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Effects of an exercise intervention for patients with advanced inoperable lung cancer undergoing chemotherapy: A randomized clinical trial

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ABSTRACT

Objective: Exercise can improve treatment-related side effects, quality of life, and function in patients with various types of cancer; however, more evidence is needed for patients with advanced inoperable lung cancer.
Material and methods: We randomized 218 patients with advanced inoperable lung cancer to a 12-week supervised, structured exercise training program (aerobic, strength, and relaxation training) twice weekly versus usual care. Primary outcome was change in maximal oxygen uptake (VO_2 peak). Secondary outcomes were muscle strength, functional capacity, forced expiratory volume in 1 s, health-related quality of life, anxiety, and depression.
Results: There was no significant difference between the intervention and control groups in VO_2 peak. There was a significant improvement in muscle strength. There was also a significant difference between the two for social well-being (Functional Assessment of Cancer Therapy—Lung, FACT-L), anxiety, and depression.
Conclusion: There was a significant reduction in the level of anxiety and depression and a significant increase in all muscle strength outcomes in the intervention group compared to patients randomized to usual care. There was a significant difference between the groups for social well-being. The primary outcome did not show a significant improvement in VO_2 peak. Based on our results, future patients with advanced inoperable lung cancer should be considered for supervised exercise during the course of their disease.

1. Introduction

Lung cancer is the most frequently occurring deadly cancer disease worldwide [1]. The best chance for cure is in the early stage of the disease, when surgery and adjuvant treatment are the preferred option. More than 70 % of patients with lung cancer are inoperable at the time of diagnosis. The survival rate for patients with lung cancer is generally 16–20 % after 5 years but an average of 10–15 months for patients with advanced inoperable lung cancer [2]. Patients with advanced inoperable lung cancer deteriorate physiologically and psychologically throughout the course of the disease due to symptoms, co-morbidities, and side effects from treatment [3]. Patients with lung cancer mainly fear losing function and independence, factors affecting their activities of daily living [4]. During the course of the disease functional capacity declines [5], and this has been demonstrated to impact treatment and survival outcomes [6,7]. Moreover, up to 44 % of patients with lung cancer experience symptoms of depression and anxiety, which is consistently higher than in other cancer types [8], and psychological distress has also been shown to affect anticancer treatment and mortality [9]. Furthermore, patients with lung cancer are often older and do not meet national guidelines for physical activity [10].

Exercise can improve treatment-related side effects, quality of life (QoL), and physical capacity in patients with various types of cancer [11]. However, this evidence does not include patients with advanced inoperable lung cancer, although our research group and others have previously shown that exercise in these patients is safe and feasible [12–14]. At present, seven randomized controlled trials (RCTs) with exercise in patients with advanced inoperable lung cancer have been published [15–21], six of which were evaluated in a recent Cochrane meta-analysis [22]. The analysis concluded that exercise training may improve or avoid the decline in exercise capacity in patients with advanced lung cancer. Due to the heterogeneity between studies, the

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small sample sizes, and the high risk of bias in the included studies, larger, high-quality RCTs are needed to confirm and expand knowledge on the effects of exercise training in this population.

The aim of this study was to evaluate the effect of a physical exercise program comprising 12 weeks of supervised, structured aerobic, strength, and relaxation training twice weekly for patients with advanced inoperable lung cancer [23]. The primary outcome was change in VO_2 peak. We hypothesized that VO_2 peak, one-repetition maximum (1RM), functional capacity (6-min walk test, 6MWT), and health-related quality of life (HRQoL) would increase and the level of anxiety and depression would decrease in patients participating in the intervention.

2. Methods

The EXHALE study (ClinicalTrials.gov identifier: NCT01881906) was a prospective, randomized, controlled intervention trial in patients with advanced inoperable lung cancer, evaluating the effect of a 12-week physical exercise intervention (INT) comprising supervised, structured exercise training (cardio, strength, and relaxation training) twice weekly versus a control group with usual care (CON). The primary outcome was VO_2 peak, while the secondary outcomes were muscle strength, functional capacity, forced expiratory volume in 1 s (FEV1), HRQoL, anxiety, and depression. The study was approved by the Danish Data Protection Agency (file no. 2008-41-2279) and by the Regional Ethics Committee of the Capital Region of Denmark (case no. HA-2008 − 06).

Inclusion criteria were as follows: the subjects were > 18 years of age, had a World Health Organization performance status of 0, 1, or 2 with stage IIIb–IV non-small-cell lung carcinoma (NSCLC) or extensive-disease small-cell lung carcinoma (ED-SCLC), and were undergoing chemotherapy at the Department of Oncology, Rigshospitalet, University of Copenhagen, Denmark. Exclusion criteria included brain or bone metastases, prolonged bone-marrow suppression, anticoagulant treatment, symptomatic heart disease (including congestive heart failure, arrhythmia, or myocardial infarction diagnosed within the previous 3 months), and inability to provide informed written consent. All patients included in the study provided written informed consent.

Patients were screened and recruited between February 2012 and January 2017 at the Department of Oncology, Rigshospitalet, University of Copenhagen. A clinical nurse specialist carried out the screening procedure for inclusion/exclusion. Eligible participants were randomly allocated 1:1 to INT or to CON. Randomization was stratified for sex and lung cancer type (NSCLC or ED-SCLC). The Copenhagen Trial Unit performed the randomization and data management.

2.1. Control group

Individuals in the control group received usual care and treatment as prescribed by their oncologist and were recommended to stay active during their chemotherapy. Patients were offered participation in the intervention after the study period (at least 13 weeks after inclusion).

2.2. Intervention

The intervention comprised supervised group training (physical training and relaxation) carried out twice weekly in groups of 10–12 patients [12,13,24]. Each session lasted 1.5 h and was supervised by a research physiotherapist. The training comprised warm-up exercises, strength training, aerobic training, and stretching. Warm-up exercises consisted of 10 min of stationary cycling, adjusted to 60–80 % of the patient's maximal heart rate (HRmax). Strength training was carried out using the following gym equipment: leg press, chest press, lateral pull down, and leg extension (Technogym™, Italy) [23]. The practical aim of the strength training was to complete three sets of five to eight repetitions, with 70–90 % of 1RM. The exercises were specifically selected to involve the largest possible number of muscle groups in the least number of exercises.

To ensure progression in the strength training, each patient was taught how to carry out the 1RM test and used each machine once every other week, after which their program was adjusted. Aerobic training was carried out as interval training on stationary bicycles. Intensity was equivalent to 70–90 % of each patient's HRmax and lasted approximately 10–15 min. After the training session, 5–10 min were dedicated to stretching the large muscle groups to increase mobility. After each session, patients participated in 15–20 min of progressive relaxation training. We previously showed that the intervention was safe and feasible in this population [12,13].

A clinical nurse specialist or a physiotherapist screened each patient prior to their participation in each physical training session and before the physiological tests. If one of the following criteria was met, the patient was prohibited from exercising/being tested on that day: diastolic blood pressure < 45 mmHg or > 95 mmHg, HRmax at rest > 115 beats/min, temperature > 38 °C, respiratory rate at rest > 30 breaths/min, infection requiring treatment, fresh bleeding, total leukocyte count < 1.0 10^9/L, or platelets < 50 10^9/L. Adverse events that we observed and that patients reported were registered during the entire study period. Most of the patients were undergoing active systemic or local treatment, subjecting them to considerable levels of treatment-related side effects (e.g. nausea, dizziness, and pain) as part of their oncological treatment. In the pre-exercise screening, potential adverse events were registered for INT. For CON, patients were asked about them at the 12-week test or they were registered in the patient record.

2.3. Study outcomes

The primary outcome was change of VO_2 peak between INT and CON from baseline to the end of the study (12 weeks). The VO_2 peak test is the gold standard for assessing cardiorespiratory fitness and includes objective criteria for reaching maximum capacity [25]. VO_2 peak was measured using cardiopulmonary exercise testing on a cycle ergometer (Monark, ergomedic 839E, Sweden). Expired gases were analyzed continuously by a metabolic breath-by-breath analysis and calculated as an average over 15 s using the Jaeger Oxycon Pro spirometer (Germany) [23]. Secondary outcomes were muscle strength measured by 1RM tests using a Technogym™ that included a leg press (lower extremity), chest press (pectoral muscles), lateral pull down (latissimus dorsi), and leg extension machine (quadriceps femoris) [26]. Functional capacity was measured by a 6MWT covering a pre-measured distance of 20 m in compliance with American Thoracic Society criteria [27]. A standard spirometry test was done in a standing position to measure FEV1 using the Jaeger Oxycon Pro spirometer. HRQoL was evaluated with the Functional Assessment of Cancer Therapy—Lung (FACT-L) instrument consisting of two parts, the general (FACT-G) part and the lung-specific (LCS) part. The FACT-G contains four general subscales: physical well-being, social/family well-being, emotional well-being, and functional well-being, while the LCS contains one lung cancer symptom-specific subscale (score range 0–28). A total FACT-L score is obtained by summing the FACT-G score and the LCS score. This ranges from 0 to 136. The trial outcome index for FACT-L was obtained by adding physical well-being, functional well-being, and LCS. Higher scores represented better HRQoL or fewer symptoms [28]. Anxiety and depression were measured using the Hospital Anxiety and Depression Scale (HADS), which is a 14-item questionnaire comprising two scales covering anxiety (HADS-A) and depression (HADS-D). HADS-A (seven items) measures generalized autonomic anxiety and indicates physiological and emotional states characterized by high muscle tension and strong feelings of subconscious and uncontrollable fear or anger. HADS-D (seven items) measures anhedonia, understood as a complete lack of pleasure or the capacity to experience it. Each item is scored on a four-point Likert-type scale [29]. Demographic data were collected using self-developed questionnaires, training diaries, and patient records. All

baseline tests (prior randomization) and 12-week tests were carried out by an exercise physiologist/physiotherapist blinded to the patient's group allocation. All questionnaires were sent to participants prior to the baseline and the 12-week tests.

2.4. Sample size calculations and statistical analysis

The sample size calculation for the primary outcome, VO_2 peak, was based on previous data, where 55 patients achieved an increase in VO_2 peak of 0.85 mL/kg/min (standard deviation = 2.48) after 6 weeks [23]. It was assumed that CON patients would experience a reduction of 0.5 mL/kg/min for VO_2 peak, providing 108 patients (54 in each arm), which is sufficient to achieve a power of 80 % (risk of type 2 error set at 0.20) using a significance level of 0.05 (risk of type 1 error set at 0.05). Based on our previous studies [12,13], we expected an attrition rate of 50 %, making it necessary to include an additional 108 patients, which meant that a sample size of 216 patients was required.

Baseline demographic variables are reported as means and standard deviations or as frequencies and percentages. In the supplementary data, we also report baseline demographic variables stratified by drop-out. The supplementary material also presents a stayer–leaver analysis for the outcomes in order to evaluate whether there is a differential drop out.

All endpoints are reported as means and standard deviations, while change scores for within-group changes are reported as means with corresponding 95 % confidence intervals. To adjust for the differential, drop-out multiple imputation was used. Missing values were imputed based on VO_2 peak, HADS-D, and three FACT subscales (LCS, trial outcome index, and FACT-G). Effect sizes—denoted as small (0.2), medium (0.5), and large (0.8), as suggested by Cohen [[30]]—were calculated as the mean difference divided by the pooled standard deviation and the root mean square error estimated from the general linear model. All analyses were done using Statistical Analysis System 9.4.

The original study protocol [23] specified within-group changes be reported using paired samples t-tests and that the two randomized groups be compared using independent sample t-tests for their change scores. Thus, results would be based on the sample of patients using only two measurements. In the event of differential drop out, the resulting estimates of the intervention effect would be biased. The supplementary data reports the originally planned analyses, in addition to analyses of all outcomes stratified according to adherence.

3. Results

Of the 1126 patients screened for eligibility, 439 (39 %) were excluded on the basis of our exclusion criteria. Among those eligible (n = 687) we randomized 218 patients (32 %), 110 of whom were allocated to INT and 108 to CON. The overall attrition rate of 37 % was due to death (n = 12), refusal to participate (n = 22), disease progression (n = 20), and absence from test (n = 27) (Fig. 1).

All patients were undergoing concurrent systemic treatment, and 67 % received radiotherapy (INT 65 %; CON 68 %) (Table 1). In all, 192 patients had NSCLC (n = 96 in both groups) and 26 had ES-SCLC (n = 14 INT; n = 12 CON). All patients completed the baseline testing. Eighty patients (36.6 %) dropped out and did not perform the 12-week test. Loss to follow-up at 12 weeks was not significantly different between the two groups. Baseline patient demographics and treatment characteristics stratified by drop out are reported in Supplementary data, Table 1a. Mean adherence to the exercise intervention (percentage of the 24 sessions attended) was 44 % (0–95 %).

Compared to those who completed the study (INT, CON), patients who dropped out had a significantly lower VO_2 peak, a significantly higher level of depression, and a significantly lower level on six out of eight subscales in FACT-L (physical well-being, functional well-being, LCS, trial outcome index, FACT-G, and FACT total score). See also Supplementary data, Table 1b.

Table 2 shows the results for aerobic capacity, functional capacity, and muscle strength. There was no significant difference in aerobic capacity VO_2 peak ($p = 0.17$) between INT and CON and a non-significant difference in functional capacity 6MWD ($p = 0.09$). There was a significant difference in strength: leg press ($p = 0.01$), leg extension ($p < 0.01$), chest press ($p < 0.01$), and lateral pull down ($p = 0.04$), with an increase in INT. The effect size ranges from small to large. See Supplementary data Tables 4 and 5 for an analysis of all outcomes stratified according to adherence.

Table 3 presents results for HRQoL, anxiety, and depression. There was a significant difference between INT and CON in the FACT social well-being subscale score ($p = 0.04$) with a decrease in the CON group and a small effect size. There was a significant difference between groups in anxiety ($p = 0.02$) and depression ($p = 0.01$), with a decrease in INT and a small effect size in both.

No serious adverse events were reported, but during the pre-screening process before each supervised training five patients were excluded from the physical training component (one or two exercise sessions out of 24) due to fever, dizziness, pain, and bodily discomfort.

4. Discussion

The EXHALE study did not show a significant improvement in the primary outcome, VO_2 peak. Patients with advanced inoperable lung cancer randomized to a 12-week exercise intervention—supervised, twice-weekly, structured cardio, strength, and relaxation training in a group—had a significant reduction in anxiety and depression levels and a significant improvement in muscle strength compared to patients randomized to CON. Social well-being was maintained in INT compared to a decrease in patients randomized to CON.

The EXHALE study included and randomized 218 patients with advanced inoperable lung cancer, which is considerably more than were included in previous randomized studies examining this patient group [15,16,20]. A recent Cochrane meta-analysis primarily examining the effects of exercise training on exercise capacity in adults with advanced lung cancer identified six RCTs involving 221 participants. The sample sizes in those studies ranged from 20 to 111 participants [22]. The review concluded that larger, high-quality RCTs are needed to confirm and expand knowledge on the effects of exercise training in this population [22].

The data comparison in our study only draws on Dhillon et al. [20] and Edbrooke et al. [21] and not the other studies because one included a small number of patients (n = 24) who were allowed to change allocation after randomization [16], another had baseline data imbalances [15], and the remaining studies used a non-compatible intervention (e.g., inspiratory muscle training) [18,19] or failed to describe the participating patients [17]. Dhillon et al. [20] randomized 112 patients with advanced-stage lung cancer to an 8-week combined home-based and supervised exercise program. Edbrooke et al. [21] also included patients with advanced-stage lung cancer in a home-based 8-week program and randomized 92 patients. Neither of these two studies found a between-group difference in their primary outcomes, fatigue [20] or 6MWT [21], or in any of their other outcomes (e.g. QoL, physical or functional status, and symptoms). The current study did not find a significant difference in the primary outcome, VO_2 peak. A possible explanation for this is that adherence to the intervention was not sufficient to improve the VO_2 peak. Per protocol analysis revealed that patients with an adherence rate > 75 % had a significantly improved VO_2 peak (Supplementary data, Table 2).

Our study identified a significant improvement in muscle strength and a reduction in depression and anxiety. There are two possible explanations for our findings, which differ from those of Dhillon et al. and Edbrooke et al. One reason is that the patients in our study were offered supervised group-based training twice a week and no home-based training. In our feasibility study, we found that patients did not comply

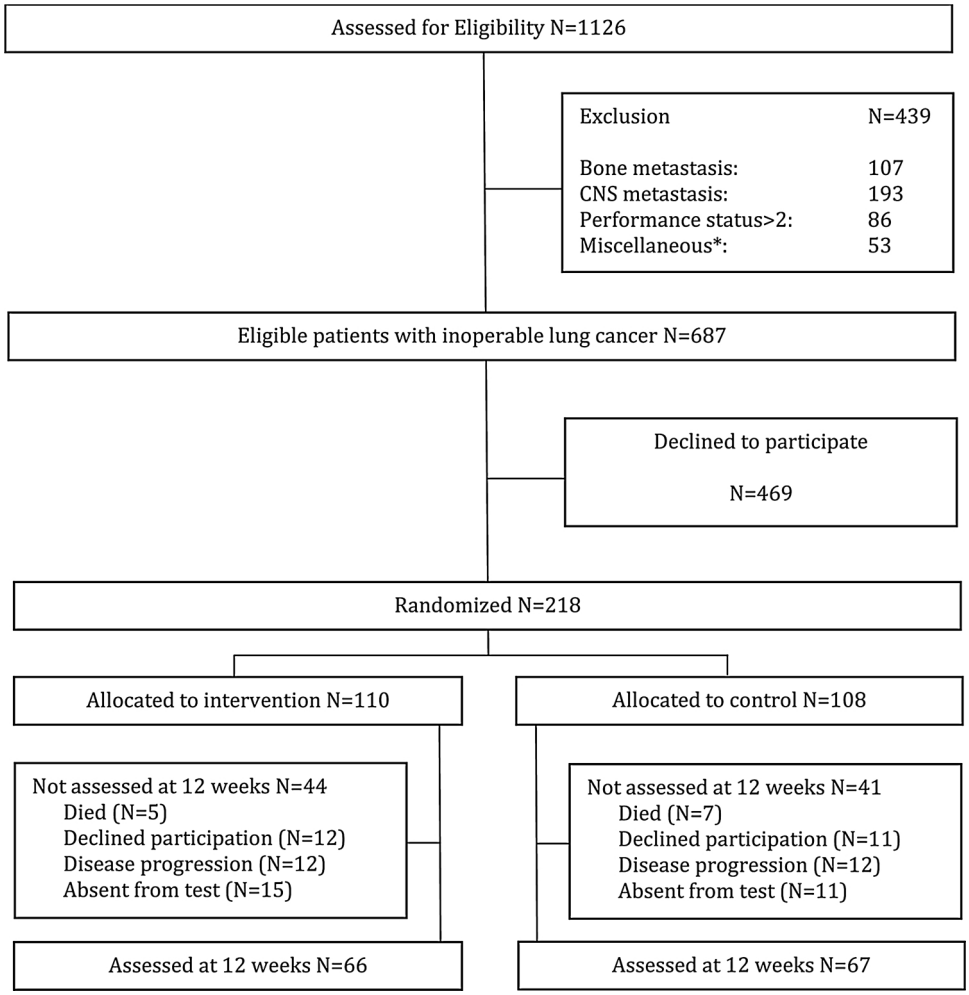

Fig. 1. Flow chart of this study. CNS, central nervous system. *Miscellaneous: prolonged bone marrow suppression, anti-coagulant treatment, symptomatic heart disease (including congestive heart failure, arrhythmia, or myocardial infarction diagnosed within the previous 3 months), and inability to provide informed written consent.

with the home-based component if also offered supervised group-based training [13]. We have previously documented that supervised group-based training was beneficial in producing emotional benefits among patients with advanced inoperable lung cancer [24]and have shown that training among peers serves as a distraction from negative thoughts [31], which might explain our observed decrease in depression and anxiety. The second explanation is that the level of exercise intensity in the interventions differed. Our goal was to reach moderate to high intensity (70–90 % of 1RM and 70–90 % of each patient's HRmax), whereas the aim of Dhillon et al. was to reach at least three metabolic equivalents of task hours per week compared to baseline, which is defined as low intensity. The intensity in the study of Edbrooke et al. was defined as moderate, but their results showed that administering this intensity could be difficult. This assumption is also strengthened when comparing the adherence rate to the intervention in our study (44 %) to that of Dhillon et al. (69 %) [20] and Edbrooke et al. (53 %) [32]. We saw an improvement in secondary outcomes (muscle strength, anxiety, and depression) despite the low adherence, whereas Dhillon et al. [20] and Edbrooke et al. [32] had a higher adherence to their intervention but no improvements.

The between-group improvements in muscle strength and the reduction in the level of depression and anxiety are factors that have a positive impact on treatment adherence and mortality, which is of great clinical importance [6,7,33–35]. A decrease in QoL and functional capacity is ranked high on the list of central concerns among patients with advanced inoperable lung cancer [4]. Patients receiving palliative care have a strong desire to be active and independent for as long as possible, even during the terminal phase [4,24]. In our study we found a significant improvement in muscle strength, which is identified as a determinant of exercise tolerance [36], which means that the patients whose muscle strength improved very likely experience an improvement in their activities of daily living. We have previously shown that supervised group-based training can create group cohesion, autonomy, and social support [24,37]. Improved muscle strength and social well-being may represent an underlying cause for the reduction in depression and anxiety.

This study has some strengths and limitations. To minimize bias, assessors (pre- and post-test) and data analysts were blinded to allocation, but participants and investigators assigned to the intervention groups were aware of the allocations. Patients were strictly informed not to reveal their group allocation to staff doing the testing. Another strength of this study is that it was performed in a hospital setting, reflecting a realistic implementation of the intervention into daily practice. The hospital/rehabilitation systems for cancer patients in the Nordic countries, Germany, and The Netherlands are based on a similar, multidimensional and multidisciplinary understanding of cancer rehabilitation, enhancing the transferability of the results. The low recruitment rate of patients to this study shows that it would be beneficial to develop new methods for recruiting and motivating patients to participate in exercise interventions.

One of the limitations in this study is the 44 % adherence rate to the intervention, which was due mainly to the symptom burden, other

Table 1
Baseline demographic and treatment characteristics of the study population.

			Total	Intervention	Control
			All (n = 218)	All (n = 110)	All (n = 108)
Age mean (SD)			64.4 (8.5)	65.2 (8.2)	63.5 (8.7)
Male n (%)			107 (49.1 %)	55 (50.0 %)	52 (48.1 %)
BMI (kg/m^2) (SD)			24.2 (4.3 %)	24.1 (4.4)	24.2 (4.3)
Smoking, n (%)					
	Current		48 (23.0 %)	19 (17.8 %)	29 (28.4 %)
	Past		150 (71.8 %)	82 (76.6 %)	68 (66.7 %)
	Never		10 (4.8 %)	6 (5.6 %)	4 (3.9 %)
Lung cancer					
	NSCLC, n (%)		**192 (**88.1 %**)**	**96 (87.3 %)**	**96 (88.9 %)**
		Stage IIIa	43 (19.7 %)	20 (18.2 %)	23 (21.3 %)
		Stage IIIB	55 (25.2 %)	26 (23.6 %)	29 (26.9 %)
		Stage IV	86 (39.4 %)	45 (40.9 %)	41 (38.0 %)
		Recurrence (stage 1a-IIIa)	8 (3.6 %)	5 (4.4 %)	3 (2.8 %)
	SCLC, n (%)		**26 (**11.9 %**)**	**14 (12.7 %)**	**12 (11.1 %)**
		LS	6 (2.7 %)	5 (4.6 %)	1 (0.9 %)
		ES	20 (9.2 %)	9 (8.2 %)	11 (10.2 %)
Chemotherapy, n (%)					
	Carboplatin–vinorelbine		7 (3.2 %)	3 (2.7 %)	4 (3.7 %)
	Carboplatin–bevacizumab–vinorelbine		3 (1.4 %)	3 (2.7 %)	0 (0.0 %)
	Carboplatin–etoposide		106 (48.6 %)	53 (48.2 %)	53 (49.0 %)
	Cisplatin–vinorelbine		9 (4.1 %)	7 (6.4 %)	2 (1.9 %)
	Cisplatin–etoposide		3 (1.4 %)	1 (0.9 %)	2 (1.9 %)
	Cisplatin–topotecan		75 (34.4 %)	35 (31.8 %)	40 (37.0 %)
	Pemetrexed		1 (0.5 %)	0 (0.0 %)	1 (0.9 %)
	Erlotinib		1 (0.5 %)	0 (0.0 %)	1 (0.9 %)
	Docetaxel		11 (5.0 %)	8 (7.3 %)	3 (2.8 %)
	Crizotinib		2 (0.9 %)	0 (0.0 %)	2 (1.9 %)
Radiotherapy n (%)			146 (67.0 %)	72 (65.5 %)	74 (68.5 %)
WHO performance status, n (%)					
	0		89 (40.8 %)	46 (41.8 %)	43 (39.8 %)
	1		105 48.2 %)	53 (48.2 %)	52 (48.2 %)
	2		24 (11.0 %)	11 (10.0 %)	13 (12.0 %)
Physical activity level pre-illness, n (%)					
	Sedentary		23 (10.6 %)	12 (10.9 %)	12 (11.1 %)
	Walking or cycling for pleasure		69 (31.7 %)	31 (28.2 %)	36 (33.3 %)
	Regular physical exercise, at least 3 h/week		110 (50.5 %)	58 (52.7 %)	52 (48.1 %)
	Intense physical activity, more than 4 h/week		6 (2.3 %)	4 (3.6 %)	2 (1.9 %)
	Missing		10 (4.6 %)	5 (4.6 %)	6 (5.6 %)

SD, standard deviation; BMI, body mass index; NSCLC, non-small-cell lung carcinoma; LS, limited stage; ES, extensive stage; WHO, World Health Organization.

Table 2
Aerobic capacity, functional capacity, and muscular strength.

Variable	group	Baseline		12 weeks		Δ					Group difference	
		Mean	SD	Mean	SD	Mean change	95 % CI	Within group *P*-value	Effect size	Diff.	95 % CI	*P*
VO_2 peak	Intervention	1.47	0.50	1.49	0.54	0.02	(–0.04 to 0.09)	0.50	0.04	0.05	(–0.04 to 0.14)	0.28
(L/min)	Control	1.35	0.45	1.32	0.40	–0.03	(–0.09 to 0.03)	0.39	–0.06			
VO_2peak	Intervention	20.6	6.7	21.1	7.3	0.5	(–0.3 to 1.3)	0.24	0.07	0.70	(–0.4 to 1.8)	0.23
(mL/min/kg)	Control	18.5	4.9	18.3	4.6	–0.2	(–1.0 to 0.6)	0.62	–0.04			
Leg press, 1RM (kg)	Intervention	72	33	98	99	25	(2–49)	0.03	0.77	29	(5–53)	0.02
	Control	72	36	68	35	–4	(–10 to 2)	0.20	–0.11			
Chest press, 1RM (kg)	Intervention	33	14	36	17	3	(1–5)	< 0.01	0.23	4	(1–6)	< 0.01
	Control	28	12	28	13	–1	(–2 to 1)	0.43	–0.05			
Lat. machine, 1RM (kg)	Intervention	36	13	37	14	1	(–1 to 3)	0.35	0.07	3	(0–5)	0.03
	Control	33	12	31	12	–2	(–3 to 0)	0.03	–0.15			
Leg extension, 1RM (kg)	Intervention	39	14	43	16	4	(2–6)	< 0.01	0.29	4	(1–7)	0.01
	Control	37	14	37	13	0	(–2 to 2)	0.97	0.00			
6-min walk distance (m)	Intervention	475	125	516	109	41	(17–64)	< 0.01	0.33	22	(–5 to 48)	0.11
	Control	443	108	462	107	19	(6–32)	< 0.01	0.18			
FEV1	Intervention	2.30	0.76	2.26	0.72	–0.03	(–0.11 to 0.04)	0.39	–0.05	0.03	(–0.07 to 0.13)	0.57
(L/sec)	Control	2.25	0.64	2.18	0.60	–0.06	(–0.12 to 0.00)	0.03	–0.10			

M, mean change; SD, standard deviation; CI, confidence interval; VO_2 peak, maximal oxygen uptake; 1RM, one-repetition maximum; FEV1, forced expiratory volume in 1 s.
For effect sizes: Cohen's d is determined by calculating as mean change divided by the baseline SD.

Table 3
Health-related quality of life, anxiety, and depression.

Variable	group	Baseline		12 weeks		Δ				Group difference		
		Mean	SD	Mean	SD	Mean change	95 % CI	Within group *P*-value	Effect size	Diff.	95 % CI	*P*
FACT physical well-being	Intervention	21.0	5.6	22.8	4.1	1.8	(0.8–2.8)	< 0.01	0.32	1.0	(–0.8 to 2.8)	0.27
	Control	19.6	6.0	20.4	5.5	0.8	(–0.6 to 2.2)	0.28	0.13			
FACT social well-being	Intervention	23.8	3.4	23.8	3.7	0.0	(–0.7 to 0.7)	0.98	0.00	1.2	(0.1–2.4)	0.03
	Control	23.1	4.1	21.8	5.5	–1.2	(–2.1 to –0.4)	< 0.01	–0.30			
FACT emotional well-being	Intervention	16.7	4.7	18.4	3.9	1.6	(0.7–2.5)	< 0.01	0.35	0.9	(–0.4 to 2.1)	0.17
	Control	17.2	4.9	18.0	4.8	0.8	(0.0–1.6)	0.06	0.16			
FACT functional well-being	Intervention	18.7	6.7	20.0	5.5	1.2	(0.0–2.5)	0.06	0.18	0.3	(–1.5 to 2.0)	0.74
	Control	17.3	6.2	18.2	5.9	0.9	(–0.3 to 2.1)	0.14	0.15			
FACT lung cancer	Intervention	20.1	4.8	21.0	4.4	1.0	(–0.1–2.1)	0.09	0.20	0.5	(–1.2–2.2)	0.56
	Control	18.8	4.5	19.3	5.1	0.5	(–0.8 to 1.7)	0.47	0.10			
FACT trial outcome Index	Intervention	59.7	15.3	63.7	12.3	4.0	(1.2–6.7)	< 0.01	0.26	1.7	(–2.4–5.9)	0.42
	Control	55.6	14.5	57.9	14.1	2.3	(–0.9 to 5.4)	0.16	0.16			
FACT general	Intervention	80.2	16.8	84.9	13.5	4.7	(1.8–7.5)	< 0.01	0.28	3.3	(–0.8 to 7.5)	0.12
	Control	77.1	16.7	78.4	17.1	1.4	(–1.7 to 4.4)	0.38	0.08			
FACT-L total score	Intervention	100.3	20.5	105.9	16.4	5.6	(2.1–9.1)	< 0.01	0.27	4.0	(–1.2–9.3)	0.13
	Control	96.1	19.4	97.7	20.4	1.5	(–2.3–5.4)	0.43	0.08			
HADS anxiety	Intervention	6.1	4.1	4.6	3.5	–1.6	(–2.3 to –0.8)	< 0.01	–0.38	–1.1	(–2.1 to –0.1)	0.03
	Control	5.3	4.4	4.8	3.9	–0.4	(–1.1 to 0.2)	0.18	–0.10			
HADS depression	Intervention	4.0	3.7	3.0	2.7	–1.0	(–1.8 to –0.2)	0.02	–0.26	–1.3	(–2.4 to –0.2)	0.02
	Control	4.3	3.6	4.6	3.2	0.3	(–0.4 to 1.0)	0.38	0.09			

M, mean change; SD, standard deviation; CI, confidence interval; ES, effect size; Diff, difference; FACT, Functional Assessment of Cancer Therapy; HADS, Hospital Anxiety and Depression Scale.
For effect sizes: Cohen's d is determined by calculating as mean change divided by the baseline SD.

appointments at the hospital, and not feeling well. Despite the low adherence rate, patients made remarkable improvements.

Another limitation was the drop-out rate of 38 % in INT and 35 % in CON, which is similar to that in the study of Dhillon et al. [20], indicating that patients with inoperable lung cancer may have difficulties in participating in exercise programs. The main reasons for dropping out were symptom burden, disease progression, physical activity preferences, and death. Patients with lung cancer generally do not have a long exercise history, which is why they may find suddenly embarking on an exercise program to fight a life-threatening disease difficult. Previous studies have emphasized the important role of oncologists and nurses in counselling and recommending exercise to patients, especially patients with no exercise history [38]. Today, it is daily practice for oncologists to recommend exercise to newly diagnosed lung cancer patients.

Finally, another limitation was the lack of long-term follow-up, although patients who wanted to continue exercising in the intervention/group setting could continue participation in the subsequent months. Some patients continued until a few weeks before death.

5. Interpretation

The EXHALE study showed that patients with advanced inoperable lung cancer randomized to a 12-week, twice-weekly exercise intervention experienced a significant reduction in the level of anxiety and depression and a significant improvement in muscle strength compared to patients randomized to usual care. The primary outcome, VO_2 peak, did not show significant improvement. The significant difference in social well-being and improvements in muscle strength indicate a possible link to the reduction in anxiety and depression and should be investigated in future studies. Based on our results, future patients with advanced inoperable lung cancer should be considered for supervised group-based exercise during the course of their disease and treatment. Patients with low VO_2 peak, a higher depression level, or reduced QoL represent a risk group and should be given additional attention in studies.

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Author contributions

Morten Quist and Karl B Christensen had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Declaration of Competing Interest

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2020.05.003.

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