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Early initiated postoperative rehabilitation reduces fatigue in patients with operable lung cancer: A randomized trial

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ABSTRACT

Introduction: Little is known about the optimal amount and timing of exercise strain in concern of the operation wound and with regard improvement of physical function and quality of life (QOL) after surgery for lung cancer. On this background, we decided to investigate the effect of early vs. late initiated postoperative rehabilitation in patients with operable lung cancer on exercise capacity, functional capacity, muscle strength, and QOL.

Methods: The study was designed as a two-armed randomized controlled trial with randomization to either early initiated postoperative rehabilitation (14 days after surgery (ERG)) or a control arm with late initiated postoperative rehabilitation (14 weeks after surgery (LRG)). The primary endpoint was a change in maximum oxygen consumption (VO2peak) from baseline to post intervention 26 weeks following lung resection. Fatigue was measured with EORTC QLQ C30 LC13.

Results: From April 2013 to June 2016, 582 patients with operable NSCLC were screened for eligibility. With 119 patients randomized in the early rehabilitation group (ERG) and 116 randomized to late rehabilitation group (LRG). There was no significant difference from baseline to 26 weeks between ERG and LRG ($p = 0.926$). There was a significant difference from baseline to 14 weeks between groups ($p = 0.0018$). There was a significant difference from 14 weeks to 26 weeks between the two groups ($p < 0.001$). We found no significant differences in QOL but we found a significant difference between ERG and LRG from baseline to 14 weeks in fatigue level in favour of ERG.

Conclusion: This is the first randomized controlled trial to investigate the effects of early vs. late initiated postoperative rehabilitation in patients with lung cancer. There is no difference in the commencement (early vs. late) of a postoperative exercise program for patients with lung cancer on exercise capacity. But to reduce fatigue patients should be recommended to initiate early exercise programs.

1. Introduction

In patients with early stage lung cancer, radical surgical resection is a prerequisite for cure and extended survival [1,2]. In addition, quality of life (QOL) and cancer related fatigue (CRF) will also be affected by the disease and side effects and symptoms of treatment [3–5]. CRF is known as one of the most distressing symptom related to cancer and cancer treatment, causing intense negative effect on functional status and QOL [6–9]. This vicious cycle of functional impairment, reduced physical capacity, increased CRF and reduced QOL is self-reinforcing

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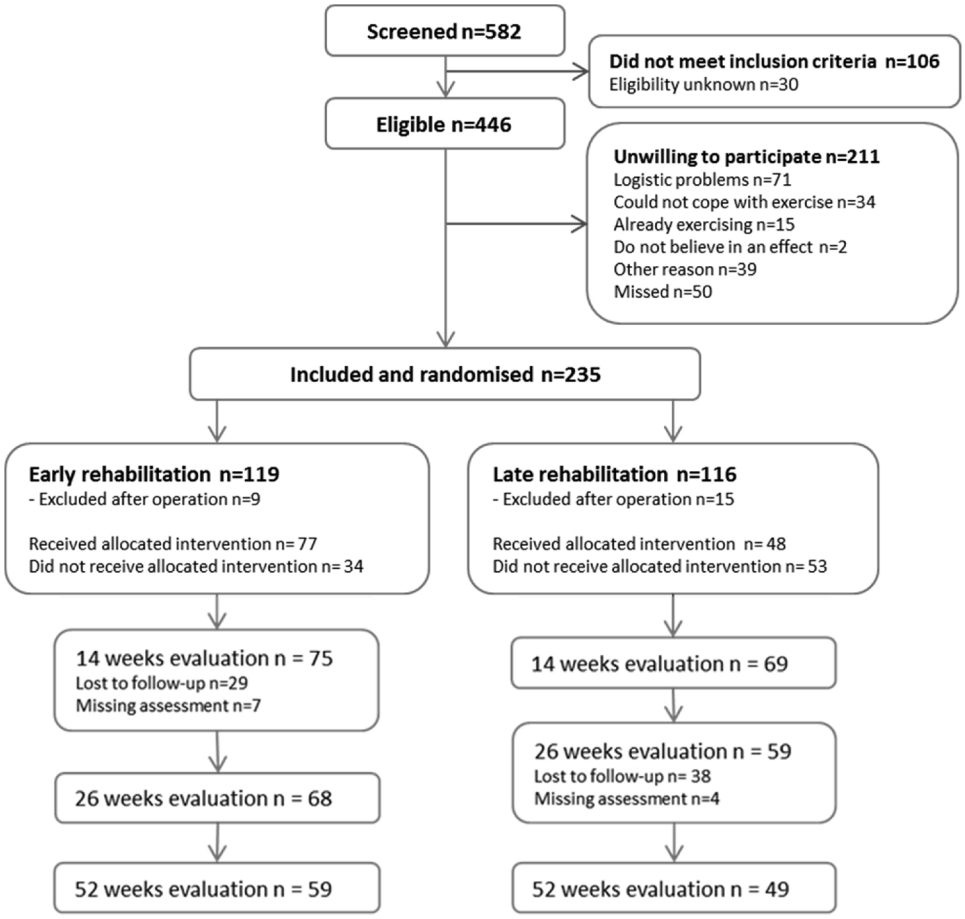

Fig. 1. Flow chart.

and may have negative fatal postoperative consequences if untreated [8,10–15].

Supervised high-intensity exercise training is associated with improved exercise capacity and QOL in most cancer patients [16,17]. Systematic reviews have reported that both pre- and postoperative exercise interventions are safe and feasible for patients with operable NSCLC, and suggest benefits on exercise capacity, symptoms as fatigue and some domains of QOL [18–20]. In addition, exercise training has also been associated with improved muscle strength, reduced post-operative complications and shorter length of stay at hospitalization [21].

American and European guidelines recommend supervised exercise-based pulmonary rehabilitation for patients with comprised lung function following lung resection for lung cancer [22], and also recommend early pre- and post-operative pulmonary rehabilitation [23]. However it is an open question which exercise program should be preferred. Therefore, in clinical practice there is great variation in rehabilitation recommendations.

Fast-track rehabilitation following surgery for lung cancer is safe and effective [24], but it is unknown how early high intensity exercise training should be initiated following lung surgery. Furthermore, knowledge about the effects of training on tissue healing [25] in patients operated for lung cancer is needed. The PROLUCA pilot study showed that postoperative rehabilitation, including supervised high intensity exercise training, is safe and feasible when initiated two weeks after lung surgery [26]. This is in accordance with the encouraging findings in other trials both with focus on lung surgery [27] and lung surgery and/or chemotherapy and/or radiotherapy [28]. Improvements in functional capacity (six-minute walk distance), work performance (ergometer work load) and reduced heart rate at rest after 28 days were demonstrated [27,28]. Little is known about the optimal amount of exercise strain on the surgical wound and the resulting improvement of physical function and QOL. In other populations e.g. patients with myocardial infarction early initiated exercise training in the acute phase (six hours to seven days) has shown to result in greater benefits on exercise capacity compared to exercise training interventions initiated in later treatment phases (7–28 days or ≥ 29 days) [29].

On this background and with the results from our feasibility study [26] we decided to investigate if the effect of early (14 days) vs. late initiated (14 weeks) postoperative rehabilitation in patients with operable lung cancer was more effective on exercise capacity, functional capacity, muscle strength, CRF and QOL.

2. Methods

2.1. Trial design

The study was designed as a two-armed randomized controlled trial with randomization in a 1:1 ratio to either an experimental arm consisting of early initiated postoperative rehabilitation or a control arm with standard late initiated postoperative rehabilitation.

2.2. Participants

Patients above 18 years of age with pathologically verified NSCLC stage I-IIIa assigned for curative intended surgery, or patients with strong clinical suspicion of lung cancer referred for explorative surgery, performance status 0–2 with respiratory and cardiac status allowing surgery in accordance with national and international guidelines [30,31]. Participants had also to be a resident in the City of Copenhagen or a surrounding municipality and able to read and understand Danish.

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

	Early group (n = 110)	Late group (n = 101)
Age	66	65
Female	64 (58)	53 (52)
BMI	25.51 (5.0)	25.21 (5.2)
Smoking status		
Current	20 (18)	19 (18)
Past	77 (70)	70 (69)
Never	13 (12)	12 (13)
Co-morbidities**		
COPD	13	16
Diabetes mellitus	13	9
Hypertension	35	32
Surgery type		
VATS	88(76)	84(83)
Open surgery	22 (19)	17 (16)
Resection degree		
Lobectomy	100 (85)	94 (84)
Pneumonectomy	2 (3)	3 (3)
Bilobectomy	4 (3)	3 (3)
Wedge resection	2 (3)	1 (6)
Segment resection	2 (2)	0
Diagnosis		
NSCLC	110	101
Pathologic stage of lung cancer		
IA	28 (25)	23 (21)
T1aN0MO	*20*	*14*
T1bN0M0	*8*	*9*
IB	37 (32)	33 (28)
T2aN0M0	*37*	*33*
IIA	11 (9)	13 (10)
T2bN0M0	*5*	*4*
T1aN1M0		*3*
T1bN1M0	*2*	*2*
T2aN1M0	*4*	*4*
IIB	17 (14)	11 (11)
T2bN1M0	*2*	*4*
T3N0M0	*15*	7
IIIA	16 (13)	19 (16)
T1aN2M0		
T1bN2M0	*1*	*1*
T2aN2M0	*5*	*2*
T2bN2M0		*4*
T3N1M0	*4*	*4*
T3N2M0	*4*	*4*
T4N0M0	*1*	*4*
T4N1M0	*1*	
IIIB	1 (1)	2 (3)
T4N0M0		*2*
T4N2M0	*1*	
Adjuvant chemotherapy		
Yes	54 (49)	50 (49)
No	56 (51)	51 (51)

Data are presented in means and (standard deviations) or Numbers and (percent). *The Danish Health Authorities alcohol recommendations; increased risk of diseases > 14 units for women and > 21 drinks for men per week. **One person can have more than one disease/condition.
Abbreviations: BMI, Body Mass Index; COPD, chronic obstructive lung disease; VATS, video-assisted thoracoscopic surgery; TNM stage 7th edition.

2.3. Study settings

Study recruitment lasted between April 2013 and June 2016. Potential patients were identified and screened for eligibility, and hereafter contacted to be informed of the study by the research coordinators at the referral departments of pulmonary medicine at Bispebjerg and Gentofte Hospitals. After referral to surgery at the Department of Cardiothoracic Surgery, Rigshospitalet, University of Copenhagen, the subjects were again contacted by telephone and once more informed of the purpose and design of the study. Written informed consent was subsequently obtained from all and baseline assessment prior to surgery was performed at Copenhagen Centre for Cancer and Health, Copenhagen, Denmark.

2.4. Interventions

The postoperative rehabilitation was the same in both intervention groups and consisted of a supervised 12-week rehabilitation program containing 24 group-based exercise sessions, three individual counseling sessions, and three group-based lessons in health-promoting behavior. If the participants had special needs in terms of smoking cessation, nutritional counselling or patient education, this was offered too. The postoperative physical exercise consisted of an individually prepared supervised strength exercise and a group-based cardiovascular exercise twice a week (60 min/sessions) on non-consecutive days for 12 weeks, a total of 24 sessions. The intervention is described in detail in Sommer et al 2016 [26].

2.5. Outcomes

The primary endpoint was a change in maximum oxygen consumption (VO_2peak) from baseline to post intervention; for the experimental group approximately 26 weeks following lung resection and for the active comparator group approximately 26 weeks following lung resection. VO_2peak was evaluated at baseline (preoperative inclusion the day before surgery), after 14 weeks (end of early initiated rehabilitation intervention and beginning of late initiated rehabilitation), 26 weeks (end of late initiated rehabilitation) and 52 weeks follow-up following surgery. VO_2 peak was evaluated by an incremental test using an electromagnetically braked cycle ergometer (Lode Corival Ergometer©) and direct measures of respiratory gases (JAEGER MasterScreen CPX©). The pedaling began at 7 W and resistance increased after a predefined 10 W ramp protocol until exhaustion or a symptom-limited VO_2peak was achieved.

Secondary endpoints included several patient-reported outcomes (PROs) and physiological measurements evaluated at baseline (preoperative inclusion the day before surgery), after 14 weeks (end of early initiated rehabilitation intervention and beginning of late initiated rehabilitation), 26 weeks (end of late initiated rehabilitation) and 52 weeks follow-up following surgery. The PROs included the European Organization for Research and treatment of Cancer (EORTC) Quality of life Questionnaire (QLQ) C-30 plus the lung cancer specific part assessing symptoms and side effects EORTC-LC13 PROs, the Functional Assessment of Cancer Therapy – Lung (FACT-L) scale assessing HRQoL, the 36-Item Short Form Health Survey (SF-36) assessing general well-being, the Hospital Anxiety and Depression Scale (HADS) assessing psychological well-being, the Multidimensional Scale of Perceived Social support (MSPSS) assessing social support, The distress thermometer and Physical activity scale ver. 2. The physiological measurements included functional capacity assessed by six-minute walking distance (6MWD) test, lung capacity assessed by spirometry, and muscle strength chest and leg press measured by one repetition maximum (1RM). In addition a change in maximum oxygen consumption (VO_2max) registered from baseline to 52 weeks following surgery was a secondary outcome.

All PROs and physiological variables were measured at baseline (preoperative inclusion the day before surgery), after 14 weeks (end of early initiated rehabilitation intervention and beginning of late initiated rehabilitation), 26 weeks (end of late initiated rehabilitation) and 52 weeks follow-up. In addition, the 6MWD, lung capacity and FACT-L were assessed two and eight weeks after baseline.

2.5.1. Data management and ethical considerations

Trial data consisting of questionnaires, physiological variables and medical data gathered from the participants' medical records were entered into a database, OpenClinica, hosted by the Copenhagen Trial Unit (CTU), Rigshospitalet, Copenhagen, Denmark. Data management was approved by the Danish national authority: Datatilsynet, with file

Table 2
VO_2Peak.

Group	N	Mean	SD	N	Mean	SD	Δ change	95% CI	Pr > |t|	Diff.	95% CI	P
Baseline 14 Weeks												
Early	108	1590	435	69	1503	421	−66	−124 to −7	0.027	−139	−224 to −54	< 0.001
Late	98	1591	526	63	1394	432	−202	−263 to −141	< 0.001			
14 weeks 26 Weeks												
Early	68	1510	407	56	1503	401	17	−34 to 68	0.504	−142	67 to 214	< 0.001
Late	63	1472	445	45	1641	488	159	−104 to −214	< 0.001			
Baseline 26 Weeks												
Early	108	1612	420	59	1536	462	−46	−104 to 12	0.119	−3	−88 to −82	0.945
Late	98	1687	521	47	1626	462	−43	−105 to 18	0.167			
Baseline 52 Weeks												
Early	108	1583	419	50	1510	387	−44	−119 to 31	0.244	11	−96 to 119	0.834
Late	98	1721	515	44	1639	474	−56	−133 to 22	0.158			

VO_2peak is expressed ml O_2/min, Abbreviations: SD, standard deviation; CI, confidence interval.

Table 3
6MWT and FEV1.

Group	N	Mean	SD	N	Mean	SD	Δ change	95% CI	Pr > |t|	Diff.	95% CI	P
6MWT												
	Baseline			**14 Weeks**								
Early	108	498	102	69	516	91	24	10 to 36	< 0.001	−22	−41 to −2	0.029
Late	98	519	110	63	517	116	2	−12 to −16	0.786			
	14 weeks			**26 Weeks**								
Early	69	525	88	54	527	87	4	−3 to 12	0.260	19	8 to 30	< 0.001
Late	68	436	104	50	559	99	23	15 to 31	< 0.001			
	Baseline			**26 Weeks**								
Early	108	501	98	59	524	85	28	16 to 41	< 0.001	3	−15 to −21	0.751
Late	98	524	119	53	549	108	25	12 to 38	< 0.001			
	Baseline			**52 Weeks**								
Early	108	508	86	51	526	88	26	12 to 40	< 0.001	10	−11 to 31	0.345
Late	98	542	93	45	557	95	16	1 to 31	0.034			
FEV1												
	Baseline			**14 Weeks**								
Early	108	2.4	0.6	69	2.25	0.65	−0.15	−0.25 to −0.1	< 0.001	−0.15	−0.25 to −0.05	0.004
Late	99	2.55	0.75	67	2.25	0.65	−0.3	−0.25 to −0.1	< 0.001			
	14 weeks			**26 Weeks**								
Early	70	2.25	0.6	57	2.3	0.55	0	0 to 0.05	0.235	0.05	0 to 0.1	0.234
Late	69	2.3	0.65	54	2.35	0.65	0.05	0 to 0.1	0.005			
	Baseline			**26 Weeks**								
Early	108	2.5	0.6	62	2.35	0.55	−0.15	−0.2 to −0.05	< 0.001	0.15	0.05 to 0.25	0.012
Late	99	2.65	0.75	60	2.35	0.65	−0.25	−0.35 to −0.2	< 0.001			
	Baseline			**52 Weeks**								
Early	108	2.4	0.65	60	2.3	0.6	−0.15	−0.2 to −0.05	< 0.001	0.1	0 to −0.25	0.028
Late	99	2.7	0.7	55	2.4	0.7	−0.25	−0.35 to −0.2	< 0.001			

6MWT is expressed in meter, FEV1 is expressed in max literO2 expired in the first second, Abbreviations: SD, standard deviation; CI, confidence interval.

nr: 30-0879 (I Suite nr.: 02,326). The trial was approved by the Danish ethical committee for research in the Capital Region of Denmark with registration number: H-3-2012-028.

The trial is also registered in ClinicalTrials.gov Protocol Registration system under Identifier: NCT02439073

2.6. Sample size

With a two-sided 5% significance level, a power of 80%, and with the smallest clinical relevant difference set at 2 mL $O_2 \cdot kg^{-1} \cdot min^{-1}$, a sample size of n = 128 participants were needed to complete the intervention. Given an anticipated high dropout rate of 40% within the first year of follow-up, the number of participants to be included was estimated to be 213. In addition 10% were anticipated to be excluded following surgery due to either inoperability, metastatic disease or no malignancy for which reason the number of patients to be included increased to 235. The change in VO_2peak was assumed to have a standard deviation of 4.0 mL $\cdot$ $kg^{-1} \cdot min^{-1}$ as observed in previous research [32,33].

2.7. Randomization

Following completion of baseline assessments, participants were sequentially numbered, stratified by type of surgery (video-assisted thoracic surgery (VATS) versus thoracotomy surgery) and randomly allocated by a computer at the CTU (equal weight 1:1) to one of the two study groups. CTU generated the allocation sequence of each participant on request of an Investigator of the trial. The same investigator assigned the participants to one of the two intervention groups.

2.8. Blinding

Assessors and data analysts were blinded to allocation, yet participants and investigators assigning to the intervention groups were aware of the allocations. Participants were strictly informed not to reveal their group allocation to the test personnel.

2.9. Statistical analysis

An intention-to-treat (ITT) analysis including all randomized participants was done. The primary analysis was a between-group difference at completion of early initiated postoperative rehabilitation and late

Table 4
EORTC C30 - baseline to 26 weeks: Score range 0–100 A high score for a functional scale represents a high / healthy level of functioning, a high score for the global health status / QoL represents a high QoL, but a high score for a symptom scale / item represents a high level of symptomatology / problems.

Variable	Group	N	Mean	SD	N	Mean	SD	Δ change	95% CI	Pr > |t|	Diff.	95% CI	P
EORTC Global Health status	Early	95	67	22	54	72	21	7	1 to 13	0.022	−3	−11 to 6	0.507
	Late	91	66	22	53	76	19	10	4 to 16	0.002			
EORTC Physical Functioning	Early	99	88	12	57	84	15	−2	−5 to 2	0.330	−1	−6 to 4	0.693
	Late	93	84	20	55	84	18	−1	−4 to 3	0.697			
EORTC Role Functioning	Early	98	82	24	56	84	26	−2	−4 to 9	0.461	0	−9 to 10	0.925
	Late	91	80	28	53	84	25	2	−5 to 9	0.564			
EORTC Emotional Functioning	Early	97	73	21	56	85	16	12	8 to 16	< 0.001	1	−5 to 7	0.749
	Late	92	71	24	54	83	20	11	7 to 15	< 0.001			
EORTC Cognitive functioning	Early	97	86	18	56	85	17	2	−3 to 6	0.485	−1	−8 to 5	0.729
	Late	92	79	22	54	83	21	3	−2 to 8	0.250			
EORTC Social Functioning	Early	97	92	16	56	91	18	1	−4 to 6	0.726	2	−5 to 9	0.595
	Late	90	91	17	52	90	20	−1	−6 to 4	0.689			
EORTC Fatique	Early	98	29	26	56	27	23	−2	−8 to 4	0.506	−3	−11 to 6	0.551
	Late	91	28	22	53	26	21	1	−6 to 7	0.850			
EORTC Nausea and vomiting	Early	97	2	7	56	4	14	0	−3 to 4	0.904	−3	−8 to 2	0.233
	Late	91	2	7	53	6	16	3	0 to 7	0.079			
EORTC Pain	Early	99	12	22	57	13	18	−1	−7 to 5	0.681	−1	−10 to 7	0.720
	Late	92	15	23	54	14	21	0	−6 to 6	0.919			
EORTC Dyspnoea	Early	96	14	21	56	26	23	9	2 to 16	0.013	−8	−18 to 2	0.114
	Late	90	15	23	52	34	28	17	10 to 24	< 0.001			
EORTC Insomnia	Early	97	27	30	55	22	26	−8	−15 to −2	0.016	6	−3 to 16	0.211
	Late	91	36	34	53	21	26	−14	−21 to −7	< 0.001			
EORTC Appetite loss	Early	98	15	22	54	4	15	−11	−17 to −5	< 0.001	−10	−19 to −1	0.035
	Late	91	13	25	53	11	25	−1	−8 to 5	0.729			
EORTC Constipation	Early	98	15	22	55	5	12	−8	−12 to −3	< 0.001	−7	−14 to −1	0.018
	Late	92	10	19	54	9	21	0	−5 to 4	0.955			
EORTC Diarrhoea	Early	97	10	19	56	7	15	−4	−8 to 1	0.094	2	−4 to 9	0.524
	Late	90	10	19	52	4	13	−6	−11 to −1	0.013			
EORTC Financial difficulties	Early	96	4	14	56	8	18	3	−1 to 6	0.103	1	−4 to 6	0.660
	Late	89	5	18	52	6	18	2	−2 to 5	0.338			

Table 5
EORTC – C30 Fatique: Score range 0–100 A high score for a symptom scale / item represents a high level of symptomatology / problems.

Group	N	Mean	SD	N	Mean	SD	Δ change	95% CI	Pr > |t|	Diff.	95% CI	P
	Baseline			**14 Weeks**								
Early	98	26	24	67	29	21	0	−5 to 6	0.911	10	2 to 18	0.017
Late	91	31	24	56	38	22	10	4 to 16	< 0.001			
	14 weeks			**26 Weeks**								
Early	74	28	19	56	26	21	−2	−7 to 2	0.278	−7	−14 to −1	0.020
Late	61	35	21	50	26	23	−10	−14 to −5	< 0.001			
	Baseline			**26 Weeks**								
Early	98	29	26	56	27	23	−2	−8 to 4	0.506	−3	−11 to 6	0.551
Late	91	28	22	53	26	21	1	−6 to 7	0.850			
	Baseline			**52 Weeks**								
Early	98	27	27	55	26	21	0	−6 to 6	0.912	−3	−12 to 5	0.431
late	91	27	22	50	27	21	4	−2 to 10	0.234			

initiated postoperative rehabilitation, 14 weeks and 26 weeks following lung resection respectively. As not all participants received adjuvant chemotherapy after lung resection, subgroup-analyses of the influence of adjuvant chemotherapy on primary and secondary outcomes was done in addition. Data from PROs was presented as mean, standard deviations (SD), median and inter-quartile range (IQR) and all change scores was presented with 95% confidence interval.

3. Results

From April 2013 to June 2016, 582 patients with operable NSCLC were screened for eligibility (Fig. 1); 106 patients were excluded, leaving 446 eligible patients. With 119 patients randomized in the early rehabilitation group (ERG) (68 females, 51 males; median age 65), and 116 randomized to late rehabilitation group (LRG) (62 females, 54 males; median age 65) the recruitment rate was 52.6%. Twenty-four patients were excluded after surgery due to no or other malignancies than operable NSCLC (9 patients in ERG, 15 patients in LRG). Dropout from baseline to 26 weeks in the ERG was 38.7% and 41.5% in LRG. In the ERG 42 patients and in the LRG 43 patients were undergoing concurrent systemic adjuvant treatment (Table 1). Baseline demographic and surgical characteristics of the study population is presented in Table 1.

3.1. Physical capacity, functional capacity and lung function

Table 2 shows the results of VO_2peak throughout the project timeline (baseline, 14 weeks, 26 weeks and 52 weeks). Primary outcome was VO2peak from baseline to 26 weeks and there was a non-significant decrease in both ERG and LRG. There was no significant difference between ERG and LRG ($p = 0.926$). However there was a significant decrease from baseline to 14 weeks in both ERG ($p = 0.027$) and LRG ($p < 0.001$) and a significant difference between the ERG and LRG groups ($p < 0.001$). There was a non-significant increase from 14 weeks to 26 weeks in ERG ($p = 0.464$) and a significant increase from 14 weeks to 26 weeks in LRG ($p < 0.001$) and a significant difference between the two groups ($p < 0.001$). From baseline to 52 weeks there were a non-significant increase in both groups (ERG, $p = 0.228$; LRG,

p = 0.158) and a non-significant difference between groups (p = 0.853). A more detailed presentation of the VO_2max is found in supplementary.

In the 6MWT (Table 3.) there was a significant increase from baseline to 26 weeks in both ERG (p < 0.001) and LRG (p < 0.001) and a non-significant difference between groups (p = 0.729). Results from baseline to 14 weeks; 14 weeks to 26 and baseline to 52 weeks are presented in Table 3. With regard to respiratory capacity expressed by FEV1 (Table 3.) there was a significant decrease from baseline to 26 weeks in both ERG (p < 0.001) and LRG (p < 0.001) and a significant difference between groups (p = 0.015). Results from baseline to 14 weeks; 14 weeks to 26 and baseline to 52 weeks are presented in Table 3. A more detailed presentation of the 6MWT and FEV1 is found in supplementary.

3.2. Quality of life

Table 4 presents the QOL results (EORTC-C30) throughout the project timeline (baseline, 14 weeks, 26 weeks and 52 weeks). There was significant improvements in EORTC Global Health Status in both group ERG (p = 0.02) and LRG (p < 0.002) from baseline to 26 weeks ERG and none significant difference between groups (p = 0.518). The remaining domains in EORTC-C30 (besides fatigue) from baseline to 26 weeks are presented in Table 4. A more detailed presentation of the EORTC is found in supplementary.

3.3. Fatigue

The development in fatigue throughout the project timeline (baseline, 14 weeks, 26 weeks and 52 weeks) is presented in Table 5. From baseline to 26 weeks there was a non-significant decrease in the ERG (p = 0.480) and in the LRG (p = 0.848) and a non-significant difference between groups (p = 0.533) in fatigue. From baseline to 14 weeks there were a non-significant increase in the ERG (p = 0.902) and a significant increase in the LRG (p < 0.001) and a significant difference between groups (p = 0.015) with regard to fatigue. From 14 weeks to 26 weeks there were non-significant decrease in the ERG (p = 0.244) and a significant decrease in the LRG (p < 0.001) and a significant difference between groups (p = 0.021). From baseline to 52 weeks there were none significant decrease in both groups (ERG, p = 0.900; LRG, p = 0.230) and no significant difference between groups (p = 0.021).

3.4. PROs

Results from SF-36, HADS, MSPSS, 1RM are presented in supplementary.

4. Discussion

This study is to our knowledge the first study to investigate the effect of early vs. late initiated postoperative rehabilitation in patients with operable lung cancer on exercise capacity (primary outcome), functional capacity and QOL. We found no significant difference between ERG and LRG from baseline to 26 weeks, but both groups who were offered the same exercise intervention with a different timeframe from baseline (14 days or 14 weeks after surgery) responded (VO_2peak) to the intervention they were allocated to when evaluated by VO2peak or functional capacity (6MWD). The design of this study was to investigate if there was any difference in the cardiovascular response when an intervention was commenced early (14 days) or late (14weeks) after surgery. Both groups had a significant decrease in VO_2peak from baseline to 14 weeks but the LRG had a significantly higher decrease in VO_2peak than the ERG. We did expect a decrease in the LRG due to the magnitude and impact of the surgery, which was the same for both groups but also due to the prolonged start of rehabilitation for the LRG. The significant decrease in the ERG was on the contrary not expected even though the ERG had a significantly smaller decrease than the LRG the ERG did not reach the same VO_2peak level as pre surgery. Other comparable studies [27,34,35] showed significant effect of an exercise intervention or at least a maintained VO_2peak or 6MWD after completion of an intervention. Edvarsen et al [34] found in a postoperative (5–7 weeks after surgery) randomized exercise intervention a significant increase in VO_2peak after a 20 weeks intervention to a level higher than from pre- surgery. The main differences between Edvarsen et al [34] and our study are the commencement of the study, training 3 times a week and the length of the intervention. Both interventions were high intensity so the differences could be found in the length of the two intervention due to the effect of progressive cardiovascular training over time [36], the intervention in Edvarsen et al [34] was 8 weeks longer than our study. Both interventions included patients receiving adjuvant chemotherapy (30% in Edvarsen et al [34] and 35% in our study) and the 8 weeks longer intervention would possible mean that patients would have terminated their planned chemotherapy at the end of the intervention and therefore performed better at the final test. The increased VO_2peak in the LRG from 14 weeks to 26 weeks shows an increase comparable to the study of Edvarsen et al [34], in the LRG 37% received chemotherapy which all was terminated at the final test at 26 weeks. To support this, we conducted a sub analysis for patients receiving chemotherapy in both ERG and LRG (appendix ii). From baseline to 14 weeks both groups receiving chemotherapy had a significant decrease in VO_2peak with a significant difference between the groups in favour of ERG. From 14 weeks until 26 weeks both groups had a significant increase in VO_2peak with a significant difference between the groups in favour of LRG. The completion of chemotherapy seems to have an effect on VO_2peak. Another explanation could be due to the recovery time after surgery. We started our intervention 14 days after surgery and Edvardsen et al 5–7 weeks after surgery, even though we showed that early rehabilitation was safe and feasible [30], we cannot rule out that this could play a role.

We found no significant differences in QOL but we found a significant difference between the groups from baseline to 14 weeks in fatigue level in favour of ERG. The ERG maintained the same level of fatigue from baseline to 14 weeks and reported no change in fatigue level throughout the whole study period (baseline, 14 weeks, 26 weeks, 52 weeks). The LRG had a significant increase in fatigue level from baseline to 14 weeks but after the LRG completed the intervention at 26 weeks the LRG had a significant decrease in fatigue level which was maintained at 52 weeks. Fatigue is known to be one of the most common and distressing side effects of cancer and its treatment and might be elevated before treatment onset and typically increases during cancer treatment [37]. No others studies as we know of have shown these convincing findings in lung cancer. On the contrary Cavalheri et al [38] found no between groups differences after a postoperative exercise intervention for patients with lung cancer. Studies within other cancer forms especially breast cancer have shown an effect of exercise on fatigue and [37,39] although one important limitation of the literature on exercise for cancer-related fatigue is the lack of studies that have specifically targeted fatigued patients. Indeed, fatigue may be a significant barrier to participation in exercise interventions, particularly among cancer survivors [40]. We did not target our intervention to fatigued patients but the LRG had an increase in fatigue from baseline to 14 weeks and began their exercise intervention with a significant higher fatigue level compared to baseline values, after 26 weeks both groups had a fatigue level lower than their baseline level. This indicates that fatigue should not be a barrier for commencing an exercise intervention.

This study has some strengths and limitations. To minimize bias aassessor (pre- and posttest) and data analysts were blinded to allocation, yet participants and investigators assigning to the intervention groups were aware of the allocations. Participants were strictly informed not to reveal their group allocation to the test personnel.

Another major strength of this study is that it was performed in a municipal setting reflecting a realistic implementation of the intervention into daily practice. The rehabilitation systems for cancer patients in the Nordic countries, Germany and the Netherlands are based on similar, multidimensional and multidisciplinary understanding of cancer rehabilitation, which also enhances the transferability of the results. The low recruitment rate of participants to this study shows that the development of new methods to recruit and motivate patients to participate in perioperative rehabilitation may be very important in the future. One of the limitations in this study was the dropout rate of the study. The dropout rate was approximal 40% in each group, this is similar to other comparable studies within exercise and lung cancer [27,35,38]. This could indicate that the population of patients being operated for lung cancer have difficulties in participating in exercise programs. Other exercise studies with patients with breast cancer reports 20%–30% dropout [41,42]. Some of the reasons to these dropouts could be due to patients' symptoms burden and physical activity preferences. Patients with lung cancer generally do not have a long exercise history and therefore may find it difficult to suddenly commencing an exercise program due to a life threating disease. Previous studies have emphasized the important role of oncologists and nurses in counselling and recommending exercise to patients, especially patients with no exercise history [43].

5. Conclusion

This is the first randomised clinically controlled trial to investigate the effects of early vs. late initiated postoperative rehabilitation in patients with operable lung cancer. We found no significant difference between ERG and LRG from baseline to 26 weeks on exercise capacity (primary outcome). Both groups were offered the same exercise intervention and responded with an increased VO_2peak independent of the allocated group from baseline (14 days or 14 weeks after surgery) to the intervention they were allocated to. We found no significant differences in QOL but we found a significant difference between ERG and LRG from baseline to 14 weeks in fatigue level in favour of ERG. The ERG maintained the same level of fatigue from baseline to 14 weeks and reported no change in fatigue level throughout the whole study period (baseline, 14 weeks, 26 weeks, 52 weeks). The LRG had a significant increase in fatigue level from baseline to 14 weeks but after the LRG completed the intervention at 26 weeks the LRG had a significant decrease in fatigue level which was maintained at 52 weeks. There is no difference on exercise capacity in the commencement (early vs. late) of a postoperative exercise program for patients with lung cancer. But to reduce fatigue patients should be recommended to initiate early exercise programs.

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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.2018.10.025.

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