83-98]	-11[5-18]	0.001
Mean EORTC QLQ-C 30, PF (points)	83 [79-87]	73 [69-78]	-9 [5-14]	<0.0001
Mean FACT-F (points)	11 [9-13]	13 [11-15]	2 [0-4]	0.02
Mean VAS pain (points)	2 [1,2]	3 [2,3]	1 [0-2]	0.05
Mean VAS dyspnoea (points)	3 [2,3]	3 [3,4]	3 [3,4]	0.03

M1: at inclusion; M2: after radical treatment; sample 1: per protocol sample (N=86), subjects assessed at M1 and M2.

FEV<sub>1</sub> : Forced Expiratory Volume in 1 s; DL,CO: Diffusion Capacity; 6MWD: 6 Minute Walking Distance; VO<sub>2</sub> peak: Peak Oxygen Consumption; Wmax: Maximal Workload; QF: Quadriceps Force; EORTC-C30, PF: European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire, Physical Functioning; FACT-F: Functional Assessment of Cancer Therapy-Scale Fatigue; VAS: Visual Analogue Scale. Numbers between [] as 95% CI.

<sup>a</sup> Paired-Ttest ΔM2-M1.

**Table 3:** Effect of the intervention in 70 randomised patients (sample 2).

	<b>CON (N= 24)</b>				<b>CRT(N=24)</b>				<b>WBVT (N= 22)</b>			
	<b>M2 Mean (95%CI)</b>	<b>M3 Mean (95%CI)</b>	<b>ΔM3-M2 Mean (95%CI)</b>	<b>Pvalue<sup>a</sup></b>	<b>M2 Mean (95%CI)</b>	<b>M3 Mean (95%CI)</b>	<b>ΔM3-M2 Mean (95%CI)</b>	<b>Pvalue<sup>a</sup></b>	<b>M2 Mean (95%CI)</b>	<b>M3 Mean (95%CI)</b>	<b>ΔM3-M2 Mean (95%CI)</b>	<b>Pvalue<sup>a</sup></b>
6MWD (m)	476(434-518)	477(433-521)	1(-33-36)	0.95	448 (406-490)	543(498-589)	95(58-132)	<0.0001	509(465-553)	546(499-594)	37	0.06
VO <sub>2</sub> peak (L/min)	1.2(1.0-1.3)	1.3(1.1-1.4)	0.1 (0-0.2)	0.08	1.1 (1.0-1.3)	1.3(1.1-1.4)	0.1 (0-0.3)	0.02	1.2(1.0-1.3)	1.4(1.2-1.5)	0.2 (0.1-0.3)	0.001
Wmax (W)	81(67-96)	88(73-103)	7(-3-17)	0.1	86(72-100)	101(86-116)	15(6-24)	0.002	90(75-104)	105(89-120)	15(6-24)	0.002
QF (Nm)	86(71-101)	95(79-111)	9(-5-23)	0.2	81 (66-96)	104(88-120)	23(10-36)	0.0009	97(81-112)	105(88-123)	9(-6-23)	0.2
QLQ-C 30	63(51-72)	70(58-81)	8(-1-18)	0.07	61 (48-71)	68(60-72)	8(-2-17)	0.1	62(56-72)	69(60-77)	7(-4-17)	0.2
Global (points)												
QLQ-C 30 PF (points)	77(68-85)	78(69-87)	2(-6-9)	0.7	70(61-79)	76(67-85)	6(-1-14)	0.09	77(68-86)	86(76-95)	8(0-16)	0.04
FACT-F (points)	13(10-16)	12(8-15)	-1 (-5-2)	0.4	14(10-17)	10(7-14)	-3 (-7-0)	0.08	14(10-18)	12(7-16)	-2 (-6-2)	0.3
VAS pain (points)	2(1-3)	3(1-4)	0(-1-1)	0.8	3(2-4)	2(1-3)	-1 (-2-1)	0.2	3(1-4)	2(1-3)	0(-2-1)	0.6
VAS dyspnoea (points)	3(2-4)	2(1-3)	-1 (-2-0)	0.08	3(2-5)	2(1-3)	-1 (-2-1)	0.2	4(3-5)	2(1-3)	-2(-3-0)	0.009

M2: after radical treatment, at randomisation; M3: at end of the intervention.

CON: Control; CRT: Conventional Resistance Training; WBVT: Whole Body Vibration Training; 6MWD: 6 Minute Walking Distance; VO<sub>2</sub> peak: Peak Oxygen Consumption; Wmax: Maximal Workload; QF: Quadriceps Force; QLQ-C30 PF: European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire, Physical Functioning; FACT-F: Functional Assessment of Cancer Therapy-Scale Fatigue; VAS: Visual Analogue Scale.

<sup>a</sup> Linear regression: ΔM3 - M2.

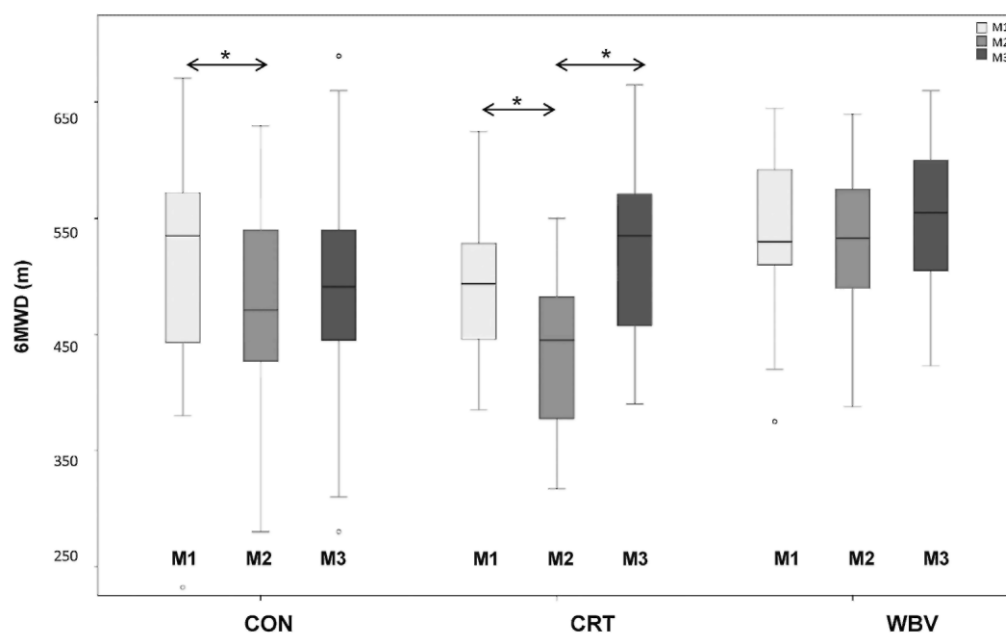
**Table 4 :** Comparison of the effect of the different interventions in 70 randomised patients (sample 2).

	CRT vs. CON		WBVT vs. CON		CRT vs. WBVT		CON vs. CRT and WBVT	
	$\Delta$ M3-M2 Mean difference between groups (95%CI)	Pvalue <sup>a</sup>	$\Delta$ M3-M2 Mean difference between groups (95%CI)	Pvalue <sup>a</sup>	$\Delta$ M3-M2 Mean difference between groups (95%CI)	Pvalue <sup>a</sup>	$\Delta$ M3-M2 Mean difference between groups (95%CI)	Pvalue <sup>a</sup>
6MWD(m)	94(43-145)	0.002	36(-14-87)	0.480	58(5-111)	0.099	-66 (-21-112)	0.009
VO <sub>2</sub> peak (L/min)	0.03 (-0.12-0.19)	1.000	0.08 (-0.08-0.24)	0.903	0.05 (-0.2-0.1)	1.000	-0.06 (-0.19-0.08)	0.815
Wmax (W)	8(-5-21)	0.669	8(-5-21)	0.693	0(-13-13)	1.000	-8 (-20-3)	0.334
QF(Nm)	14(-4-33)	0.390	0(-20-20)	1.000	15(-5-34)	0.417	-7 (-24-10)	0.780
QLQ-C30 Global (points)	-1(-14-12)	1.000	-2 (-16-12)	1.000	1(-13-15)	1.000	1(-10-12)	1.000
QLQ-C30 PF (points)	5(-6-15)	1.000	7 (-4-18)	0.693	-2 (-12-8)	1.000	-6 (-15-4)	0.472
FACT-F (points)	-2 (-7-3)	1.000	-2 (-6-5)	1.000	-1(-7-5)	1.000	2 (-3-6)	1.000
VAS pain (points)	-1(-3-1)	0.873	0(-2-1)	1.000	-1 (-2-1)	1.000	1 (-1-2)	0.704
VAS dyspnoea (points)	0(-2-2)	1.000	-1 (-2-1)	1.000	1(-1-3)	1.000	0(-1-2)	1.000

M2: after radical treatment, at randomisation; M3: at end of the intervention.

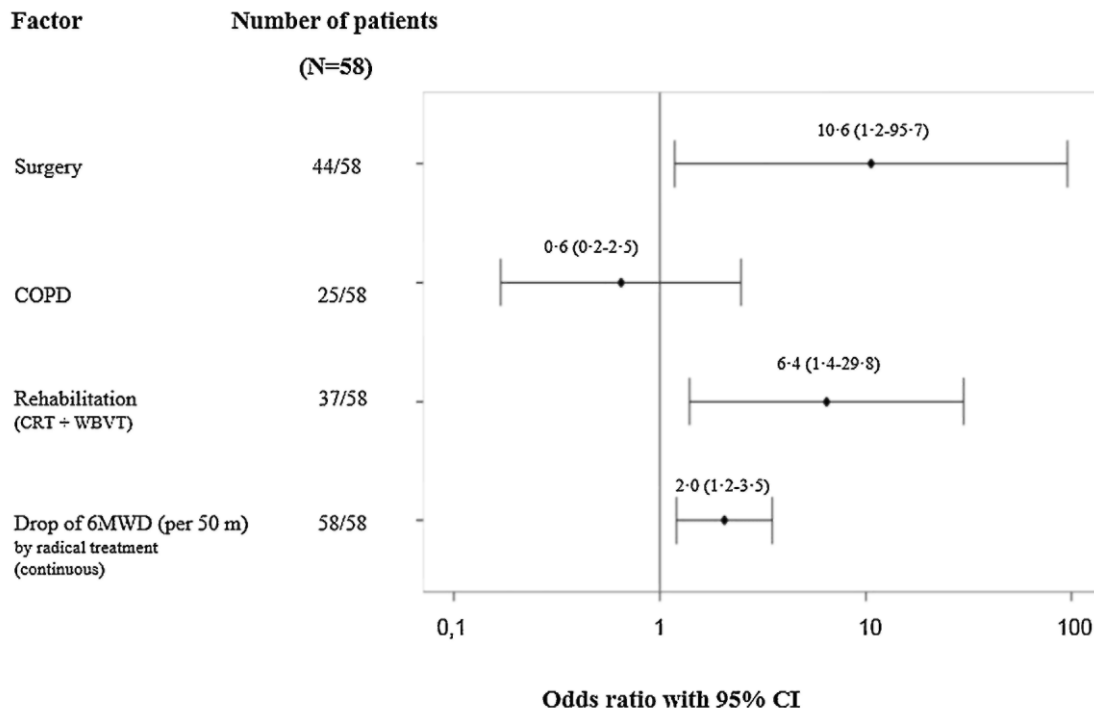
CON: Control; CRT: Conventional Resistance Training; WBVT: Whole Body Vibration Training; 6MWD: 6 Minute Walking Distance; VO<sub>2</sub> peak: Peak Oxygen Consumption; Wmax: Maximal Workload; QF: Quadriceps Force; QLQ-C30 PF: European Organisation for Research and Treatment of Cancer Quality of Life Cancer Questionnaire, Physical Functioning; FACT-F: Functional Assessment of Cancer Therapy-Scale Fatigue; VAS: Visual Analogue Scale. <sup>a</sup> Linear regression:  $\Delta$ M3 - M2; Bonferonni corrected P values.

**Fig. 2.** 6MWD at different time points in participants completing the intervention (sample 3). The mean 6MWD decreased significantly in the control (CON) and the conventional resistance training (CRT) group after radical treatment (M2). After intervention (M3), the 6MWD increased only significantly in the CRT group. The changes over time observed in the whole body vibration training (WBVT) group were not significant.



M1 : at registration; M2: after radical treatment; M3: after intervention; CON: control group; CRT: conventional resistance training group; WBV: whole body vibration group \*: <005

**Fig. 3.** Multiple logistic regression of clinically relevant factors and exercise training on MCID of 6MWD in sample 3. Surgical treatment, comorbid COPD, the magnitude of decrease in 6MWD after radical treatment and the allocation to either CRT or WBVT, were taken in consideration as relevant factors to predict reaching the MCID of at least 54 m in 6MWD after 12 weeks of intervention. Patients, who underwent surgery, were 10 times more likely to reach this MCID. Patients allocated to either conventional resistance training (CRT) or whole body vibration training (WBVT) were 6 times more likely to reach the MCID. Patients, who showed a decrease of more than 50 m in 6MWD after radical treatment were 2 times more likely to reach this endpoint.



MCID: Minimal Clinically Important Difference; 6MWD: 6 Minute Walking Distance; PP: Per Protocol; COPD: Chronic Obstructive Pulmonary Disease; CRT: Conventional Resistance Training; WBVT: Whole Body Vibration Training

#### 4. Discussion

The present study shows that a 12-week rehabilitation programme in patients with lung cancer significantly improves exercise capacity, muscle strength and QpL, after a previously significant decrease of those variables following treatment with radical intent. The improvement in 6MWD was limited to CRT and was not observed with WBVT. Together with surgery as part of the radical treatment, the magnitude of the decrease in 6MWD by the radical treatment was predictive for reaching the change in 6MWD of 54 m.

Surgery, chemotherapy, and radiation therapy are known to decrease exercise capacity, muscle strength and QpL in lung cancer patients [15,17,20,27,28,35,36]. The results of the present study are in line with previously reported data. More importantly, the present study shows that the decrease in 6MWD after radical treatment recovered with CRT and not after usual care. The improvement in 6MWD with CRT largely exceeds the generally accepted threshold of 54 m reported in COPD patients and ranges between the 40 and 145 m improvement observed in previous studies in lung cancer patients [3,14]. The impact of rehabilitation on 6MWD after thoracotomy for NSCLC was previously investigated in two randomised trials. A home-based training programme, initiated after hospital discharge, yielded no effect [2], whereas an ambulatory programme starting four weeks after surgery resulted in a modest improvement of 35 m [29]. Possibly, residual post-operative pain may have interfered with training intensity in that trial. In the present study, rehabilitation was not started before the seventh post-operative week, at which time post-operative pain had almost completely disappeared.

The improvement in 6MWD observed with WBVT (37 m) was neither clinically nor statistically significant. One possible explanation is that the decrease in 6MWD after radical treatment was less pronounced in WBVT than in the other groups, leaving less room for improvement. Another possibility is that WBVT induced an insufficient training effect to improve the 6MWD. Indeed, to increase walking distance, improvement in both muscle strength and muscle power are required, something that is not obtained by performing static exercises on a



vibrating platform [21]. Whether longer sets of dynamic training on WBVT are more effective, remain to be investigated.

The 6MWD improved more in patients who underwent a surgical resection than in non-surgically treated patients. Presumably, the decrease in 6MWD in surgically treated patients was due to immediate effects of immobilisation, pain and ventilatory impairment [12], whereas the decrease in functional exercise capacity caused by chemotherapy and radiotherapy may have been long lasting by attenuating normal cardiovascular and/or skeletal muscle adaptation to exercise training [17]. Theoretically, the significantly longer interval between M1 and M2 in non-surgically treated patients could have resulted in a more pronounced deterioration of the general condition. However, the 6MWD at M1 and M2 was not significantly different for both subgroups. That patients with a low 6MWD after radical treatment were more likely to reach the MCID in 6MWD after the intervention, should be attributed to the availability of a larger room for improvement, as has previously been shown in COPD patients [31].

A MCID for maximal exercise capacity in radically treated lung cancer patients has not yet been uniformly defined. Whereas some claim that an increase of 15% in  $VO_{2max}$  is clinically meaningful, others propose a 10% increase to be clinically relevant in severe deconditioned and post-operative lung cancer patients [12]. In COPD, a 10-W increase in  $W_{max}$  is considered a meaningful increase [25]. Although this MCID was reached in the majority of CRT and WBVT-patients, this increase was not statistically significant compared to CON-patients, because the present study was not powered for that outcome.

In rehabilitation, an improvement in QoL is as important as an increase in physiological outcomes. Conflicting results have been reported on the effect of post-treatment exercise intervention on QoL in patients with lung cancer [14]. In the present study, physical functioning, fatigue and dyspnoea all improved with both training programme, whereas dyspnoea significantly decreased with WBVT. A possible explanation of the beneficial effect of WBVT on dyspnoea is that it promotes aerobic fitness [4].

An important strength of the REINFORCE-study is its multicentre randomised two-tier design with inclusion of consecutive patients, representative for the average cancer population, managed in a department of respiratory medicine. The structured and supervised programme ensured not only the safety of the participants but also assured monitoring of the training intensity. Furthermore, 54 m is a tougher MCID-threshold than the proposed 35 m [22]. The included patients were carefully selected in terms of degree of disability, excluding those who did not need rehabilitation, an increasingly important issue in the light of optimal use of health care resources. Lastly, the results of the ITT-analysis were not significantly different from the PP-analysis.

Weaknesses of this study are its high dropout rate, leading to an already low sample size. The dropout rate is comparable to the one observed in our pilot study [3] and reflects the heterogeneity of the impact of the disease and its treatment on fitness, despite thorough staging and a comprehensive radical treatment. The inclusion of non-surgically treated patients may have diluted the observed effect, as surgical patients benefit most from a rehabilitation programme. However, by including such patients, the present trial addresses a group of patients, representative for the larger community of lung cancer patients. Another weakness is the inclusion of three mesothelioma patients whereas the radical treatment intent in these patients is debatable.

Our data question the use of WBVT as a training modality in a rehabilitation programme for radically treated lung cancer patients. Possibly, the present training modality with WBVT did not induce enough fatigue of the quadriceps muscle.

Additionally, a substantial number of patients did not reach the MCID for 6MWD. It remains a challenge to identify patients who do not respond to a rehabilitative intervention. An analysis of the predictive value of biomarkers is ongoing. Future studies should also address the sustainability of the observed improvements. Interestingly, another group is currently investigating the importance of timing, duration and components of an oncological rehabilitation programme in postsurgical lung cancer patients [16].

## 5. Conclusion

This study allows to conclude that a rehabilitation programme should be proposed to all patients with lung cancer treated with radical intent, who exhibit a certain degree of disability related to the malignancy or its treatment. In these patients, rehabilitation improves and restores their functional and maximal exercise capacity, muscle strength and QoL to at least baseline levels. A vibration platform does not fully substitute for conventional multi-gym equipment.

## Conflicts of interest statement

We declare no conflict of interest for all the authors and that the grant provider had no influence on the design and outcome of the study, nor on its analysis or content of this manuscript.

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### **Appendix A. Supplementary data**

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.lungcan.2015.05.013>

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