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Critical Reviews in Oncology/Hematology 114 (2017) 63–76

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review

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Contents

ARTICLE INFO

Article history:
Received 19 December 2016
Received in revised form 22 March 2017

Keywords:
Non-small cell lung cancer
Prehabilitation
Rehabilitation

ABSTRACT

This systematic review aimed to examine physical fitness, adherence, treatment tolerance, and recovery for (p)rehabilitation including a home-based component for patients with non-small cell lung cancer (NSCLC). PRISMA and Cochrane guidelines were followed. Studies describing (home-based) prehabilitation or rehabilitation in patients with NSCLC were included from four databases (January 2000–April 2016, $N = 11$). Nine of ten rehabilitation studies and one prehabilitation study (437 NSCLC patients, mean age 59–72 years) showed significantly or clinically relevant improved physical fitness. Three (27%) assessed home-based training and eight (73%) combined training at home, inhospital (intramural) and/or at the physiotherapy practice/department (extramural). Six (55%) applied supervision of home-based

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http://dx.doi.org/10.1016/j.critrevonc.2017.03.031

Physical therapy
Compliance
Tolerance
Home

components, and four (36%) a personalized training program. Adherence varied strongly (9–125% for exercises, 50–100% for patients). Treatment tolerance and recovery were heterogeneously reported. Although promising results of (p)rehabilitation for improving physical fitness were found (especially in case of supervision and personalization), adequately powered studies for home-based (p)rehabilitation are needed.

1. Introduction

Non-small cell lung cancer (NSCLC) concerns 85% of all lung cancer patients (Netherlands Cancer Registry, 2016a). Five-year survival rates remain low ranging from 55%, 41%, 13%, to 2% for stage I, II, III and IV, respectively (Netherlands Cancer Registry, 2016b). Standard curative treatments, including lung resection (Vansteenkiste et al., 2014) and concurrent chemoradiation (Eberhardt et al., 2015), lead to adverse events in ≥50% of patients and frequently require hospitalization (Janssen-Heijnen et al., 2004; Schild et al., 2003). High age (Netherlands Cancer Registry, 2016c), smoking-related comorbidities, frailty, poor performance status, and long-term physical inactivity are often present in patients with NSCLC (Janssen-Heijnen et al., 2004; Hsu et al., 2015; Semrau et al., 2014; Granger et al., 2014). These characteristics may affect mobility, independence, treatment tolerance, recovery, and prognosis (Gridelli et al., 2007; Cardenal et al., 2015; Glotzer et al., 2013; Kale et al., 2015; Hoogeboom et al., 2014). Resistance and endurance training can increase the functional and physiological reserve, thereby creating a safety margin to meet potential enlarged demands of cardiac output and other physical capacities at the time of disease and interventions (Hoogeboom et al., 2014; Carli and Zavorsky, 2005). Prehabilitation (therapeutic training before undergoing treatment) (Carli and Zavorsky, 2005) and rehabilitation (therapeutic training during and after treatment) (Spruit et al., 2013) can optimize physical fitness, treatment tolerance, recovery, and survival (Singh et al., 2013; Ni et al., 2016; Bade et al., 2015), even in older cancer patients (Chou et al., 2012; Jack et al., 2011; Kilari et al., 2016). However, intramural training (inhospital) or extramural training (at the physiotherapy practice or department) may counteract compliance of high-risk patients because of commuting problems, accessibility of services, multimorbidity, and vulnerability (Temel et al., 2009; Oosting et al., 2012). A personalized training program in a home-based setting might overcome these barriers and enhance both motivation and adherence, especially for vulnerable and older patients (Bade et al., 2015). Therefore, the aim of this study is to systematically review the literature regarding feasibility and effectiveness of prehabilitation and rehabilitation including a home-based component in patients with NSCLC by evaluating physical fitness, and to describe adherence and treatment tolerance, and recovery.

2. Methods

The Cochrane guidelines for systematic reviews (The Cochrane Collaboration, 2011) and PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (Moher et al., 2009) were followed. Databases Pubmed, Medline, Embase, and PEDro were searched for eligible articles describing patients with NSCLC undergoing prehabilitation or rehabilitation including a home-based component focusing on physical fitness (Table 1). Search terms were explored on free text words to avoid exclusion of recently published articles. Inclusion was limited to studies in English or Dutch language between January 1, 2000 and April 11, 2016. The primary outcome was physical fitness and secondary outcomes were patient adherence, exercise adherence, treatment tolerance, and recovery. Studies were excluded when insufficient training information was available to distinguish prehabilitation and rehabilitation, and when no physical intervention was applied.

2.1. Study selection

All search results were combined and duplicates removed. Assessment of title, abstract and full-texts according to eligibility criteria was performed independently by reviewers MP and ED. Inclusion of eligible studies was discussed until consensus. If no consensus was reached, a third person (BB) determined eligibility. Studies were included when full-text was available. Reference tracking was performed after full-text assessment in order to include additional relevant studies.

2.2. Data collection process and items

For each included article, the following information was independently collected, compared, and combined: first author, publication year, study type (prehabilitation/rehabilitation, country, type of study, randomization), demographics (number of patients with NSCLC, stage of disease, age, sex, treatment, comorbidity, performance status), description of the intervention (exercise content, frequency, intensity, measurement times, exercise time, follow-up, time of delivery, controls), and outcomes (physical fitness, patient adherence, exercise adherence, treatment tolerance, recovery). Physical exercises consisted of resistance and endurance training, and training effects were mainly evaluated by the 6-minute walk test (6MWT) distance. Results were described as mean ± standard deviation, mean (range), or mean difference ± standard deviation. A minimal clinically important gain of ≥42 m or 9.5% change was considered clinically relevant for 6MWT distance (Granger et al., 2015). Patient adherence was described; both patient and exercise adherence (percentage) were considered sufficient above 70%. Treatment tolerance and recovery were displayed by adverse events (numbers, including postoperative complications) and hospitalization time (days, mean ± standard deviation). Differences between outcomes were considered statistically significant if $P < 0.05$.

2.3. Qualitative and quantitative assessment

Methodological quality was independently assessed by using the domain-based evaluation for systematic reviews by the Cochrane 'Risk of bias tool' (Cochrane Statistical Methods Group and Cochrane Bias Methods Group, 2011a). Selection-, performance-, detection-, attrition-, and reporting bias were scored present (+) or absent (−). Low, moderate, or high risk of bias was determined by the percentage of present bias, corresponding to high (≤17%), moderate (18–33%), or low (≥50%) methodological quality, respectively. Therapeutic validity for quality of the training content was assessed by the CONTENT scale (Consensus on Therapeutic Exercise Training) (Hoogeboom et al., 2012; Herbert and Bø, 2005). Nine items regarding patient eligibility, competences and setting, rationale of the study, content of the study, and adherence were scored as performed (+) or not performed

Table 1
Combinations of text words per database of the literature search.

Databases	Population *Non-small cell lung cancer patients*	Intervention *Home-based (p)rehabilitation*	Outcome *Physical fitness*
Embase, Pubmed, Medline[a]	(Non-small cell lung cancer OR NSCLC OR lung cancer) **AND** (patient OR geriatric OR elderly OR aged OR high-risk OR vulnerable OR frail) **NOT** (children OR caregiver OR tuberculosis OR aneurysm)	(prehabilitation OR before OR prior to OR presurgical OR preoperative OR during OR undergoing OR rehabilitation OR perioperative OR following OR postoperative OR lung resection OR lobectomy OR physical therapy OR training OR exercise OR physiotherapy OR physical therapy modality) **AND** (home-based OR living environment OR outpatient OR home OR home-based intervention) **NOT** (costs OR lung cancer screening OR drug-reimbursement OR homeopathy OR oxygen OR video-assisted)	(Physical activity OR fitness OR physical function OR functional status OR ADL OR strength OR resistance OR physical endurance) **NOT** (Genetic OR genomic OR gene OR radon OR air pollution OR asbestos OR cell dynamics OR drug-resistance OR smoking)
PEDro[a]	Lung cancer	Exercise[b] **AND** home[b]	

[a] Free text words were applied to all search terms; filters were applied to language (English and Dutch included) and publication date (Jan-1-2000 until Apr-11-2016 included); search terms for population, intervention and outcome were all combined by 'AND'.
[b] Truncation of search terms.

(−), where ≥6 times 'performed' indicated high therapeutic validity. The interobserver agreement was calculated by Cohen's Kappa, with poor (<0.20), reasonable (0.21–0.40), moderate (0.41–0.60), good (0.61–0.80) or very good (>0.80) agreement (Petrie and Sabin, 2009). A meta-analysis could not be performed due to clinical and statistical heterogeneity in patient samples, exercise design, study execution, and reporting of physical outcomes.

3. Results

The literature search identified 141 hits, leading to 107 unique studies of which 74 did not meet inclusion criteria. Thirty-three studies were selected for full-text assessment and 24 of them were excluded (conference paper with no available full-text version, $n = 16$), no physical outcome ($n = 3$), no home-based intervention ($n = 2$) or other reasons ($n = 3$). Reference tracking identified two additional articles. Eventually, 11 studies were included (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). The PRISMA flow diagram is shown in Fig. 1 (Moher et al., 2009).

3.1. Study characteristics

Fourhundred-fiftyone lung cancer patients were included (97% NSCLC) with various stages of disease and treatment regimens. Ranges for sample size and mean age were 5–131 participants and 59–72 years, respectively. In Table 2, characteristics of included studies are displayed.

Only one study described prehabilitation (Coats et al., 2013) and ten studies described rehabilitation (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). Home-based training alone was examined in three studies (27%) (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014). One study (9%) combined home-based and extramural training (Brocki et al., 2014), six studies (55%) combined home-based and intramural training (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Kuehr et al., 2014; Quist et al., 2012), and one study (9%) combined all three (Granger et al., 2013). The intervention period lasted four to 16 weeks. The home-based training component mainly consisted of resistance exercises (muscle strength) and endurance exercises (cardiorespiratory fitness) (Arbane et al., 2011; Brocki et al., 2014; Cheville et al., 2013; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014), or mere walking (Andersen et al., 2011, 2013; Arbane et al., 2014; Quist et al., 2012). Only four interventions (36%) were personalized (Andersen et al., 2013; Arbane et al., 2011; Granger et al., 2013; Hoffman et al., 2014). Supervision was performed by telephone calls (Arbane et al., 2014; Cheville et al., 2013; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014), home visits (Arbane et al., 2014; Granger et al., 2013; Hoffman et al., 2014), or during intramural sessions (Andersen et al., 2011, 2013; Arbane et al., 2014; Brocki et al., 2014; Kuehr et al., 2014; Quist et al., 2012). The number of home-based training sessions varied between twice a week (Brocki et al., 2014; Cheville et al., 2013) and once a day (Andersen et al., 2013; Arbane et al., 2014; Brocki et al., 2014; Granger et al., 2013), and moderate intensity was mainly applied. Intramural and extramural training consisted of supervised endurance training combined with resistance exercises. The number of sessions varied from twice a day postoperatively (Arbane et al., 2011; Granger et al., 2013) to once a week (Brocki et al., 2014), from 10 to 30 min (Granger et al., 2013) up to 1.5 h (Andersen et al., 2011, 2013) at moderate or high intensity. These sessions took place during hospitalization after surgery followed by home-based training alone (Arbane et al., 2011, 2014; Brocki et al., 2014), intramural training combined with concurrent home-based exercises (Andersen et al., 2011; Kuehr et al., 2014; Quist et al., 2012), or intramural training with home-based exercises in between (Andersen et al., 2013; Granger et al., 2013). Five studies (45%) included a control group that received regular care (Arbane et al., 2011, 2014; Granger et al., 2013), home-based exercises (Brocki et al., 2014), or no exercises (Cheville et al., 2013).

Physical fitness was mainly measured by cardiorespiratory fitness (6MWT distance) (Arbane et al., 2011; Brocki et al., 2014; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012) and muscle strength (kilogram of resistance per muscle group) (Arbane et al., 2011, 2014; Coats et al., 2013; Kuehr et al., 2014; Quist et al., 2012). All studies (100%) reported patient adherence (percentage) and most described reasons for drop-out. Six studies (55%) reported on compliance of home-based exercises (percentage) (Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). Treatment tolerance and recovery were

Table 2
Description of demographics and results of included (home-based) (p)rehabilitation studies.

First author, year	Study type 1. (P)rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Andersen, 2011	1. Rehabilitation 2. Denmark 3. PCT 4. NA	*N* = 24 **NSCLC** *N* = 19 **Age** *mean (range)* Men 64 (55–77) Women 67 (48–76) **Treatment** *N* Surgery 5, CT 19, RT 8, TKI1	**Home-based** 5/wk for 7 weeks unsupervised diary-based aerobic (walking) + breathing **Intramural (simultaneously)** 2/wk for 7 weeks supervised group sessions, aerobic (walking (85% VO_{2max})) + breathing **Control** NA	1. T0 1st supervised training T1 last supervised training 2. Home training NR; Intramural 90 3. Wk1-10/11 4. After surgery; during CT, RT, or TKI	1. ISWT *med diff (range)* +9% (−77; 39%) *P* = 0.021 ESWT *med diff (range)* +109% (−70; 432%) *P* = 0.002 FEV_1 *med diff (range)* 0% (−0.3; 0.6%) *P* = NR 2. **Drop-out** *with reasons (N)* home-based NR; intramural 29%, <65% of sessions present (3), incomplete data ISWT (4) **Compliance** *(N)* NR; continued after intervention (7) 3. NR
Andersen, 2013	1. Rehabilitation 2. Denmark 3. PCT 4. NA	*N* = 51 **NSCLC** *N* = 39 **Age** *mean* ± *SD* Men 65 ± 8, women 65 ± 7 **Treatment** *N* Surgery 10, CT 26, RT 3, TKI 2	**Intramural** 2/wk for 3 weeks aerobic (cycling and walking (Borg RPE 16–18)) + breathing Repetition of this design after home training **Home-based** 7/wk for 3 weeks (between intramural sessions) personalized unsupervised diary instructed aerobic + breathing **Intramural** 2/wk for 3 weeks intramural regimen **Control** NA	1. T0 1 t supervised training T1 last supervised training 2. Home training NR; Intramural 90 3. Wk1–13 4. Unclear (after surgery); during or after CT, RT, and TKI	1. VO_{2max} ($ml/O_2/kg/min$) *mean* ± *SD* T0 14 ± 3 T1 14 ± 3 *P* = 0.763 FEV1 (L) *mean* ± *SD* T0 2.0 ± 0.6 T1 2.0 ± 0.5 *P* = NS 2. **Drop-out** *with reasons (N)* 43%, withdrawal after first session (7), withdrawal after home sessions (9), <65% present at second session (6); After intervention, not continuing physical activity (8), LFU (3) **Compliance** *(N)* NR; continued after intervention (18) 3. NR
Arbane, 2011	1. Rehabilitation 2. UK 3. RCT 4. Block randomization	*N* = 26/25 **NSCLC** *N* = 26/25 **Stage** *N* I 15/10, II 6/6, III 2/0, IV 0/5, NR 3/4 **Age** *mean (range)* 62.6 (32–47)/65.4 (47–82) **Sex** NR **Treatment** *N* Surgery 26/25	**Intramural** 2/day for 5 days postoperative mobility + resistance (seated leg raises) + aerobic (walking, cycling 60–80% HR_x) **Home-based** 12 weeks personalized (based on hobbies) aerobic (walking) + strength (not specified) with monthly supervision/home visit **Control** Monthly check-up calls and usual care including breathing + mobilization	1. T0 preoperative T1 postoperative day5 T2 postoperative wk12 2. NR 3. Preoperative-postoperative wk12 4. After surgery	1. 6MWT (m) *mean* ± *SD* T0 466.6 ± 1021/ 4557 ± 98.0; T1 336.7 ± 84.1/308.7 ± 124.8; T2 480.2 ± 110.0/448.2 ± 95.1 *P* = 0.89§; *P* < 0.00† Quads strenght (kg) *mean* ± *SD* T0 33.2 ± 15.2/ 29.1 ± 10.9; T1 37.6 ± 27.1/21.5 ± 7.7; T2 34.2 ± 9.4/26.4 ± 9.7; *P* = 0.04*; *P* = 0.70† 2. **Drop-out** *with reasons (N)* 15%/32%, IG: palliative care (1), no surgery (1), refused measurement (1), no reason (1); CG: ITU admission (1), no reason (1), palliative care (1), withdrawal (1), refused (3) **Compliance** *(N)* NR 3. Length of hospital stay (days) *mean* ± *SD* 8.9 ± 3.3/11.0 ± 8.9 *P* = NR; A priori post-operative complications *(N)* 2/3 *P* = NR

Arbane, 2014	1. Rehabilitation 2. UK 3. RCT 4. Online randomization	*N* = 64/67 **NSCLC** *N* = 64/67 **Stage** *N* I 24/ 29, II 12/12, III 6/8, IV 7/2, NR 15/16 **Age** *mean* ± *SD* 67 ± 11/68 ± 11 **Sex** *N(%) female* 35(55)/24(36) **Treatment** *N* Surgery 64/67 **Comorbidities** *N(%)* COPD 34(53)/29(43)	**Intramural** 1/day for 5 days postoperative supervised strength (ankle lift (10-RM)) + aerobic cycling (max 60% heart rate reserve), intensity increases daily **Home-based** 7/wk for 4 weeks unsupervised walking by pedometer and weekly calls **Control** Monthly check-up calls and usual care including pain relief by breathing and mobilization exercises	1. T0 preoperative T1 postoperative day5 T2 postoperative wk4 2. Home training 30 Intramural 30 3. Preoperative-postoperative wk4 4. After surgery	1. ISWT (m) med(IQR) T0 290(180–440)/290(200–450); T1 110(NR)/135(NR); T2 350(NR)/290(NR); *P* > 0.05[†]; *P* > 0.05[§] Quads strength (kg) mean change diff(95%BI) T2 4.7(0.18–0.20); *P* = 0.04[‡] in COPD patients 2. **Drop-out** *with reasons (N)* 38%/43% IG: inoperable (3), no cancer (6), ITU admission (4), withdrawal (6), moved (1), rehospitalized (1), deceased (1), failed activity monitor (2); CG: inoperable (4), no cancer (1), no NSCLC (2), deceased (4), ITU admission (9), refusal (1), withdrawal (2), additional surgery (1), moved (1), failed activity monitor (4) **Compliance** *(N)* NR 3. Length of hospital stay (days) *mean(range)* 7.5(5–8)/7.1(6–8) *P* > 0.05[‡] A priori postoperative complications *(n(%))* 20(31)/22(33) *P* = NR
Brocki, 2014	1. Rehabilitation 2. Denmark 3. RCT 4. Computer-generated randomization tables	*N* = 39/39 **NSCLC** *N* = 39/36 **Stage** *N* I 16/10, II 17/14, III 4/7, unknown 2/15 **Age** *mean* ± *SD* 64 ± 10/65 ± 9 **Sex** *N(%) female* 19(46)/13(35) **Treatment** *N* Surgery 41/37 **Comorbidities** *N* COPD 8/5, DM 5/3, CVD 8/12, previous malignancy 12/13	**Extramural** 1/wk for 10 weeks starting wk3 postoperative supervised group aerobic (walking with increasing intensity) + strength + breathing **Home-based (simultaneously)** 2/wk strength + 7/wk aerobic (walking, cycling (BORG RPE 11–12)) diary based; wk3–4months postoperative **Control** 2/wk strength + 7/wk aerobic (walking, cycling (BORG RPE 11–12)) diary based at home	1. T0 postoperative wk3 T1 4 months after baseline T2 1 year after baseline 2. Home training 30 Extramural 60 3. Baseline-12 months after baseline 4. After surgery	1. 6MWT (m) *mean* ± *SD* T0 427 ± 124/407 ± 102; T1 *mean diff baseline* 61 ± 52/55 ± 45 *P* = 0.57[‡] T2 *mean diff baseline* 65 ± 70/60 ± 45 *P* = 0.93[‡] FEV1 (L) *mean* ± *SD* T0 1.73 ± 0.5/1.9 ± 0.6; T1 *mean diff baseline* 0.14 ± 0.3/0.1 ± 0.4 *P* = 0.84[‡] T2 *mean diff baseline* 0.1 ± 0.4/0.06 ± 0.4 *P* = 0.84[‡] 2. **Drop-out** *with reasons (N)* 28%/14% IG: deceased (3), withdrawal (8); CG: deceased (2), withdrawal (3) **Compliance** Home-based (IG/CG %) 43%/14%; extramural (IG *N*) 17 in 10 sessions, 8 in 9, 5 in 8 and 2 in 6–7 sessions 3. Length of hospital stay (days) *mean* ± *SD* 9 ± 5/10 ± 5 *P* = NR
Cheville, 2013	1. Rehabiliation 2. United States 3. RCT 4. Unblinded block randomization	*N* = 26/33 **Lung cancer** *N* = 16/18 **Stage** *N* IV 26/33 **Age** *mean* ± *SD* 63.8 ± 12.5/65.5 ± 8.9 **Sex** *N(%) female* 17(51.5)/14(42.4) **Treatment** *N* (NR 5/4) RT 4/4, CT 24/25	**Home-based** 2/wk for 8 weeks strength (Borg CR10) + 4/wk for 8 weeks aerobic (walking, 1 mile/20 min) diary based and every two weeks check-up calls **Control** No exercises or monitoring during intervention period	1. T0 wk1 T1 wk8 2. Home training 20 3. Baseline-12 months 4. During (palliative) treatment	1. Mobility *mean diff* ± *SD* 4.88(4.66)/0.23(5.22) *P* = 0.002 Activity *mean diff* ± *SD* 1.56 ± 5.53/0.94 ± 5.91 *P* = 0.74 Steps/day (*N*) *mean* T0 3200/NR; T1 4400/NR; *P* = NR *Self-reported Ambulatory Post Acute Care Daily Activities Short Form 2. **Drop-out** *with reasons (N)* 27%/9% IG: deceased (5), LFU (1), fracture (1); CG: deceased (2), LFU (1) **Compliance** *(N)* IG: 26, 77% 3. No adverse events during home-based program, difference deceased participants IG/CG NS

Table 2 (*Continued*)

First author, year	Study type 1. (P)rehabilitation 2. Country 3. Type of study 4. Randomization	Demographics (IG/CG)	Intervention exercise (IG/CG)	Intervention 1. Measurement times 2. Exercise time (min) 3. Follow-up 4. Delivery	Outcomes (IG/CG) 1. Physical fitness 2. Patient adherence (drop-out) Exercise adherence (compliance) 3. Treatment tolerance and recovery
Coats, 2013	1. Prehabilitation 2. Canada 3. PCT 4. NA	*N* = 13 **NSCLC** *N* = 13 **Stage** *N* I 5, II 4, III 0, IV 2 **Age** *mean* ± *SD* 59 ± 9 **Sex** *N* female 5 **Treatment** *N* Awaiting surgery 10, CT 1, CT palliative 1, RT + CT palliative 1 **Comorbidities** *N* COPD 5, hypertension 5, dyslipidemia 3, DMII 2, anxiety 2	**Home-based** 3–5/wk for 4 weeks diary based aerobic (cycling (Borg BS≥6)) + strength and weekly check-up calls **Control** NA	1. T0 baseline T1 wk4 2. Home training 30 3. Wk1–4 4. Before treatment	1. VO_{2max} (mL/kg/min) *mean* ± *SD* T0 21.6 ± 7.8; T1 23.3 ± 7.5 *P* > 0.05 VO_{2max} (L/min) *mean* ± *SD* T0 1.63 ± 7.8; T1 1.75 ± 0.71 *P* > 0.05 CWCE (s) *mean* ± *SD* T0 264 ± 79; T1 421 ± 241 *P* < 0.05 6MWT(m) *mean* ± *SD* T0 540 ± 98; T1 568 ± 101 *P* < 0.05 Muscle strength (kg) *mean increase (SD); % ± SD m. deltoideus:* 1.82 ± 2.83; 18 ± 31; *P* < 0.05; *m. triceps:* 1.32 ± 1.75; 14 ± 25; *P* < 0.05; *m. hamstrings*: 3.41 ± 3.7; 27 ± 40; *P* < 0.05; *Handgrip, m. biceps and m. quadriceps* NS 2. **Drop-out** *with reasons (N) 0%* **Compliance** (%) Aerobic (125); strength (84); recruitment (50) 3. No adverse events
Granger, 2013	1. Rehabilitation 2. Australia 3. RCT 4. Computer-generated randomization tables	*N* = 7/8 **NSCLC** *N* = 2/5 **Age** *mean* ± *SD* 57 ± 16.2/72.4 ± 12.4 **Sex** *% female* 57.1/37.5 **Treatment** *N* Surgery 7/8	**Intramural** From postoperative until discharge aerobic (walking (Borg BS 4) 2/day, cycling 1/day) + strength (Borg RPE 13) 1/day **Home-based** 7/wk for 2 weeks after discharge personalized aerobic (walking (Borg BS 4)) + strength 1/wk check-up calls and 3 home visits **Extramural** 2/wk for 8 weeks after home training aerobic (walking and cycling (Borg BS 4)) + strength (Borg RPE 13) **Control** Standard care + breathing	1. T0 preoperative<2wk T1 postoperative wk2 T2 postoperative wk12 2. Home training 30 Intramural 10–30 Extramural 30 3. Preoperative-wk12 4. After surgery	1. 6MWT (m) *mean* ± *SD* T0 677.0 ± 89.3/435.8 ± 98.2; T1 647.5 ± 53.1/426.0 ± 64.3; T2 705.7 ± 65.3/458.2 ± 38.6 *P* = 0.024‡ at T2; others NR TUG (s) *mean* ± *SD* T0 6.3 ± 1.6/9.0 ± 2.6; T1 4.4 ± 2.6/6.0 ± 3.2; T2 4.9 ± 0.8/6.8 ± 1.5 *P* = 0.041‡ at T2; others NR 2. **Drop-out** *with reasons (N)* 43%/38% IG: not present for testing (1), LFU (2); CG: not present for testing (2), LFU (1) **Compliance** *(%)* home-based NR; intramural (71); extramural (81) 3. Length of hospital stay (day) *mean(range)* 4(3–9)/6(3–17); *P* = NR
Hoffman, 2014	1. Rehabilitation 2. United States 3. PCT 4. NA	*N* = 5 **NSCLC** *N* = 5 **Stage** *N* IIA 1, IIB 2, IIIA 2 **Age** *mean* ± *SD* 63.4 ± 7.3 **Sex** *N female* 3 **Treatment** *N* Surgery+ CT 5 **Karnofsky PS** *N* 70% 2, 90% 3 **Comorbidities** *mean N (range)* 5.4 (2–12)	**Home-based** 5/wk for 16 weeks from day 4 post-operative personalized aerobic (walking (≤3MET)) + balance by Nintendo Wii Fit. Two home visits and weekly check-up calls **Control** NA	1. T0 preoperative T1 postoperative wk5 T2 postoperative wk16 2. home-training 5 + daily 5 increase 3. Baseline-wk16 4. After surgery and during CT	1. 6MWT (m) *mean* ± *SD* T0 413 ± 32; T1 382 ± 108; T2 463 ± 62 *P* = NR Walking time (min) *mean* ± *SD* T0 NR; T1 24.0 ± 4.3; T2 31.0 ± 6.5 *P* = NR 2. **Drop-out** 0% **Compliance** *% ± SD(range)* Walking 92.6 ± 4.6 (87.0–98.1); Balance 94.7 ± 7.0 (82.5–100) 3. Length of hospital stay (day) *mean* ± *SD(range)* 8.4 ± 2.6(5–12) *P* = NR

Kuehr, 2014	1. Rehabilitation 2. Germany 3. PCT 4. NA	*N* = 40 **NSCLC** *N* = 40 **Stage** *N* IIA 2, IIIA 3, IIIB 8, IV 27 **Age** *mean* ± *SD(range)* 60 ± 12(22–75) **Sex** *N(%) female* 16(40) **Treatment** *N* Surgery 3, concurrent CHRT 4, sequential CHRT 1, CT 33	**Intramural** 5/wk for 8 weeks of which 3 times supervised aerobic (walking, cycling (Borg RPE 12–14)) + strength (resistance (Borg RPE 14–16)) **Home-based (simultaneously)** 3/wk for 8 weeks diary based aerobic (walking (Borg RPE 12–14)) + strength (resistance (Borg RPE 14–16)) and weekly check-up calls **Control** NA	1. T0 baseline T1 wk8 T2 wk16 2. Home training NR Intramural NR 3. Baseline-wk16 4. After surgery, during CHRT and CT	1. 6MWT(m) *mean* ± *SD* T0 493 ± 100; T1 525 ± 95 *P* < 0.01; T2 543 ± 120 *P* = 0.46 Knee flexion (Newton) *mean* ± *SD* T0 140 ± 41; T1 177 ± 61 *P* < 0.01; T2 192 ± 57 *P* < 0.01 Knee extension (Newton) *mean* ± *SD* T0 201 ± 86; T1 279 ± 71 *P* < 0.01; T2 327 ± 116 *P* < 0.01 Other muscle strengths reported but NS 2. **Drop-out** *with reasons (N)* 50% T0 fatigue (4), pneumonia (1), deceased (1), pain (1), infection (1), stroke (1); T1 stress (4), moved (1), metastases (1), dyspnea (1), pneumonia (1), stopped treatment (1); T2 no time (4), LFU (5) **Compliance** *(%)* overall (82), home-based (77), intramural (95) 3. NR
Quist, 2012	1. Rehabilitation 2. Denmark 3. PCT 4. NA	*N* = 29 **NSCLC** *N* = 19 **Age** *mean(range)* 63(45–80) **Sex** *N(%) female* 16(55.2) **Treatment** *N* CT 27, CHRT 2 **Physical activity before diagnosis** *N* Sedentary (2), <3 h/wk 14, ≥3 h/wk 12, >4 h/wk 1	**Intramural** 2/wk for 6 weeks supervised strength (resistance (70–90% 1RM)) + aerobic (cycling (85–95% max HR)) + stretching **Home-based (simultaneously)** 3/wk for 6 weeks unsupervised diary based aerobic (walking) + relaxation **Control** NA	1. T0 baseline T1 wk6 2. Home training 20–60 Intramural 90 3. Baseline-wk6 4. During CT and CHRT	1. VO_{2max}(L/min) *mean* ± *SD* T0 1.48 ± 0.41; T1 1.57 ± 0.41 *P* = 0.014 6MWT (m) *mean* ± *SD* T0 524.7 ± 88.5; T1 564.0 ± 88.6 *P* = 0.006 FEV1 (L) mean ± SD T0 1.76 ± 0.70; T1 1.96 ± 0.63 *P* = 0.061 Muscle strength(kg) mean ± SD *Leg press*: T0 70.34 ± 26.9; T1 86.9 ± 28.8 *P* = 0.000; *Chest press* T0 30.8 ± 13.2; T1 40.3 ± 16.3 *P* = 0.000; *Lat machine*: T0: 35.8 ± 13.8; T1 39.2 ± 17.6 *P* = 0.049; *Abdominal crunch*: T0 24.9(10.7); T1 29.5(11.3) *P* = 0.000; *Lower back*: T0 35.3 ± 14.1; T1 43.1 ± 16.2 *P* = 0.000; *Leg extension*: T0 38.6 ± 15.5; T1 45.1 ± 18.9 *P* = 0.000 2. **Drop-out** *with reasons (N)* 21% Loss of motivation (3), worsened PS(3) **Compliance** *(%)* home-based 8.7%, intramural 73.3% 3. No adverse events

Abbreviations: 6MWT = 6-Minute Walking Test; Borg BS = Borg CR 10 Breathlessness Scale; BORG RPE = Borg Rating of Perceived Exertion Scale; CG = Control Group; CHRT = CHemoRadioTherapy; CI = Confidence Interval; COPD = Chronic Obstructive Pulmonary Disorder; CR = Category Ratio; CT = ChemoTherapy; CVD = CardioVascular Disease; CWCE = Constant Workrate Cycle Exercise; diff = difference; DM = Diabetes Mellitus; ESWT = Endurance Shuttle Walk Test; FEV1 = Forced Expiratory Volume in 1 second; HR = Heart Rate; IG = Intervention Group; ISWT = Incremental Shuttle Walk Test; kg = kilogram; IQR = Inter Quartile Range; L = Liter; LFU = Lost to Follow Up; max = maximal; m = meter; med = median; MET = Metabolic Equivalents; min = minute; ml = milliLiter; N = Number; NA = Not Applicable; NR = Not Reported; NS = Not Significant; NSCLC = Non-Small Cell Lung Cancer; O_2 = oxygen; PCT = Patient Cohort Trial; PS = Performance Status; RCT = Randomized Controlled Trial; RM = Repeat Maximum; RT = RadioTherapy; s = second; SD = Standard Deviation; subj = subjects; TKI = Tyrosin Kinase Inhihibitor (targeted therapy); UK = United Kingdom; VO_{2max} = maximal oxygen uptake; WHO = World Health Organization; wk = week.

† Within subjects group time effect.

‡ Between subjects group time effect.

§ Between groups.

Table 3
Physical outcomes including significance and clinical relevance of changes of included studies according to measuring instruments.

Outcome *unit*	First author, year	Measurement times (IG/CG)		*Mean ± SD; (range)*		*1. Absolute change [percentage] (IG/CG)* *2. Mean ± SD of change (range) [95%CI] (IG/CG)*			*1. P*-value 2. Clinically relevant change[a]
		Baseline	Postoperative	End iv	Post iv	T0–T1	T0–T2	T1–T2	
Prehabilitation – cardiorespiratory fitness									
VO_{2max} mL/kg/min	Coats, 2013	21.6 ± 7.8		23.3 ± 7.5		1. +1.7 [7.8%]			1. > 0.05 2. No
VO_{2max} L/min	Coats, 2013	1.63 ± 7.8		1.75 ± 0.71		1. +0.12 [+7.4%]			1. >0.05 2. No
6MWT m	Coats, 2013	540 ± 98		568 ± 101		1. +28 [+5.2%] 2. +28 ± 29			1. < **0.05** 2. No
CWCE s	Coats, 2013	264 ± 79		421 ± 241		1. +57 [+59.5%] 2. +157 ± 195			1. < **0.05** 2. yes
Rehabilitation – cardiorespiratory fitness									
VO_{2max} mL/kg/min	Andersen, 2013	14 ± 3		14 ± 3		1. +0.0 [+0.0%]			1. 0.763 2. No
VO_{2max} L/min	Quist, 2012	1.48 ± 0.41		1.57 ± 0.41		1. +0.09 [+6.1%] 2. +0.09 [0.02;0.16]			1. 0.014 2. NR
FEV_1 L	Andersen, 2013	2.0 ± 0.6		2.0 ± 0.5		1. +0.0 [+0.0%]			1. NS 2. No
FEV_1 L	Brocki, 2014	1.73 ± 0.5/1.9 ± 0.6		Mean diff 0.14 ± 0.3/0.1 ± 0.4	Mean diff 0.1 ± 0.4/0.06 ± 0.4	1. +0.14/+0.1 [+8.1/+5.3%] 2. 0.02 [−0.14;0.17][§]	1. +0.1/+0.06 [+5.8/+3.2%] 2. 0.02 [−0.14;0.18] [§]	1. −0.04/−0.04	1. T1 0.84 T2 0.84 2. No
FEV1 L	Quist, 2012	1.76 ± 0.7		1.96 ± 0.6		1. +0.20 [+11.4%] 2. 0.20 [−0.01;0.41]			1. 0.061 2. No
6MWT m	Arbane, 2011	466.6 ± 102.1/ 455.7 ± 98.0	D5 336.7 ± 84.1/ 308.7 ± 124.8	480.2 ± 110.0/ 448.2 ± 95.1		1. −129.9/ −147 [−27.8/ −32.3%]	1. +13.6/−7.5 [+2.9/−1.6%]	1. +143.5/+139.5 [+42.6/+45.2%]	1. < **0.001**[†]; 0.89[‡] 2. Yes
6MWT m	Brocki, 2014	427 ± 124/ 407 ± 102		Mean diff +61 ± 52/+55 ± 45	Mean diff +65 ± 70/+60 ± 45	1. +61 ± 52/ +55 ± 45 [+14.3/+13.5%] 2. 8.33 [−20;36.27]	1. +65 ± 70/ +60 ± 45 [+15.2/+14.7%] 2. 1.31 [−28.18;30.8]	1. +4.0/+5.0	1. T1 0.57[§] T2 0.93[§] 2. Yes
6MWT m	Granger, 2013	677.0 ± 89.3/ 435.8 ± 98.2	Wk2 647.5 ± 53.1/ 426.0 ± 64.3	705.7 ± 65.3/ 458.2 ± 38.6		1. −29.5/−9.8 [−4.4/−2.3%]	1. +28.7/+22.4 [+4.2/+5.1%]	1. +58.2/+32.2 [+9.0/+7.6%]	1. T2 **0.024**[§] 2. Yes
6MWT m	Hoffman, 2014	413 ± 32 (367–452)	Wk5 382 ± 108 (202–480)	463 ± 62 (383–529)		1. −31 [−7.5%]	1. +50 [+12.1%]	1. +81 [+21.2%]	1. NR 2. Yes
6MWT m	Kuehr, 2014	493 ± 100		525 ± 95	Wk 16 543 ± 120	1. +32 [+6.5%]	1. +50 [+10.1%]	1. +18 [+3.4%]	1. T0–T1 < **0.01** T0–T2 0.46 2. Yes
6MWT m	Quist, 2012	524.7 ± 88.5		564.0 ± 88.6		1. +39.3 [+7.6%] 2. +39.3 [12.5;66.1]			1. **0.006** 2. No
ISWT m	Andersen, 2011	NR		Med diff % +9.0(−77;39)		2. +9.0% (−77;39)			1. **0.021** 2. NR
ISWT m	Arbane, 2014	290(180–440)/ 290(200–450)	D5 110/135	350/290		1. −180/−155 [−62/−53%]	1. +60/+0 [+21/+0%]	1. +250/+155 [+227/+115%]	1. >0.05[§]; >0.05[¶] 2. Yes
ESWT m	Andersen, 2011	NR		Med diff % +9(−70;432)		2. +9% (−70;432)			1. **0.002** 2. NR
Steps/day n	Cheville, 2013	3200		4400		1. +1200 [+37.5%]			1. NR 2. NA
Walking time min	Hoffman, 2014	NR	Wk 5 24.0 ± 4.3	31.0 ± 6.5		1. +7.0 [+29%]			1. NR 2. NA
TUG s	Granger, 2013	6.3 ± 1.6/9.0 ± 2.6	Wk2 4.4 ± 2.6/ 6.0 ± 3.2	4.9 ± 0.8/6.8 ± 1.5		1. −1.9/−3.0 [−30.2/−30%]	1. −1.4/−2.2 [−22.2/−24.4%]	1. +0.5/+0.8 [+11.4/+13.3%]	1. **0.041**[§] 2. No
Mobility likert scale	Cheville, 2013	NR/NR		NR/NR		2.+4.88 ± 4.66[2.96; −6.80]/ +0.23 ± 5.22[−1.76;2.22]		1. **0.002** 2. NA	
Activity likert scale	Cheville, 2013	NR/NR		NR/NR		2. +1.56 ± 5.53[−0.72;3.82] /+0.94 ± 5.91[−1.26;3.14]		1. 0.74[‡] 2. NA	

Prehabilitation – muscle strength									
m. deltoi-deus kg	Coats 2013	NR		NR		1. +1.82 ± 2.83 [+18.0% ± 31.0]			1. < **0.05** 2. NA
m. triceps kg	Coats 2013	NR		NR		1. +1.32 ± 1.75 [+14.0% ± 25.0]			1. < **0.05** 2. NA
m. ham-strings kg	Coats 2013	NR		NR		1. +3.41 ± 3.7 [+27.0% ± 40.0]			1. **<0.05** 2. NA
Rehabilitation – muscle strength									
m. quadri-ceps kg	Arbane 2011	33.2 ± 15.2/ 29.1 ± 10.9	D5 37.6 ± 27.1/ 21.5 ± 7.7	34.2 ± 9.4/26.4 ± 9.7		1. +4.4/−7.6 [+13.3/−26.1]	1. +1.0/−2.7 [+3.0/−9.3%]	1. −3.4/+4.9 [−9.0/+22.8%]	1. 0.70[‖]; **0.04**[§] 2. NA
Extension knee N	Kuehr 2014	201 ± 86		279 ± 71	Wk16 327 ± 116	1. +78[+38.8%]	1. +126[+62.7%]	1. +48[+17.2%]	1. T0–T1 **<0.01** T0–T2 **<0.01** 2. NA
Extension leg kg	Quist et 2012	38.6 ± 15.5		45.1 ± 18.9		1. +6.5[+16.8%] 2. 6.5[4.1–8.9]			1. **0.000** 2. NA
Press leg kg	Quist 2012	70.34 ± 26.9		86.9 ± 28.8		1. +16.56[+23.5%] 2. +16.5[11.5–21.7]			1. **0.000** 2. NA
Extension elbow N	Kuehr 2014	124 ± 44		136 ± 44	Wk16 129 ± 41	1. +12[+9.7%]	1. +5[+4.0%]	1. −7[−5.1%]	1. T0–T1 **<0.01** T0–T2 0.49 2. NA
Flexion knee N	Kuehr 2014	140 ± 41	–	177 ± 61	Wk16 192 ± 57	1. +33[+23.6%]	1. +52[+37.1%]	1. +15[+8.5%]	1. T0–T1 **<0.01** T0–T2 **<0.01** 2. NA
Flexion elbow N	Kuehr 2014	144 ± 52	–	152 ± 55	Wk16 158 ± 69	1. +8[+5.6%]	1. +14[+9.7%]	1. +6[+3.9%]	1. T0–T1 **0.02** T0–T2 0.68 2. NA
Hip flexion N	Kuehr 2014	133 ± 48	–	137 ± 54	Wk16 135 ± 62	1. +5[+3.8%]	1.+2[+1.5%]	1. −2[−1.5%]	1. T0–T1 0.21 T0–T2 0.26 2. NA
Hip abduction N	Kuehr 2014	153 ± 45	–	164 ± 48	Wk16 161 ± 48	1. +11[+7.2%]	1. +8[+5.2%]	1. −3[−1.8%]	1. T0–T1 **<0.01** T0–T2 0.73 2. NA
Chest press kg	Quist 2012	30.8 ± 13.2	–	40.4 ± 16.3	–	1. +9.6[+31.2%] 2. +9.5[6.4–12.7]	–	–	1. **0.000** 2. NA
Lat ma-chine kg	Quist 2012	35.8 ± 13.8	–	39.2 ± 17.6	–	1. +3.4[+9.5%] 2. +3.4[0.0–6.7]	–	–	1. **0.049** 2. NA
Abdominal crunch kg	Quist 2012	24.9 ± 10.7	–	29.5 ± 11.3	–	1. +4.6[+18.5%] 2. +4.6[3.2–6.0]	–	–	1. **0.000** 2. NA
Lower back kg	Quist 2012	35.3 ± 14.1	–	43.1 ± 16.2	–	1. +7.8[+22.1%] 2. +7.8[4.8–10.8]	–	–	1. **0.000** 2. NA

Abbreviations: 6MWT = 6-Minute Walking Test; CG = Control Group; CI = Confidence Interval; CWCE = Constant workrate Cycle Exercise; D = day; diff = difference; ESWT = Endurance Shuttle Walk Test; FEV_1 = Forced Expiratory Volume in 1 second; IG = Intervention Group; ISWT = Incremental Shuttle Walk Test; iv = intervention; kg = kilogram; L = Liter; m = meter; MCID = Minimal Clinically Important Difference; med = median; mL = milliliter; min = minutes; *n* = Number; N = Newton; NA = Not Applicable; NS = Not Significant; NR = Not Reported; s = seconds; SD = Standard Deviation; T0 = baseline; T1 = first measurement time; T2 = last measurement time VO_{2max} = maximum oxygen uptake; wk = week.

[a] MCID-values for aerobic outcomes: VO_{2max} increase of 3.5 mL/min/kg (Myers et al., 2002); 6MWT increase of ≥42 m or 9.5% change (Granger et al., 2015); CWCE increase of ≥100 s (Redelmeier et al., 1997); FEV1 increase of 0.23 L (Laviolette et al., 2008); ISWT increase of 70 m (Santanello et al., 1999); ESWT increase of 154–164 m (Houchen-Wolloff et al., 2015); TUG (s) decrease of ≥0.8 s (Altenburg et al., 2015); MCID-values not found for: Steps/day (N); Walking time (min); Mobility (likert scale); Activity (likert scale) and muscle strengths.

[†] Within subjects group time effect.

[‡] Between subjects group time effect.

[§] Between groups.

[‖] Between measurement times.

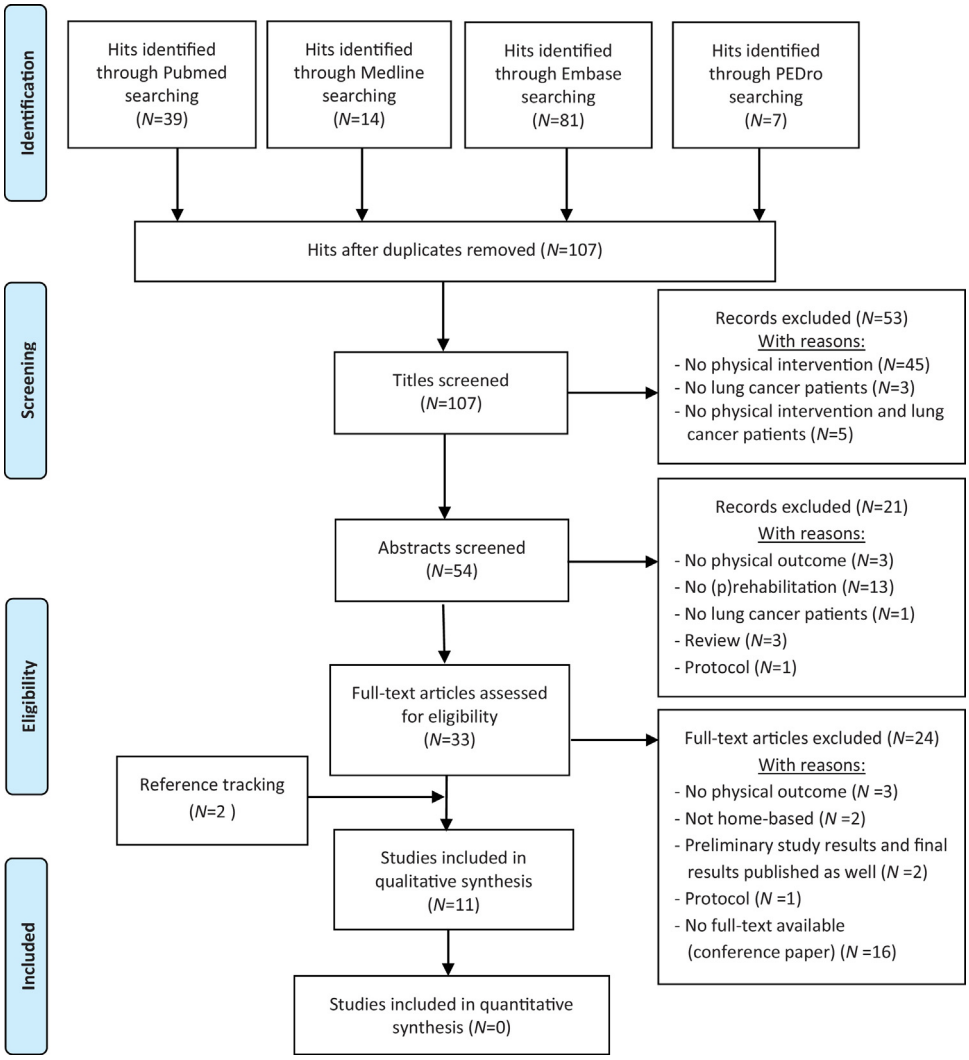

Fig. 1. PRISMA flow diagram displaying the selection of studies and reasons for exclusion.

described as adverse events (including post-operative pulmonary complications) (Cheville et al., 2013; Coats et al., 2013), or hospitalization days (Arbane et al., 2011, 2014; Brocki et al., 2014; Granger et al., 2013; Hoffman et al., 2014). Other results of physical outcomes are displayed according to measuring instruments in Table 3 (Myers et al., 2002; Redelmeier et al., 1997; Laviolette et al., 2008; Santanello et al., 1999; Houchen-Wolloff et al., 2015; Altenburg et al., 2015; Wright et al., 2011).

3.2. Results of individual studies

The prehabilitation study and six rehabilitation studies (64%) described significantly improved physical fitness after (home-based) training (Andersen et al., 2011; Arbane et al., 2011; Coats et al., 2013; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012). Three additional rehabilitation studies (27%) indicated improved physical fitness as well, although significance was not reported (Brocki et al., 2014; Cheville et al., 2013; Hoffman et al., 2014). Specific outcomes are displayed in Table 2. The 6MWT distance was described in seven studies (64%), including the prehabilitation study, and showed a significant improvement of 28–65 m (5.2–43%) (Arbane et al., 2011; Brocki et al., 2014; Coats et al., 2013; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014; Quist et al., 2012). In five of them, this gain was clinically relevant (Arbane et al., 2011; Brocki et al., 2014; Granger et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014). Muscle strength increased significantly during training sessions for most muscle groups (Arbane et al., 2014; Coats et al., 2013; Kuehr et al., 2014; Quist et al., 2012). All studies described patient adherence and varied from 50% (Kuehr et al., 2014) to 100% (Coats et al., 2013; Hoffman et al., 2014). Main reasons for dropout were clinical deterioration, incomplete data-assessment, dying, and withdrawal from study-protocol. In all three studies examining home-based training alone, patient adherence was sufficient (72%, 100%, and 100%, respectively) (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014). In three of eight studies combining home-based with extramural and/or intramural training, patient adherence was sufficient (71%, 72%, and 79%, respectively) (Andersen et al., 2011; Brocki et al., 2014; Quist et al., 2012), and varied from 50 to 68% in the remaining five studies (Andersen et al., 2013; Arbane et al., 2011, 2014; Granger et al., 2013; Kuehr et al., 2014). Reported exercise adherence for the home-based component varied from 9% (Quist et al., 2012) to 125% (Coats et al., 2013) and was sufficient in four of six studies (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014; Kuehr et al., 2014). Six studies included adverse events or hospitalization time (55%). For surgical patients, hospitalization varied in the intervention group from four (Granger et al., 2013) to nine days (Brocki et al., 2014), compared to six (Granger et al., 2013) to eleven days (Arbane et al., 2011) in the control group. Adverse events were absent (Coats

Table 4
Results of methodological quality according to 'the Cochrane risk of bias tool'.

First author year	Randomization (selection bias)	Equal groups (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Selective drop-out (attrition bias)	Selective reporting (reporting bias)	Methodological quality
Andersen 2011	+	NA	NA	NA	–	–	Mode-rate
Andersen 2013	+	NA	NA	NA	+	–	Low
Arbane 2011	–	–	+	–	+	+	Low
Arbane 2014	+	–	+	+	+	+	Low
Brocki 2014	–	–	+	–	–	–	High
Cheville 2013	+	–	+	+	–	+	Low
Coats 2013	+	NA	NA	NA	–	–	Mode-rate
Granger 2013	–	+	+	–	+	+	Low
Hoffman 2014	+	NA	NA	NA	–	–	Mode-rate
Kuehr 2014	+	NA	NA	NA	+	–	Low
Quist 2012	+	NA	NA	NA	+	+	Low

Risk of bias: + 'present', – 'absent'; *Methodological quality*: present bias ≤17% 'high', 18–33% 'moderate', ≥50% 'low'; NA 'not applicable'.

et al., 2013; Quist et al., 2012) or occurred infrequently during the postoperative period (Arbane et al., 2011).

3.3. Qualitative assessment

Only one study (9%) had a high methodological quality and was at risk for performance bias as participants nor personnel were blinded (Table 4; Cochrane Statistical Methods Group and Cochrane Bias Methods Group, 2011a; Brocki et al., 2014). Therapeutic validity was low in this study due to insufficient eligibility criteria for therapist and setting, rationale for the training program, and monitoring or personalization of the intervention (Table 5; Hoogeboom et al., 2012). A moderate methodological quality was found in two rehabilitation studies and one prehabilitation study (45%), where especially selection bias could influence study outcomes (Andersen et al., 2011; Coats et al., 2013; Hoffman et al., 2014). Additionally, therapeutic validity was high in all studies. In the seven remaining rehabilitation studies, a low methodological quality was found due to selection (Andersen et al., 2013; Arbane et al., 2014; Cheville et al., 2013; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012), reporting (Arbane et al., 2011, 2014; Cheville et al., 2013; Granger et al., 2013; Quist et al., 2012), performance (Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013), and attrition bias (Andersen et al., 2013; Arbane et al., 2011, 2014; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012). Of these seven studies, three had a low therapeutic validity due to lack of eligibility criteria (Arbane et al., 2011, 2014; Kuehr et al., 2014; Quist et al., 2012), lack of rationale for the content and intensity of the program (Arbane et al., 2011; Quist et al., 2012), or no personalized exercises (Arbane et al., 2014; Kuehr et al., 2014; Quist et al., 2012). The three studies assessing home-based training alone had a high therapeutic validity, and a moderate (Coats et al., 2013; Hoffman et al., 2014), and low (Cheville et al., 2013) methodological quality. The interobsever agreement for methodological quality was very good (kappa 0.80) and for therapeutic validity good (kappa 0.76).

Across included studies, only one described specific demands for therapist and setting (Hoffman et al., 2014) and four did personalize exercises (Andersen et al., 2013; Arbane et al., 2014; Granger et al., 2013; Hoffman et al., 2014). Selective dropout in six studies could have led to attrition bias (Andersen et al., 2013; Arbane et al., 2011, 2014; Granger et al., 2013; Kuehr et al., 2014; Quist et al., 2012). Five studies did not display results entirely or did not report on significance, thereby inducing reporting bias (Arbane et al., 2011, 2014; Cheville et al., 2013; Granger et al., 2013; Quist et al., 2012). The included randomized controlled trials did not perform blinding for randomization, participants, or personnel. Therefore, these studies were at risk for performance and detection bias (Arbane et al., 2011, 2014; Brocki et al., 2014; Cheville et al., 2013; Granger et al., 2013).

4. Discussion

The aim of this systematic review was to evaluate feasibility and effectiveness of prehabilitation and rehabilitation including a home-based component for patients with NSCLC and to describe physical fitness, adherence, treatment tolerance, and recovery.

4.1. Summary of evidence

Ten rehabilitation studies and one prehabilitation study were included (451 patients with NSCLC). Patients included in this review were diagnosed with stage I–IV disease, and most underwent surgery with or without (neo)adjuvant treatment (308 of 496 (62%)). However, studies in which patients received radiotherapy, chemotherapy, chemoradiotherapy, or palliative care were also included. Rehabilitation studies including a home-based component showed significantly or clinically relevant increased physical fitness. Home-based prehabilitation may increase physical fitness as well, although only one published study was found. Patient adherence and exercise adherence were generally higher and sufficient in home-based interventions compared to combinations of home-based, intramural- and/or extramural training. It remains unclear wether home-based prehabilitation can lead to less adverse events or hospitalization time, while rehabilitation including a home-based component might improve recovery after treatment.

Highest patient adherence and/or exercise adherence together with significant or clinically relevant improvements in physical fitness can be reached by home-based interventions, as was seen in three studies including home-based interventions only (Cheville et al., 2013; Coats et al., 2013; Hoffman et al., 2014). However, it should be mentioned that these were two pilot studies (Coats et al., 2013; Hoffman et al., 2014) and one randomized controlled trial (Cheville et al., 2013), and other included studies with a home-based component did not always report compliance of home-based exercises (Andersen et al., 2011, 2013; Arbane et al., 2011, 2014; Granger et al., 2013). Still, physical fitness did not differ between home-based training alone and those with additional extramural sessions (Brocki et al., 2014). Probably, newly diagnosed lung cancer patients show interest and motivation for exercise programs, in which home-based training during treatment was preferred (Karvinen et al., 2016). As patients with NSCLC are often older and frail (Hsu et al., 2015; Semrau et al., 2014; Hoogeboom et al., 2012), commuting and accessibility to in- and outpatient facilities hin-

Table 5
Results of therapeutic validity according to 'The CONTENT scale'.

First author year	Description patient selection	Adequate patient selection	Eligibility criteria for therapist and setting determined and adequate	Therapeutic exercise based on a priori aims and intentions	Rationale for content and intensity described and plausible	Intensity described	Therapeutic exercise monitored and adjusted when necessary	Exercises personalized and contextualized to individual	Adherence determined and acceptable	Therapeutic validity
Andersen 2011	+	+	–	+	+	+	+	–	+	High
Andersen 2013	+	+	–	+	–	+	+	+	–	High
Arbane 2011	+	+	–	+	–	–	+	+	–	Low
Arbane 2014	+	+	–	+	+	+	–	–	–	Low
Brocki 2014	+	+	–	+	–	+	–	–	+	Low
Cheville 2013	+	+	–	+	+	+	–	–	+	High
Coats 2013	+	+	–	+	+	+	+	–	+	High
Granger 2013	+	+	–	+	–	+	+	+	+	High
Hoffman 2014	+	+	+	+	+	+	+	+	+	High
Kuehr 2014	+	+	–	+	+	–	+	–	–	Low
Quist 2012	+	+	–	+	–	+	+	–	–	Low

Score: + 'performed', – 'not performed'; *Therapeutic validity:* high '≥6 times +', low '<6 times +'.

der participation in clinic-based exercise programs (Oosting et al., 2012). Therefore, exercise programs should be delivered at the patient's own living situation to optimize adherence (Oosting et al., 2012). Furthermore, regular supervision (Dalal et al., 2010), and a personalized training program (Spruit et al., 2013; Royal Dutch Physiotherapy Society, 2008; Netherlands Cancer Registry, 2011; Pouwels et al., 2015) can further increase adherence rates by facilitating motivation and a physically active lifestyle, as is recognized by the CONTENT scale (Hoogeboom et al., 2012; Herbert and Bø, 2005). At the time of cancer diagnosis, patients are more susceptible to persue a healthy lifestyle to optimize treatment outcomes and general health (Westmaas et al., 2015). In two included studies, increased physical fitness maintained several weeks (Kuehr et al., 2014), and ten months (Brocki et al., 2014) after the intervention without additional exercise instructions. This was previously found in surgical patients with NSCLC receiving prehabilitation and/or rehabilitation ((p)rehabilitation), although home-based exercises were not included in these studies (Ni et al., 2016; Cavalheri et al., 2014). Despite the fact that improvement of treatment tolerance or recovery is the driving force behind the concept of (p)rehabilitation, it was either not reported or reported by diverse parameters (number of complications or hospitalization days). Trials mainly included fit and selected patients without comorbidities, leaving older and high-risk patients underrepresented (Kilari et al., 2016).

Most rehabilitation studies combine intramural and/or extramural training with home-based exercises. Also, there is heterogeneity in the contents of training sessions, and their planning and sequences. Higher training intensity and use of devices such as bicycles and treadmills were more present in intramural and extramural sessions, whereas home-based sessions included lower intensity and more simple instruments. The broad patient population provided in our review included different stages of disease, treatment options, age groups, and physical fitness. This heterogeneity reflects everyday clinical care and probably explains the observed wide range of effect sizes and maximal capable improvements in treatment outcomes. However, it hinders the interpretation of summarized results, and effects of interactions between training contents and patient characteristics are warranted. Furthermore, natural physical recovery comes into play as increased physical fitness cannot be explained by the intervention solely, emphasizing the importance of control groups in studies.

4.2. Strengths and limitations

Strengths of this study are the independent literature search, selection, and data extraction by two reviewers with good agreement, thereby preventing errors in study and data selection, and limiting reporting bias (Cochrane Statistical Methods Group and Cochrane Bias Methods Group, 2011b). Also, therapeutic validity was assessed, providing more insight in reported study outcomes, as a low therapeutic quality might explain decreased effectiveness of the intervention compared to what was expected (Hoogeboom et al., 2012). Nevertheless, the outcomes of this systematic review should be interpreted carefully due to several contstraints. Only three studies incorporated home-based training alone for (p)rehabilitation. The eight remaining studies included home-based, intramural- and/or extramural components and as a result, seperate effects of a home-based training component could not be attributed. Also, several pilot studies were included. This means that evidence is still lacking and powered randomized controlled trials are required. Especially for home-based prehabilitation, not all potential eligible studies were available. As negative and non-significant outcomes are less likely to be published, publication bias could lead to a more positive scope of outcomes. Regarding methodological quality, cut off values were not present and categories were arbitrarily chosen. This could lead to an over-

estimation of methodological quality as some types of bias are determined by more than one study characteristic (The Cochrane Collaboration, 2011). Moreover, some components did apply to randomized controlled trials only. Since clinical and statistical heterogeneity impeded the interpretation of patient characteristics and exercise contents, the internal validity of summarized effect sizes for the 6MWT distance is questionable. Therefore, a meta-analysis could not be performed despite the vast number of studies and patients included (Herbert and Bø, 2005). Furthermore, the goal of (p)rehabilitation will be different for patients receiving surgery, radiotherapy, chemoradiotherapy, chemotherapy, and palliative treatment. As the included patient group was heterogeneous with different prognoses and applied treatment regimens, various effects can be expected which cannot be explained by (lack of) effectiveness of (p)rehabilitation.

Several types of bias could influence methodological quality. Selection bias in non-randomized studies and omission of blinding participants or personnel could lead to increased motivation and more positive study results. Although it is almost impossible to perform blinding during physical interventions, one study was able to apply this on outcome assessors and patients (Granger et al., 2013). Attrition bias could have influenced results, although most patients indicated a reason for withdrawal. Nevertheless, some were unknown and could disguise potential negative treatment effects such as worse physical functioning or fatigue (Ni et al., 2016; Pouwels et al., 2015). Selective reporting is a concern as data regarding statistical significance were not always displayed for the home-based component specifically. Yet, evaluating whether there was a clinically relevant improvement in cardiorespiratory fitness after (p)rehabilitation was possible for all studies using the 6MWT distance. As only physical fitness was included in the search strategy, missing values for adherence treatment tolerance, and recovery were foreseen.

With regard to therapeutic validity, small sample sizes and patient cohort studies allow researchers to provide a flexible training scheme which can be easily monitored and adapted, thereby increasing patient and exercise adherence (Dalal et al., 2010; Pouwels et al., 2015). As a result, effect rates could be based on individually optimized, but slightly incomparable exercise programs (Hoogeboom et al., 2012; Herbert and Bø, 2005). Mainly larger studies disregard components like personalization of exercises and supervision for increasing quality and effectiveness of the intervention. Absolute training effects are more easy to compare in non-personalized fully structured training sessions (Thorsen et al., 2005), resulting in higher methodological quality. However, the main goal of home-based (p)rehabilitation should be to enhance and preserve wellbeing and everyday life in patients with NSCLC (Salander and Lilliehorn, 2016). Therefore, a patient tailored program with a necessity-based design should be at best interest, together with the highest therapeutical and methodological quality (Gridelli et al., 2007; Kilari et al., 2016). Furthermore, all patients with NSCLC can benefit from increasing endurance and muscle strength in order to optimize treatment outcomes by home-based (p)rehabilitation. However, the selection of patients should mainly focus on older and high-risk patients and how to increase accessibility to home-based, supervised, and personalized sessions in order to maximize training, physical fitness, adherence, treatment tolerance, and recovery (Kilari et al., 2016).

In conclusion, this systematic review showed positive and encouraging results of (home-based) (p)rehabilitation on physical fitness for patients with NSCLC. Although included studies varied in quality, and quantity, results of this review indicate that combining (home-based) resistance and endurance training, as well as supervision and personalization, seem necessary to optimize physical fitness, adherence, treatment tolerance, and recovery. Although different training contexts have been included in this review, home-based training alone has not been studied extensively and several studies were underpowerd. Therefore, additional randomized controlled trials are required. This sets priority for prospective trials including older and high-risk patients with NSCLC, in which supervision, personalization, and high methodological and therapeutic quality in a home-based context are investigated. Ultimately, more evidence for home-based (p)rehabilitation can be gathered leading to improved physical fitness, patient adherence, exercise adherence, and especially recovery and treatment tolerance in this predominantly high-risk patient group.

Conflict of interest

None.

Acknowledgements

The responsibility for the content of the manuscript is taken by ED. Both ED and MP have made substantial contributions to the acquisition of data, analysis and interpretation. All authors contributed to the interpretation and critical revision of the contents of the manuscript, provided approval for the current manuscript version, and agreed to be accountable for all aspects of the work and remaining questions. This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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