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Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis

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Abstract

Lung cancer is the leading cause of cancer-related death worldwide. For early stages of the disease, lung resection surgery remains the best treatment with curative intent, but significant morbidity is associated, especially among patients with poor pulmonary function and cardiorespiratory fitness. In those cases, the implementation of a preoperative exercise-based intervention could optimize patient's functional status before surgery and improve postoperative outcomes and enhance recovery. The aim of this systematic review is to provide the current body of knowledge regarding the effectiveness of a preoperative exercise-based intervention on postoperative and functional outcomes in patients with lung cancer submitted to lung resection surgery. A systematic review of the literature using CINAHL, EMBASE, MEDLINE, Pubmed, PEDro and SCOPUS was undertaken in September 2015 yielding a total of 1656 references. Two independent reviewers performed the assessment of the potentially eligible records against the inclusion criteria and finally, 21 articles were included in the review. Articles were included if they examined the effects of an exercise-based intervention on at least one of the selected outcomes: pulmonary function, (functional) exercise capacity, health-related quality of life (HRQoL) and postoperative outcomes (length of stay and postoperative complications). Fourteen studies were further selected for a meta-analysis to quantify the mean effect of the intervention and generate 95% confidence intervals (CIs) using the Cochrane Review Manager 5.0.25. For two of the outcomes included (exercise capacity and HRQoL), studies showed large heterogeneity and thus, a meta-analysis was considered inappropriate. Pulmonary function (forced vital capacity and forced expiratory volume in 1 s) was significantly enhanced after the intervention [standardized mean difference (SMD) = 0.38; 95% CI 0.14, 0.63 and SMD = 0.27, 95% CI 0.11, 0.42, respectively]. In comparison with the patients in the control groups, patients in the experimental groups spent less days in the hospital (mean difference = −4.83, 95% CI −5.9, −3.76) and had a significantly reduced risk for developing postoperative complications (risk ratios = 0.45; 95% CI 0.28, 0.74). In conclusion, preoperative exercise-based training improves pulmonary function before surgery and reduces in-hospital length of stay and postoperative complications after lung resection surgery for lung cancer.

Keywords: Lung cancer • Exercise • Preoperative care

INTRODUCTION

Lung cancer is the leading cause of cancer-related death worldwide [1] and is expected to exceed cardiovascular diseases as the top cause of death in the next few years [1]. According to the American Cancer Society, lung cancer accounts for 13% of all new cancer diagnoses and 27% of cancer deaths [1]. In Spain, the latest report of the National Institute of Statistics [2] demonstrated that in 2013, 21 664 people died of lung cancer, representing a 0.8% increase in comparison with the previous data.

Approximately 85% of all diagnoses of lung cancer correspond to non-small-cell lung cancer (NSCLC) [3, 4]. For early stages of the disease (Stages I and II), lung resection surgery is the treatment of choice [5, 6]. Unfortunately, only ∼20–25% of all cases are considered eligible to undergo surgery at the time of diagnosis [5, 7]. On top of that, individuals with lung cancer are frequently old [8], had a smoking history [9], exhibit low cardiorespiratory fitness [10] and suffer from cardiovascular and respiratory comorbidities, which are known to negatively impact surgical tolerability and increase perioperative risk [7, 11]. Both cardiopulmonary fitness (VO_{2peak}) and functional capacity are considered strong predictors of postoperative complications, postoperative mortality and long-term survival in NSCLC [12–15]. Aerobic training is contemplated as the best way to improve cardiopulmonary fitness and exercise

performance in healthy adults [10]. In addition, when part of a pulmonary rehabilitation programme, aerobic training (AT) has demonstrated to improve dyspnoea, functional capacity and health-related quality of life (HRQoL) in patients with a variety of chronic respiratory diseases [16–19]. During the past decade, there has been a growing interest regarding the role of a pulmonary rehabilitation programme in the perioperative period of lung resection surgery. To date, only pulmonary rehabilitation has been used routinely for selected high-risk patients undergoing thoracic surgery, including lung transplantation and lung reduction volume surgery, to increase their functional capacity and prevent further clinical and physical deterioration [17, 20, 21]. However, it is unclear whether an exercise intervention could yield similar effects in the lung cancer population. To answer this question, several systematic reviews including one focused on preoperative exercise training alone have been published and they conclude that exercise training is safe in the lung cancer setting and appears to increase functional capacity and reduce postoperative morbidity [22–26]. However, none of these reviews have performed a meta-analysis to measure the effect size of the interventions on the reported outcomes. Therefore, the aims of this systematic review are (i) to investigate the impact of a preoperative exercise-based intervention on functional outcomes in patients awaiting lung cancer surgery, (ii) to establish the effectiveness of the intervention on postoperative complications and hospital length of stay (LOS) in comparison with standard care (no prehabilitation) and (iii) to conduct a meta-analysis and pool results to measure the effects of the intervention in each of the outcomes examined.

MATERIALS AND METHODS

Protocol

A protocol for this systematic review has been registered in the PROSPERO database under the registration number CRD42015024283. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines were applied [27].

Eligibility criteria

Articles were deemed eligible if they were (i) randomized or non-randomized controlled trials (RCTs and nRCTs), cohort studies or case–control studies involving patients with suspected or confirmed NSCLC or lung malignancy, (ii) preoperative exercise-based intervention, involving both endurance and/or resistance training and (iii) reported results on at least one of the following outcomes: exercise capacity, functional capacity, HRQoL, pulmonary function or postoperative complications and length of stay. Systematic or narrative reviews, abstracts and conference papers were excluded as well as non-preoperative interventions and studies involving other cancer patients. Only articles published in English, Spanish or French were included.

Type of interventions

Studies must evaluate an exercise-based intervention focused on endurance or resistance training or a combination of both. Additionally, studies could include other interventions such as breathing exercises (BEs), incentive spirometry, inspiratory muscle training (IMT), stretching or relaxation and education regarding exercise and physical activity.

Outcomes

Studies must provide results from at least one of the following outcomes: (i) exercise capacity or functional exercise capacity; (ii) pulmonary function; (iii) HRQoL or (iv) postoperative outcomes.

Information sources and search strategy

Prior to this systematic review, the Cochrane Library, PROSPERO and PEDro were searched to ensure that no other similar review was published or being undertaken at the moment. The following databases were searched to identify potentially eligible records: CINAHL (1982–2014), EMBASE (1974–2014), MEDLINE (1950–2014), PEDro (1990–2014), PUBMED (1974–2014) and SCOPUS (1975–2014). A manual crossed search was also conducted among the previous identified records. No restrictions were applied. The following terms were combined in the database search: 'Exercise Therapy' OR 'Exercise Training' OR 'Pulmonary Rehabilitation' AND 'Lung Neoplasms' OR 'Lung Cancer'. For the PEDro database, we introduced only the term 'Lung Cancer' as it is a specific physiotherapy database. The full description of the search terms can be found in Supplementary File 1. The last search was conducted on 17 September 2015.

Study selection

A flow diagram of the study selection process is shown in Fig. 1. One reviewer (Raquel Sebio Garcia) performed the search and initial eligibility assessment on the basis of title and abstracts against the inclusion criteria. After removing for duplicates and not relevant records, two independent reviewers (Raquel Sebio Garcia and Maria Isabel Yáñez Brage) assessed all abstracts and identified the potentially eligible records. Full-text analyses of those deemed eligible were conducted by two independent reviewers (Raquel Sebio Garcia and Maria Isabel Yáñez Brage). In the presence of a disagreement, this was settled by a third reviewer (Esther Giménez Moolhuyzen). All references were stored in Endnote X7 (Thomson Reuters, Thomson Corporation, USA) during the study period.

Data collection process

Data from each article were extracted by one reviewer (Raquel Sebio Garcia) into a standardized form. Another review author checked the extracted data. Disagreements were resolved by a discussion between the two authors. If no agreement was achieved, it was planned for a third author to decide. Data extracted were stored in a Microsoft Office Excel 2010 (Microsoft Corporation®, Redmond, Washington, USA) spreadsheet.

Data items

Collected items were classified into four main categories: (i) design, (ii) participants, (iii) intervention and (iv) outcomes. A complete list of the items included can be found in Supplementary File 2. Authors were contacted by e-mail when any of the listed items were missing or insufficiently described. Sixteen authors were reached and after two attempts, six (37.5%) responded.

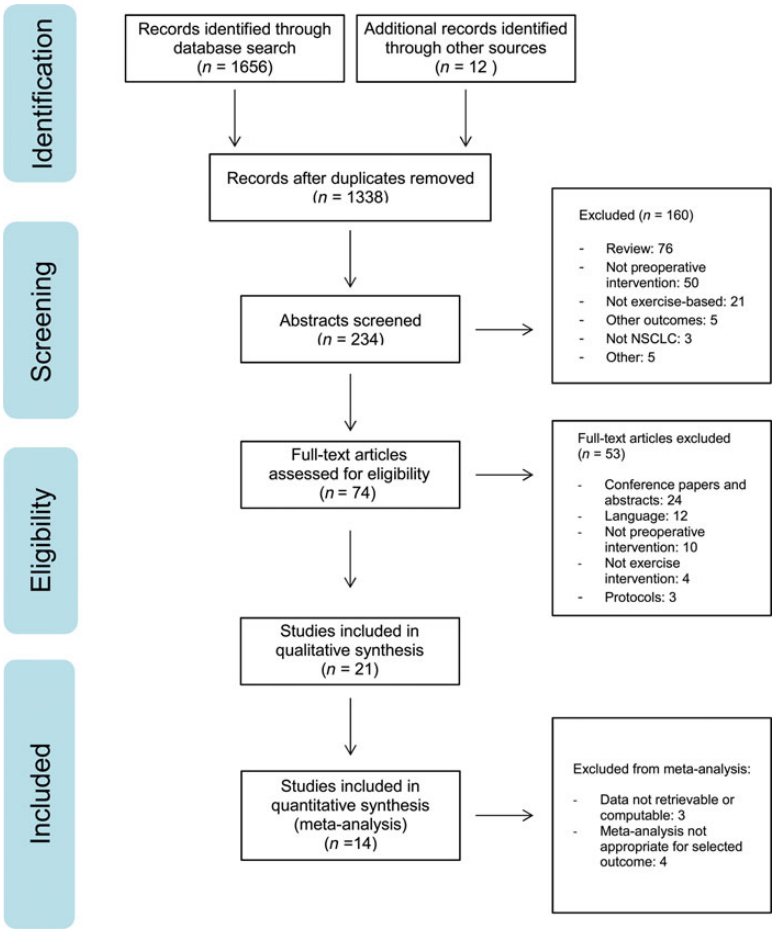

Figure 1: PRIMSA study flow diagram of the selection process. NSCLC: non-small-cell lung cancer; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

Risk of bias in individual studies

The assessment of risk of bias was conducted using the PEDro scale for RCTs and the Newcastle–Ottawa quality assessment scale (NOS) for cohort studies. The evaluation was conducted independently by two reviewers for each article (Raquel Sebio Garcia and Esther Giménez Moolhuyzen). In case of a disagreement, this was settled by a third reviewer (Maria Isabel Yáñez Brage).

Summary measures

The principal summary measures of this systematic review were differences in mean change of exercise capacity (VO_{2peak}) and functional capacity (metres) before and after a preoperative rehabilitation programme. Secondary summary measures include mean differences in pulmonary function (pre–post-intervention), mean differences in hospital LOS and risk ratios (RRs) of postoperative complications. Two articles [28, 29] reported data as median and range (or interquartiles) and estimations of the mean and SD were made according to the available formulas [30].

Synthesis of results and statistical analysis

For each outcome of interest, the standardized or mean difference (continuous variables) or RR (dichotomous variables) was calculated and 95% confidence intervals (CIs) were computed for statistical significance. Forest plots were generated to illustrate the study-specific effect size. Meta-analyses and pooled estimated effect sizes were undertaken when considered appropriate according to the number of studies included, measurement properties and between-studies variability. Heterogeneity was assessed using the χ^2 and the I^2. A P-value of ≤ 0.1 for the χ^2 or $I^2 \geq 50\%$ was considered as substantial heterogeneity and a subgroup analysis was run to explore possible reasons. All analyses were performed using the Review Manager® (RevMan) 5.3 version for Windows® (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration) based on a random-effects model.

RESULTS

Study selection

A flow diagram of the study selection is shown in Fig. 1. Six databases were screened yielding a total of 1656 studies. Additionally, 12 studies were identified from cross-manual search and personal records, accounting for a total of 1668 references. After removing from duplicates and non-relevant records, 234 articles were assessed by title and abstract, and 51 were selected for full-text analysis. Finally, 21 articles involving 17 participant samples fulfilled the inclusion criteria and were included in the review.

Study characteristics

The main characteristics of each study included are summarized in Table 1.

Design. This systematic review included five RCTs [12, 29, 36, 39, 44], three nRCTs [40, 43, 46], three retrospective cohort studies [31, 37, 47], one prospective cohort study [28] and nine prospective case series [14, 32–35, 38, 41, 42, 45]. Seven studies compared a rehabilitation programme versus no intervention (control group) [12, 28, 36, 39, 43, 45, 46], whereas three studies compared two different interventions [29, 37, 44]. One study [12] evaluated two RCTs at the same time, but only one of them (#2) was included in this review since data from the first study were incomplete.

Participants. A total of 1189 patients participated in the studies, 595 subjects in the rehabilitation groups and 594 in the controls. The mean age was 64.8 ± 5.28 in the experimental groups and 64.3 ± 6.3 in the controls, and almost 62% were men in both the groups. All studies included patients with NSCLC or a mixed cohort of lung cancer types [32, 34, 35]. Most patients were diagnosed with an early stage of the disease (Stages I–IIIA) and three studies included individuals who had undergone or were undergoing neoadjuvant therapy [42, 43, 47]. Lung resection was mostly performed by an open thoracotomy [14, 28, 31, 39–41, 43, 45, 47], whereas some studies included a small percentage of patients operated by video-assisted thoracic surgery (VATS) also [12, 29, 37, 46]. Only in one study, patients were operated by VATS alone [42] (data retrieved from the authors). The extent of parenchyma resected varied across studies with lobectomy being the most common procedure according to the international guidelines [4, 5].

Type of interventions. A brief summary of the interventions is presented in Table 2.

Studies were undertaken in Europe [14, 28, 33, 36, 38, 39, 41, 45], Asia [31, 37, 40, 43, 46, 47] and America [12, 29, 32, 34, 35, 42, 44]. The majority of them were conducted as an outpatient intervention at a hospital or a training facility. Only one investigation tested a home-based intervention [42]. Four studies resumed the rehabilitation programme after surgery [28, 31, 36, 43]. Three studies provided standard postoperative physiotherapy care until hospital discharge [38, 45, 47].

The modality of exercise prescribed was predominantly AT for lower and/or upper limbs [31–35, 37–41, 47] or a combination of aerobic plus strength training [12, 14, 28, 42]. Only two studies focused on strength training alone [43, 45]. Breathing exercises or incentive spirometry was performed in 15 of the 21 studies [12, 14, 28, 31, 33, 36–41, 43, 45, 47]. Inspiratory muscle training was also performed in four studies [12, 29, 41, 44]. Other minority interventions included educational sessions [28, 33, 38, 45], relaxation techniques [38, 43, 47], stretching [14, 29, 44], non-invasive ventilation [38] and functional electrical stimulation of the abdominal muscles [33].

The total duration of the interventions ranged from 1 week to 10 (median 4) weeks with a median frequency of five sessions per week (range 2–14). Intensity was described in the studies as moderate to high and was generally individually tailored according to the patient's tolerance. Adherence was poorly assessed [32, 34, 35, 42] and only two adverse events were recorded (abnormal decline in systolic blood pressure) [32].

Outcomes

Primary outcomes. Cardiopulmonary fitness (measurement of VO_{2peak}) was the main [14, 32, 39, 42] or the secondary [34, 35, 38, 40, 41] outcome in nine studies. Functional capacity (field test) was also assessed in 11 studies [12, 28, 29, 32, 33, 35, 36, 41, 42, 44, 45].

Pulmonary function was measured in 13 studies as the primary [29, 33, 38, 40, 41, 45, 47] or secondary end-point [14, 28, 31, 32, 37, 39]. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1) and diffusion of carbon monoxide (DLCO) were frequently reported. Maximal inspiratory and expiratory pressures were also examined in one study [29].

Only four articles assessed the impact of the preoperative rehabilitation programme on HRQoL as the primary [34, 43] or the secondary outcome [42, 44] using a lung cancer-specific questionnaire [34, 43] or a generic instrument [42, 44].

Nine studies reported the postoperative outcomes as the primary [12, 31, 36, 37, 46] or secondary [28, 29, 40, 45] study end-point. Postoperative morbidity (frequency of postoperative complications) and postoperative LOS were recorded.

Secondary outcomes. Other additional outcomes assessed in the studies were the feasibility [42] and cost-effectiveness of the intervention [28, 46], muscle strength [42], fatigue [34], inflammatory markers [35] and fibrinogen and albumin levels [44].

Risk of bias within studies. Risk of bias for individual studies was assessed by two independent reviewers (Raquel Sebio Garcia and Esther Giménez Moolhuyzen) achieving a total agreement of 69.8% according to the Kappa index with the largest difference between raters being of 2 points. The results are provided in Tables 3 and 4. Table 3 displays the quality evaluation of the RCTs and nRCTs, whereas Table 4 depicts the results of the NOS scale for the observational studies. The median score for the RCTs and nRCTs according to the PEDro scale was 5 (range 2–8). This falls below the published score in PEDro for moderate to high quality (6/10 points), but it is similar to the mean found in the specific cardiothoracic research [48]. On the other hand, the median score for the observational studies according to the NOS was 6 (range 4–8), which is classified as high risk of bias [49].

Results from individual studies. Studies reported a statistically significant mean change in VO_{2peak} after the interventions [32, 34, 35, 38–41]. Coats *et al.* [42] found no difference in VO_{2peak}, but they reported a significant and clinically meaningful improvement in the constant endurance test (CET) after 4 weeks of a home-based endurance and strength training. Two studies also registered an increase in the maximal workload (WMax) achieved during the cardio-pulmonary exercise test [14, 40].

Changes in functional capacity measured with the six-minute walk test (6MWT) demonstrated an improvement from baseline to post-intervention [28, 29, 32–34, 41, 42]. Benzo *et al.* [12] failed to find any significant difference after the training, but data from this study were not retrievable and therefore it was not possible to obtain the mean difference and 95% CI. Pehlivan *et al.* [36] found a significant improvement in exercise performance, but since they used a non-standardized test the results were not incorporated into the forest plot.

Both FVC and FEV1 were significantly enhanced after the intervention compared with baseline [28, 29, 33, 36–38, 40, 41, 45, 47]. Jones *et al.* [32] found no differences in any of the pulmonary function parameters after 8 weeks of intense aerobic exercise training. Only two studies compared the pulmonary function between

Table 1: Characteristics of the studies included in the systematic review

	Study	Design	Participants	Type of cancer	Stage	Outcomes
1	Sekine *et al.* [31]	Retrospective cohort study	22 (rehabilitation) + 60 (historical controls)	NSCLC	I–IV	LOS PPC Pulmonary function (postoperative FEV1)
2	Jones *et al.* [32]	Prospective case series	20	Lung cancer and other primary tumours	I–IIIA	Exercise capacity (VO_{2peak}) Functional capacity (6MWT) Pulmonary function (FEV1, FVC and DLCO)
3	Cesario *et al.* [33]	Prospective case series	12	NSCLC + severe COPD	IA–IIB	Pulmonary function Functional capacity (6MWT)
4	Bobbio *et al.* [14]	Prospective case series	12	NSCLC	I–IIIA	Exercise capacity (VO_{2Max}, WMax) Pulmonary function (FEV1, FVC and DLCO)
5	Peddle *et al.* [34]	Prospective case series	9	Lung cancer and other primary tumours	I–IV	HRQoL (FACT-L; TOI and LCS) Exercise capacity (VO_{2peak})
6	Jones *et al.* [35]	Prospective case series	20	Lung cancer and other primary tumours	I–IIIA	Exercise capacity (VO_{2peak}) Functional capacity (6MWT) Inflammatory markers
7	Pehlivan *et al.* [36]	RCT	60	NSCLC	IA–IIIB	LOS PPC Pulmonary function (FEV1, FVC, PaO_2, $PaCO_2$, SpO_2, DLCO) Exercise performance (no standardized test)
8	Benzo *et al.* [12] (Study 2)	RCT	19 (rehabilitation 10 + 9 controls)	NSCLC + COPD	NR	PPC LOS Functional capacity (SWT)
9	Harada *et al.* [37]	Retrospective cohort study	50 (CVPR 29 + CHPR 21)	NSCLC + impaired PF	I–IV	Postoperative complications Pulmonary function (VC, FEV1)
10	Bagan *et al.* [38]	Prospective case series	20	NSCLC	IA–IIB	Exercise capacity (PPO VO_{2Max}) Pulmonary function (ppo-FEV1)
11	Stefanelli *et al.* [39]	RCT	40 (20 rehabilitation + 20 controls)	NSCLC + COPD	I–II	Exercise capacity (VO_{2peak}) Pulmonary function (FEV1, FVC, FEV1/FVC, DLCO)
12	Fang *et al.* [40]	nRCT	61 (39 rehabilitation + 22 controls)	NSCLC + COPD	NR	Pulmonary function (FVC, FEV1, FEV1/FVC, DLCO, MVV) Exercise capacity (VO_{2peak}) Postoperative complications LOS HRQoL (results not reported)
13	Divisi *et al.* [41]	Prospective case series	27	NSCLC + COPD	I–IIB	Pulmonary function (FVC, FEV1, FEV1/FVC, PEF, DLCO) Exercise capacity (VO_{2peak}) Functional capacity (6MWT)
14	Morano *et al.* [29]	RCT	24 (12 PR + 12 CPT)	NSCLC + impaired pulmonary function	I–IIIA	Lung function (FVC, FEV1, MIP, MEP, PaO_2, $PaCO_2$, SpO_2, MIP, MEP) Functional capacity (6MWT) PPC LOS
15	Bradley *et al.* [28]	Prospective cohort study	363 (58 rehabilitation + 305 controls)	NSCLC	NR	Functional capacity (6MWT) Pulmonary function (FEV1) PPC LOS
16	Coats *et al.* [42]	Prospective case series	16	NSCLC	I–IV	Exercise capacity (VO_{2peak}, endurance time) Functional capacity (6MWT) Muscle strength HRQoL (SF-36)
17	Li *et al.* [43]	nRCT	48 (24 rehabilitation + 24 controls)	NSCLC	II–IIIB	HRQoL (EORTC QLQ-C30)

18	Morano *et al.* [44]	RCT	24 (12 PR + 12 CPT)	NSCLC + impaired pulmonary function	I–IIIA	Levels of fibrinogen and albumin HRQoL HADS
19	Mujovic *et al.* [45]	Prospective case series	83	NSCLC + COPD	NR	Pulmonary function (FVC, FEV1, $FEF_{25,50\%}$, SaO_2) Functional capacity (6MWT) PPC LOS
20	Gao *et al.* [46]	nRCT	142 (71 rehabilitation + 71 controls)	NSCLC + high surgical risk	I–IV	Postoperative complications LOS Average hospital cost
21	Tarumi *et al.* [47]	Retrospective cohort study	82	NSCLC + chemoradiotherapy	IIB–IV	Pulmonary function

NSCLC: non-small-cell lung cancer; LOS: length of stay; PPC: postoperative pulmonary complications; FEV1: forced expiratory volume in 1 s; VO_{2peak}: peak oxygen consumption; 6MWT: six-minute walk test; FVC: forced vital capacity; DLCO: diffusion of carbon monoxide; WMax: maximal workload; HRQoL: health-related quality of life; FACT-L: Functional Assessment of Cancer Therapy-Lung Cancer; TOI: trial outcome index; LCS: lung cancer subscale; RCT: randomized controlled trial; PaO_2: partial pressure of oxygen; $PaCO_2$: partial pressure of carbon dioxide; SpO_2: oxygen saturation; SWT: shuttle walk test; CVPR: conventional preoperative pulmonary rehabilitation; CHPR: comprehensive preoperative pulmonary rehabilitation; nRCT: non-randomized controlled trial; VC: vital capacity; PPO VO_{2peak}: predicted postoperative VO_{2peak}; ppo-FEV1: predicted postoperative FEV1; MVV: maximal voluntary ventilation; MIP: maximal inspiratory pressure; MEP: maximal expiratory pressure; NR: not reported; SF-36: Short Form 36 Health Survey; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HADS: Hospital and Anxiety Distress Scale; $FEF_{25,50\%}$: forced expiratory flow at 25 and 50%; COPD: chronic obstructive pulmonary disease; PF: pulmonary function; PEF: peak expiratory flow; PR: pulmonary rehabilitation; CPT: conventional physical therapy.

groups after surgery. Sekine *et al.* [31], using an historical control group, found that patients who had completed the prehabilitation programme experienced a smaller reduction in FEV1 1 month after surgery ($P = 0.023$). On the other hand, Stefanelli *et al.* [39] compared both groups 60 days postoperatively and found no significant difference between groups.

Assessment of HRQoL after the training yielded no significant improvement in any of the major domains [34, 42, 44]. However, in comparison with the patients in a control group, Li *et al.* [43] found that patients who underwent the rehabilitation programme displayed higher scores in several domains of the EORTC QLQ-C30 both at 3 and 6 months after surgery. Owing to the small number of studies and uniqueness measurement properties of the questionnaires, mean differences and 95% CIs were not calculated for this outcome.

Finally, in terms of postoperative outcomes, hospital LOS (from surgery till hospital discharge) was significantly reduced in comparison with the standard care, with the exception of the study conducted by Benzo *et al.* [12], where the authors were only able to find a trend towards a reduction which was almost statistically significant ($P = 0.058$). Postoperative morbidity was also significantly reduced, although studies have shown significant heterogeneity [12, 28, 29, 31, 36, 37, 40, 46]. Again, Benzo *et al.* [12] reported only a significant difference in the chest tube duration and incidence of prolonged air leak, whereas Harada *et al.* [37] found that the differences in the rate of postoperative pulmonary complications (PPCs) were only significant among patients presenting with several comorbidities (CCI ≥3).

Synthesis of results. For the primary outcomes (exercise and functional capacity), a large between-study heterogeneity was found and therefore it was not appropriate to conduct a meta-analysis and pool results.

For each of the other outcomes of interest (pulmonary function and postoperative outcomes), a random-effects meta-analysis was performed to estimate the pooled effect size of the interventions pre–post-intervention or in comparison with a control group. Pooled estimates of effect sizes showed a significant increase for both FEV1 [standardized mean difference (SMD) = 0.27, 95% CI 0.11, 0.42] and FVC (SMD = 0.38, 95% CI 0.14, 0.63; Fig. 2A and B). In the postoperative outcomes, a significant reduction in both hospital LOS (mean difference = −4.83, 95% CI −5.90, −3.76) and postoperative complications (RR = 0.45, 95% CI 0.28, 0.73) was obtained (Figs 3 and 4), although the latter showed substantial heterogeneity ($\chi^2 = 20.08$, $P = 0.005$; $I^2 = 65\%$). To elucidate the possible reasons, we conducted a subgroup analysis according to the type of complications reported (pulmonary alone versus pulmonary and others) and found that when pulmonary complications were analysed separately, heterogeneity was significantly reduced without affecting the pooled effect size (RR = 0.55; 95% CI 0.34, 0.89; $I^2 = 27\%$). Heterogeneity was also reduced when patients without impaired pulmonary function were analysed separately. Furthermore, in this subgroup, the RR for developing postoperative complications was not statistically significant (RR = 0.67; 95% CI 0.42, 1.07; $I^2 = 15\%$).

DISCUSSION

This systematic review aimed to examine the current body of evidence on the benefits of engaging in a preoperative exercise-based intervention for individuals with lung cancer. The results

Table 2: Description of interventions included in the studies

Study	Setting	Timing	Type of intervention					Intensity	Duration of session (AT)	Frequency	Length of intervention	Adherence
			AT	ST	BE	IMT	Other[a]					
Sekine *et al.* [31]	Supervised + unsupervised	Pre- + postoperative		–		–	–	NR	45′ (30′)	Everyday	2 weeks	NR
Jones *et al.* [32], Peddle *et al.* [34] and Jones *et al.* [35]	Supervised	Preoperative		–	–	–	–	Continuous and interval: 60–100% of VO^{a}_{2peak}	20–30′	5/week	4–10 weeks	72, 88 and 78%, respectively
Cesareo *et al.* [33]	Supervised	Preoperative		–		–		80% Wmax	3 h (NR)	5/week	4 weeks	NR
Bobbio *et al.* [14]	Supervised + unsupervised	Preoperative				–		50–80% of WMax	90′ (40′)	5/week	4 weeks	80%
Pehlivan *et al.* [36]	Supervised	Pre- + postoperative		–		–	–	%maxHR (Karvonen formula)	NR	3/day	1 week	NR
Benzo *et al.* [12] (Study 2)	Supervised + unsupervised	Preoperative					–	Borg scale	NR (20′)	5/week	2 weeks (10 sessions)	100%
Harada *et al.* [37]	Supervised	Preoperative		–		–		Borg scale	NR	CHPR: 2/week CVPR: 1/week	2–5 weeks	NR
Bagan *et al.* [38]	Supervised	Pre- + postoperative				–		Continuous: 20–30 weeks	NR (30′)	Daily	2 weeks	NR
Stefanelli *et al.* [43]	Supervised	Preoperative		–		–	–	Continuous: at least 70% Wmax	3 h (30)	5/week	3 weeks	NR
Fang *et al.* [40]	Supervised	Preoperative		–		–	–	Interval: 60–80% Wmax	NR (40′)	5/week	2 weeks	NR
Divisi *et al.* [41]	Supervised	Preoperative		–			–	Incremental up to 100% of Wmax	90′ (40′)	6/week	4–6 weeks	NR
Morano *et al.* [29] and Morano *et al.* [44]	Supervised	Preoperative			–			80% Wmax	NR (30′)	5/week	4 weeks	NR
Bradley *et al.* [28]	Supervised	Pre- and postoperative				–	–	Up to 60% Wmax	60′ (NR)	2/week	Variable	NR
Coats *et al.* [42]	Home-based	Preoperative			–	–	–	Continuous (60–80% Wmax)	NR (30′)	3–5/week	4 weeks	75%
Li *et al.* [43]	Supervised	Preoperative	–			–		NR	NR	NR	NR	NR
Mujovic *et al.* [45]	Supervised	Preoperative	–			–		NR	45′ (NA)	3/day; 5/week	2–4 weeks	NR
Gao *et al.* [46]	Supervised	Preoperative		–		–	–	Borg scale (5–7)	1.5–2 h (30–40′)	2/day	3–7 days	NR
Tarumi *et al.* [47]	Supervised (in-patient)	Pre- and postoperative		–		–		?	NR (45′)	5/week	10 weeks	NR

AT: aerobic training; ST: strength training; BE: breathing exercises; NR: not reported; CHPR: comprehensive preoperative pulmonary rehabilitation; CVPR: conventional preoperative pulmonary rehabilitation; VO_{2peak}: oxygen consumption peak; Wmax: maximal workload; maxHR: maximal heart rate; IMT: inspiratory muscle training; COPD: chronic obstructive pulmonary disease; PF: pulmonary function; PEF: peak expiratory flow; PR: pulmonary rehabilitation; CPT: conventional physical therapy.
[a]Education, relaxation, stretching and/or nutritional support.

Table 3: Quality assessment of RCTs and nRCTs with PEDro scale

Study	Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapist	Blind assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimate and variability	Total score
Benzo *et al.* [12] (Study 2)	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6/10
Pehlivan *et al.* [36]	No	Yes	No	Yes	No	No	No	Yes	No	Yes	Yes	5/10
Stefanelli *et al.* [39]	No	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4/10
Fang *et al.* [40]	No	No	No	No	No	No	Yes	Yes	No	Yes	Yes	4/10
Morano *et al.* [29]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	8/10
Morano *et al.* [44]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7/10
Gao *et al.* [46]	No	No	No	No	No	No	No	Yes	No	Yes	Yes	3/10
GLOBAL score (median)												5/10

RCT: randomized controlled trial; nRCT: non-randomized controlled trial.

drawn support the hypothesis that a preoperative pulmonary rehabilitation programme focused on exercise can significantly reduce hospital stay and the incidence of PPCs by enhancing pulmonary function and more likely, exercise tolerance. However, we have found quite heterogeneity among the studies in terms of the intervention prescribed (such as modality of exercise, mode of delivery and frequency, duration) as well as the type of participants included (such as stage of the disease, pre-existing comorbidities and extent of resection), which makes it difficult to draw definitive conclusions.

When setting up a pulmonary rehabilitation programme, there are several factors that should be taken into consideration to maximize the results. In the lung cancer setting, the effectiveness of the intervention appears to be highly influenced by the clinical features of the participants (stage of the disease, presence of comorbidities and baseline status), but also the instruments used to quantify the results. Conventionally, interventions designed to enhance cardiorespiratory fitness in chronic respiratory conditions should last between 8 and 12 weeks, with longer training periods resulting in larger improvements [19, 50]. However, in the presence of lung cancer, the urge to proceed with surgery as soon as possible requires shorter interventions. In a recent systematic review of the effects of prehabilitation in postoperative outcomes, 6–8 weeks have been proposed as an adequate balance between feasibility and efficacy [51], which is consistent with the current time-frame found in most centres. Despite this, Study 1 in the RCT of Benzo *et al.* [12] was promptly closed after 1 year of recruitment because patients or providers were not willing to delay surgery for 4 weeks. On the other hand, Coats *et al.* [42] concluded that a home-based rehabilitation programme for 4 weeks in presurgical lung cancer patients was safe and feasible. Although the recruitment rate for this study was low, (50%) adherence was fairly good (75%) and the completion rate was 81%. Surgery was not delayed in any case although in the study by Divisi *et al.* nine patients needed 2 more weeks of prehabilitation to reach operation criteria.

Measurement tools in the lung cancer setting are diverse and their responsiveness is likely to be related to the stage of the disease [52]. Peak oxygen consumption (VO_{2peak}) provides the gold standard for evaluating cardiorespiratory fitness in healthy subjects [53] and is a strong and reliable predictor of postoperative mortality and morbidity, HRQoL and long-term survival in NSCLC [6, 13, 14, 53–55]. Aerobic training is considered the best way to improve VO_{2peak} in healthy subjects [10] and it has also been successfully prescribed to individuals with several chronic diseases [56–58]. The studies included in this systematic review support the hypothesis that AT is able to improve cardiopulmonary fitness in patients with NSCLC. However, due to the large heterogeneity found in the studies, estimated of pooled effect sizes were not obtained and we cannot draw definitive conclusions. There was only one study that did not report improvements in VO_{2peak} after the training, but patients showed an increment in functional capacity (6MWT) and endurance time (CET) [42]. It has been suggested that a maximal exercise test is not the best instrument to detect intervention-related changes in chronic respiratory diseases [59]. Furthermore, patients were already fit at baseline (107% of predicted VO_{2peak}), so it is likely that the intensity and/or frequency of the training was insufficient to elicit further improvements in this outcome.

Functional capacity was also significantly enhanced across studies, but heterogeneity was found to be substantial and thus a meta-analysis was considered inappropriate. The 6MWT was the most common measure in the studies, according to the literature

[52]. Four of six studies reported an increment of more than 42 m, which has been recently established as the upper limit of the minimally important difference in individuals with lung cancer [60]. Lately, the shuttle walk test (SWT) has gained popularity in the determination of the 6MWT because of its similarity and good correlation with the gold standard (VO_{2peak}) [61]. In this review, only one study used an SWT to measure functional capacity and found no difference after a 10-session, twice-daily intervention of moderate aerobic and strength training [12]. In this study, intensity was moderate according to the Borg scale [12, 13], and it could be insufficient to induce any physiological change leading to an increase in functional performance.

Table 4: Quality assessment of cohort studies and case series studies with Newcastle–Ottawa scale for cohort studies

Study	Selection	Comparability	Outcome	Total score
Sekine *et al.* [31]	XXXX	XX	XX	8/9
Cesario *et al.* [33]	XX	NA	XXX	5/9
Jones *et al.* [32]	XXX	NA	XXX	6/9
Bobbio *et al.* [14]	XXX	NA	XXX	6/9
Peddle *et al.* [34]	XXX	NA	XXX	6/9
Harada *et al.* [37]	XXXX	XX	X	7/9
Bagan *et al.* [38]	XXX	NA	X	4/9
Divisi *et al.* [41]	XXX	NA	XXX	6/9
Bradley *et al.* [28]	XXX	XX	XX	7/9
Coats *et al.* [42]	XXX	NA	XXX	6/9
Mujovic *et al.* [45]	XXX	NA	XXX	6/9
Tarumi *et al.* [47]	XXX	NA	XXX	6/9
GLOBAL score (median)				6/9

Given the important role that pulmonary function plays in stratifying patients for postoperative risk [7], optimizing FEV1 and DLCO through targeted exercises could result in a higher number of patients undergoing surgery with curative intent, improving their prognosis and prolonging lifespan. In the meta-analysis, pooled results have shown that a significant increase in both FEV1 and FVC can be achieved after a preoperative pulmonary rehabilitation program. Conversely, there is currently no evidence to support that the addition of BE or IMT to an exercise intervention provides any additional benefit in patients with chronic obstructive pulmonary disease (COPD) [18]. However, BE has been insufficiently described in the literature and is arbitrarily used in to refer to several interventions [62], which can lead to undesirable and biased results in this and similar population.

The HRQoL was infrequently assessed in studies included in this systematic review. Preoperative HRQoL (and physical functioning especially) has been associated with greater overall and cancer-related survival in early stages of NSCLC [63]. Unfortunately, research conducted so far in cancer patients yielded unfavourable results, showing little to no change in HRQoL with a perioperative intervention [22, 23, 64]. This is consistent with our systematic review, where studies failed to find any significant improvement in HRQoL after the rehabilitation programme [34, 42, 44]. Interestingly, Li *et al.* [43] found that in comparison with the patients in a control group, patients in the intervention arm showed great improvements in global health, physical functioning and symptom severity, both at 3 and 6 months after the surgery. However, this was a non-randomized study with several methodological flaws, so these findings should be interpreted carefully.

Finally, postoperative morbidity is regarded as the main cause for increased overall hospital costs and long-term impairment. PPCs are particularly the most costly and are associated with an increase in hospital LOS in comparison with patients without

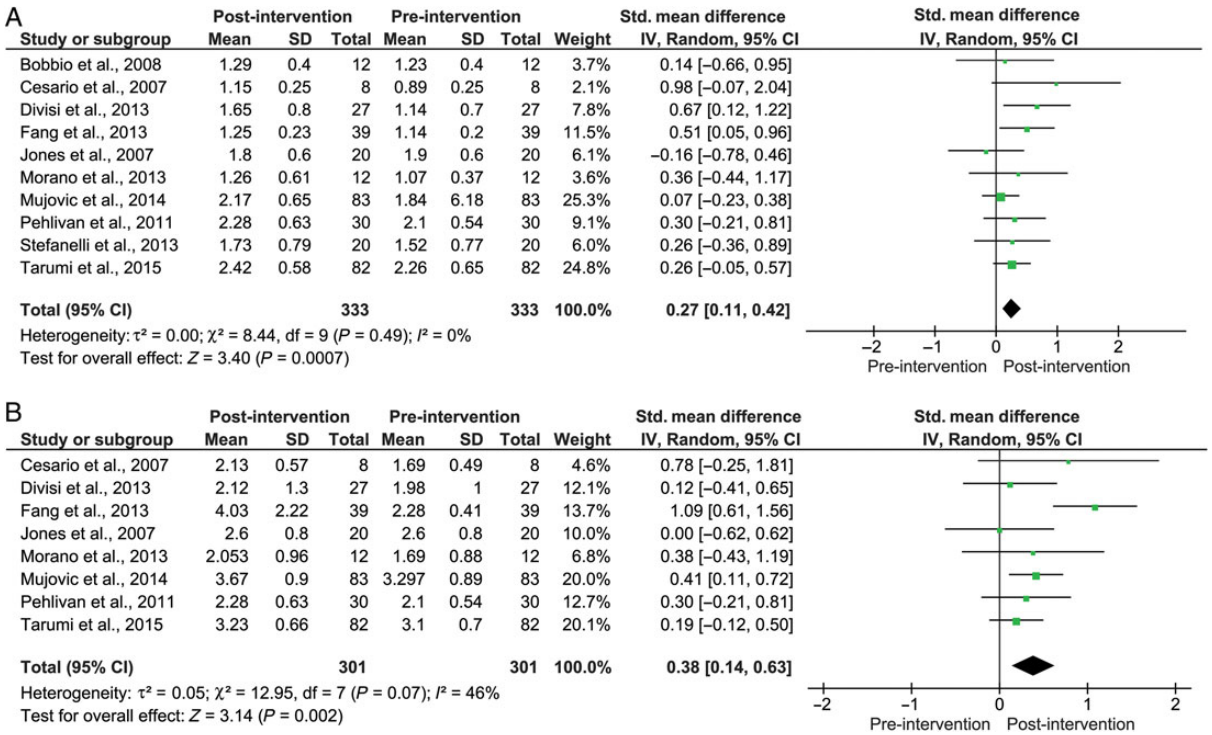

Figure 2: Pooled effect size of the interventions on forced expiratory volume in the first second (**A**) and forced vital capacity (**B**). 95% CI: 95% confidence interval; SD: standard deviation.

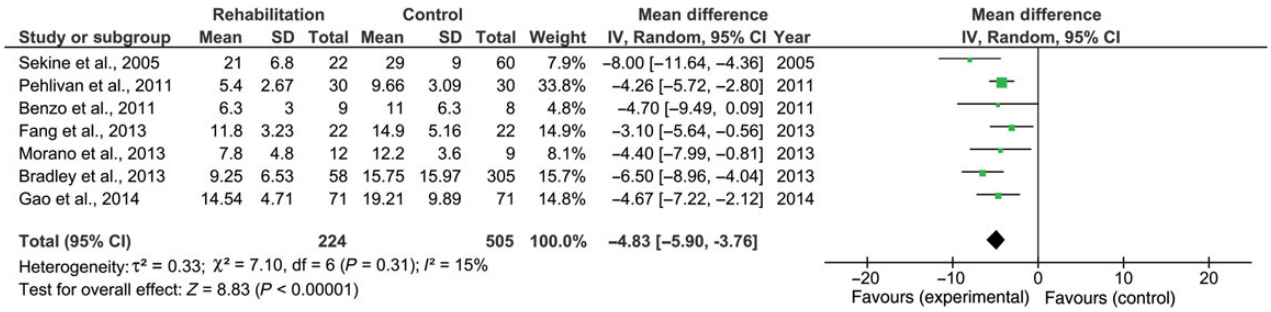

Figure 3: Meta-analysis and pooled estimated effect size for postoperative length of stay in the intervention and control group. 95% CI: 95% confidence interval; SD: standard deviation.

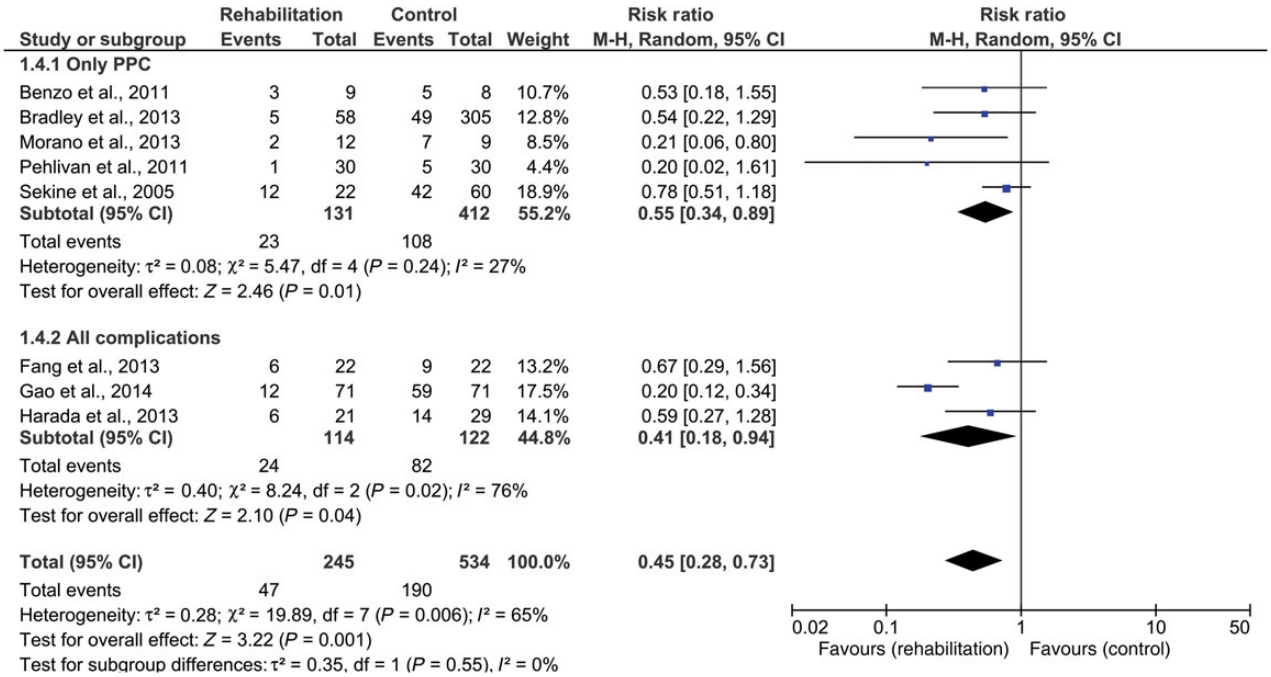

Figure 4: Subgroup analysis for postoperative complications (pulmonary versus all complications). 95% CI: 95% confidence interval; SD: standard deviation; STD: standardized; PPCs: postoperative pulmonary complications.

complications [65, 66]. In the long term, PPCs have been also shown to have an impact on cancer-related survival [67] increasing the risk of mortality regardless the stage of the disease. Risk factors associated with higher rates of postoperative complications include advance age (over 70 years old), ppo-FEV1 or ppo-DLCO less than 60%, cardiovascular morbidity, low cardiorespiratory fitness, smoking status, high BMI and the presence of COPD [10, 68–71]. Numerous studies have been undertaken to assess the efficacy of several interventions to prevent complications after thoracic surgery, but results are inconsistent [71–74]. In this meta-analysis, a significant reduction in both postoperative LOS and postoperative complications has been reported, with the latter showing a relative risk reduction of 55% in those patients undergoing rehabilitation in comparison with the patients in the standard care. Furthermore, when only pulmonary complications were taking into consideration, we observed that the mean effect size was maintained and heterogeneity between studies was remarkably reduced ($\chi^2 = 5.47$, df = 2; $P = 0.24$; $I^2 = 27\%$). However, the studies included in the review encompassed both patients with and without impaired pulmonary function. As previously mentioned, COPD is a well-established risk factor for PPCs; therefore, those patients with normal pulmonary function may not show the same reduction in postoperative morbidity after a preoperative pulmonary rehabilitation programme. The same rationale could be extended to those patients operated with VATS. As reported in the majority of comparative studies performed, patients undergoing VATS experience less postoperative morbidity and shorter LOS [75–77]. However, even though VATS is gaining popularity for the treatment of lung cancer, more than 75% of the surgeries are still performed using the traditional approach [78], hence the relevance of this particular topic.

Limitations

This systematic review and meta-analysis have several limitations. First, in view of the lack of RCTs in the topic, we also included non-randomized controlled trials and observational studies, which are more easily biased and can potentially affect the validity and reliability of the findings. Another major limitation is that most patients were operated using an open approach; thus, it is not known whether these findings could be also found in VATS given that this approach has shown significantly less morbidity. Finally,

the assessment of publication bias was not considered appropriate in the meta-analyses because of the small number of studies involved. However, the novelty of the research field (the oldest article being published in 2005), plus the differences in the results (with some studies showing little or no results), indicates that publication bias has probably not influenced our results.

CONCLUSIONS

The results of this systematic review indicate that an exercise-based intervention performed in the preoperative period of lung cancer surgery appears to increase exercise capacity and significantly enhance pulmonary function before surgery. Furthermore, prehabilitation of patients with lung cancer could be a more effective way to reduce postoperative pulmonary complications and length of stay than postoperative physiotherapy alone. However, there was quite heterogeneity in terms of the exercise prescribed, intensity of the programme, total duration and also the characteristics of the patients; hence, further research is warranted in more homogeneous samples to corroborate these findings.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *ICVTS* online.

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