



Original Article

Perioperative exercise intervention in patients with lung cancer: A systematic literature review of randomized controlled trials

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ABSTRACT

Objectives: During perioperative, lung cancer (LC) patients are often left to experience debilitating disease-related symptoms, impaired physical activity and health-related quality of life (HRQoL), and social difficulties, despite the progress achieved in terms of treatment efficacy. Nonpharmacological intervention, such as exercise, has been identified as an effective strategy in LC patients before and after lung resection. Therefore, we aimed to assess evidence of the effect of perioperative exercise among patients with LC. **Materials and Methods:** Seven databases were searched from January 1998 to September 2020. All randomized controlled trials (RCTs) that evaluated the effect of exercise on the physical and psychological status of patients with LC during the perioperative period were reviewed. Two reviewers independently assessed the quality of all studies included here using the revised Cochrane risk of bias tool for RCTs. **Results:** Seventeen RCTs (1199 participants) published between 2011 and 2019 met for this literature review. The outcome measures that emerged from these studies included subjective outcomes, such as HRQoL, pain score, fatigue, and objective effects, such as cardiorespiratory fitness, pulmonary function, physical activity, and biological markers. Overall, these studies suggest that exercise should be an optimal option for LC; however, its efficacy and effectiveness regarding HRQoL should be investigated further. **Conclusion:** Perioperative exercise could be included in the rehabilitation program of patients with LC. More extensive, high-quality RCTs evidence is needed on the ideal exercise type, duration, intensity, and timing across the LC perioperative care.

KEYWORDS: *Cardiorespiratory fitness, Exercise training, Health-related quality of life, Lung cancer, Perioperative*

INTRODUCTION

Lung cancer (LC) is the leading cause of cancer-related death and is the most frequent cancer in both sexes [1]. Non-small cell LC (NSCLC) accounts for around 85% of all cases of LC with small cell LC being the other subtype of LC. Complete surgical resection remains a prerequisite for a cure and extended survival beyond 5 years in patients with early-stage NSCLC [2]. However, many patients with resectable lung tumors have abnormal lung function, usually because of tobacco use, chronic obstructive pulmonary disease, coronary artery disease, and/or old age as comorbidities [3,4]. This specific group of patients has an increased risk of postoperative (post-OP) complications (PPCs), such as lung collapse and pneumonia [5]. Moreover, some patients with LC have significantly reduced daily functional capacity from multifactorial origins: (i) muscle mass deficit caused by both the underlying comorbidities [6] and cancer and/or by

the inactive lifestyle [7]; (ii) side effects of the anticancer treatment; and (iii) psychiatric problems of anxiety-depression associated with the diagnosis and adverse effects of its treatment and mortality [8,9]. This multifactorial presentation exhibited a complex interaction with preoperative (pre-OP) physical functioning, deconditioning because of hospitalization, and the appearance of surgical stress.

All of these deleteriously disturbed outcomes can induce physical, psychological, and social difficulties, which exert a negative effect on health-related quality of life (HRQoL) [10]; patients who receive lung resection exhibit


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short-term (4 months) and long-term (4 years) impairments in HRQoL [11]. Therefore, a growing interest has arisen regarding the use of nonpharmacological interventions, such as exercise, in various types of cancer, which has been identified as an effective approach to improve cardiorespiratory function, psychological outcome, and HRQoL, as well as to reduce dyspnea, fatigue, emotional distress, treatment-related adverse events, and daily functional capacity in patients with LC [12-14]. In a recent serial Cochrane meta-analysis [15,16], Cavalheri *et al.* [15] examined eight RCTs to determine the effects of exercise training on exercise capacity and adverse events in 450 patients after lung resection combined with or without chemotherapy for NSCLC. They concluded that exercise training improved the cardiorespiratory fitness (6-minute walk test [6MWT]) and quadriceps muscle force of patients following lung resection for NSCLC. Peddle-McIntyre *et al.* [16] analyzed six randomized controlled trials (RCTs) that compared exercise training with no exercise training in 221 patients with advanced LC and concluded that exercise training might improve or avoid the decline in exercise capacity in these patients. The findings described above were appraised using the Cochrane Collaboration risk of bias tool version 1 [17].

The pre-OP exercise offered to patients with NSCLC may decrease the risk of PPCs, and post-OP training among patients with NSCLC is associated with improvement of cardiorespiratory fitness and self-reported outcomes, such as fatigue, psychosocial well-being, and HRQoL [18]. However, the previously published meta-analyses [15,16,19] based on these studies differed in design, type of intervention, follow-up time, exercise prescription, and outcome measurements. They exhibited a high risk of bias in the majority of the included studies.

In this article, we performed a literature review of RCTs to evaluate the available evidence related to the impact of exercise interventions on cardiorespiratory function, psychological status, HRQoL, and PPCs in patients with LC. The cornerstone of clinical research on interventions is generally considered to be the RCT because it confers the least biased estimates of the effect of treatment. We also used an updated appraisal tool, the Cochrane Collaboration risk of bias tool version 2 for RCT [20], to investigate the role of exercise training in patients with LC during the perioperative period.

MATERIALS AND METHODS

The review methodology was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [21]. A comprehensive electronic database search (i.e., PubMed, Medline, Embase, CINAHL, Cochrane Library, and Chinese databases) from 1998 to September 2020 was conducted for human studies in adults older than 18.

Inclusion and exclusion criteria

The following inclusion criteria are listed per population, intervention, comparison, and outcome format: (i) participants: were defined as patients with LC who accepted lung resection within 1 year of the diagnosis. Studies that also included

patients with other types of cancer were not considered eligible for inclusion in this study; (ii) intervention and comparison: an intervention group (IG) engaging in any form of exercise protocol that was compared with a control group by (a) having just regular care without exercising (e.g., usual care) or (b) having a low-impact physical activity (e.g., walking or breathing training); (iii) outcome measure: cardiorespiratory function, psychosocial well-being, or biological indicators were included to provide a comprehensive evaluation of the effects of exercise on patients with LC.

Data extraction and quality appraisal

Data were extracted twice by Huang and then verified by Peng. We extracted details on study location, design, participant characteristics, exercise intervention, comparators, and outcomes from each study included in this review. The relevant data extracted regarding participants' characteristics included diagnosis, surgery type, and mean age, while the characteristics of the exercise and control interventions included the type, duration, frequency, intervention timing, and intensity. Any discrepancies on the extracted data were discussed and decisions were based on consensus. A third reviewer was consulted to decide on a disagreement when necessary.

Ethical approval

Ethical approval will not be required because this study will retrieve and synthesize data from already published studies.

RESULTS

Systematic search

A series of studies have investigated the impact of exercise on cardiorespiratory function, psychosocial well-being, or biological indicators in LC patients during perioperative. Finally, 17 studies that met the inclusion criteria were eligible for quality assessment [Figure 1].

Quality assessment

Table 1 shows the results of the quality assessment of the 17 studies; the methodological quality of the 17 RCTs was appraised using RoB 2.0 [20], as follows. (i) Allocation bias domain: we found that one study [22] had a high ROB of baseline characteristic difference between the intervention and control groups and some-concern risk of sufficient concealment process. We determined that six studies [23-28] had a some-concern risk of bias as the authors failed to report adequate information about the allocation concealment. We rated the remaining studies as having a low risk of allocation bias; (ii) performance bias domain: it is not practical to blind participants to the randomization to an exercise intervention versus a control intervention. Because of other algorithms used to reach effect to adherence intervention, we assessed all studies as being at some-concern risk of performance bias; (iii) attrition bias domain: we rated four studies as having a high risk of attrition bias [28-31]. This judgment was based on disparities or >20% dropout rates between the intervention and control groups. Moreover, without an appropriate sensitivity analysis of the withdrawal rate, these studies may result in unobserved compliance status, affecting the true value. We classified three studies [13,23,32] as

Table 1: Risk of bias summary: review authors' judgements about each risk of bias item for each included study

Study, year	Allocation bias	Performance bias	Attrition bias	Detection bias	Reporting bias	Overall bias
Arbane <i>et al.</i> , 2011 [13]	L	S	S	L	L	H
Stafanelli <i>et al.</i> , 2013 [22]	H	S	L	L	L	H
Benzo <i>et al.</i> , 2011 [23]	S	S	S	L	L	H
Edvardsen <i>et al.</i> , 2015 [24]	S	S	L	L	L	H
Lai <i>et al.</i> , 2017 [25]	S	S	L	L	L	H
Lai <i>et al.</i> , 2017 [26]	S	S	L	L	L	H
Pehlivan <i>et al.</i> , 2011 [27]	S	S	L	L	L	H
Stigt <i>et al.</i> , 2013 [28]	S	S	H	S	S	H
Brocki <i>et al.</i> , 2014 [29]	L	S	H	L	L	H
Messaggi-Sartor <i>et al.</i> , 2019 [30]	L	S	H	L	L	H
Sebio García <i>et al.</i> , 2017 [31]	L	S	H	L	L	H
Cavalheri <i>et al.</i> , 2017 [32]	L	S	S	L	L	H
Morano <i>et al.</i> , 2014 [33]	L	S	L	H	L	H
Bhatia <i>et al.</i> , 2019 [34]	L	S	L	L	L	S
Huang <i>et al.</i> , 2017 [35]	L	S	L	L	L	S
Karenovics <i>et al.</i> , 2017 [36]	L	S	L	L	L	S
Licker <i>et al.</i> , 2017 [37]	L	S	L	L	L	S

Categories: L: Low risk of bias, S: Some concern, H: High risk of bias

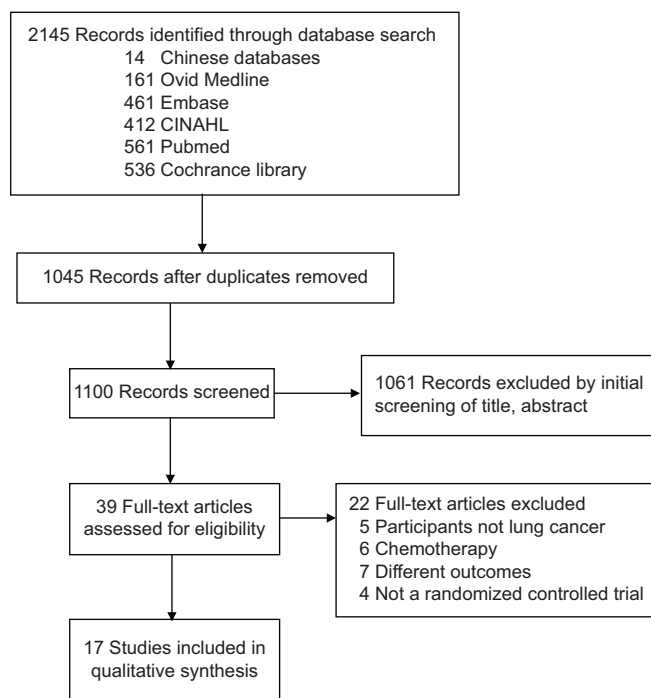


Figure 1: PRISMA flow diagram showing the number of studies identified and selected for inclusion in the literature review

being having a some-concern risk of attrition bias, and rated the remaining studies as having a low risk of attrition bias; (iv) detection bias domain: we found that one study was at a high risk of detection bias [33]. Because of the absence of blinding of the assessor to all measurement outcomes, the results were subjective and may have been influenced by the knowledge of an intervention; (v) reported bias domain: we assessed one study [28] as being at some-concern risk of reported bias because of insufficient objective measurement outcomes. We judged the remaining studies to be at a low risk of reported bias. All studies were performed to be free of other sources of bias; (vi) overall bias domain: four of the reviewed

studies were rated as having a “some-concern” overall risk of bias [34-37], whereas the remaining 13 studies were rated as having a “high” overall RoB.

Characteristics of the included studies

We included 17 studies in this review [13,22-37], which represented a total of 1199 participants with operable stage I-IV LC. The mean age of the participants ranged from 54 to 72 years, and the surgery type was open thoracotomy or video-assisted thoracic surgery. The studies were published between 2011 and 2019. The sample size of the included studies ranged from 17 to 151 subjects.

The details of each exercise program described in the included studies exhibited considerable variation, according to the perspective of the frequency/intensity/time/type principle adopted by the current the American College of Sports Medicine exercise guidelines for cancer survivors [38]. The intervention was performed including either a pre-or post-OP setting: from a median of 25 days before undergoing operation (OP) [36] to 1-8 weeks post-OP [13,30], depending on the OP date [31]. The exercise frequency applied most often was two or three times per week, and the time per session ranged from 5 to 60 min. Across the studies, all levels of exercise intensity used different target measurements, i.e., 60%–80% of maximal heart rate [13,24,27], 50%–100% of peak work rate [28-31,33,34,36,37], score of 5–6 on the Borg scale [26,34], and 70% of the cardiopulmonary exercise test [22], or were not reported [23,25,32,35].

The outcomes were evaluated most frequently using the 6MWT of cardiorespiratory function [13,28-30,32-36]; however, three of these studies [13,29,31] did not show any significant between-group differences. Three studies found a significant difference in the peak expiratory flow (PEF) [25,26,35] of pulmonary function tests (PFTs). Eleven of these studies evaluated the quality of life of the patients. Six of these studies [24-26,30,32,35] used the European Organization for Research and Treatment of

Cancer, Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), and three studies [13,25,26] used the EORTC QLQ-LC13 (modular supplement of the EORTC QLQ-C30). All of the reported studies showed no significant between-group differences in the EORTC QLQ-C13 item. The 36-item Short-Form Health Survey version 2 (SF-36) was also used in six studies [24,28,31-33], three of which reported significant differences between groups [24,29,31]. The PPC variable was analyzed in seven studies, five of which (71%) showed a significant decrease in the IG. Three out of these five studies applied the pre-OP program for 1 week, twice a day [23,25,26], whereas the remaining two studies [30,37] administered the pre-OP program 3 times per week over 2–4 weeks. Two out of the seven studies (29%) did not report significant results [13,31].

The dropout rates reported in these studies ranged from 0% [23,27,33] to 55% [31] regarding IG, and from 0% [23,25-27,33] to 50% [31] regarding the CG (control group). The three studies reported adverse events related to the exercise interventions: One case of hip fracture during a balance training [24] and two events of knee pain [25,35]. Five studies did not report the dropout rate.

DISCUSSION

This systematic review of 17 RCTs investigated the impact of exercise interventions on cardiorespiratory function, psychosocial status, and PPCs during the perioperative period in patients with LC. The included studies exhibited a diverse range of exercise programs and outcome variables regarding the physiological and psychological outcomes; significant positive effects were noted in most related studies regarding the physiological domain. In addition, one study that investigated the impact of aerobic exercise (AE) combined with inspiratory muscle training (IMT) on biological markers reported significantly better results when compared with the CG. One of the challenges in our review was the reporting of dropout rates. A series of studies reported low adherence to and high dropout rate from exercise programs, worry of the extra burden, and thoughts of limited possible benefits [39-43]. Patients with LC are insufficiently active or sedentary, and mostly lack interest and motivation, which represent vital contributors to the outcome. The studies that reported the dropout rates found that they were reasonably low for pre-OP interventions, whereas they were higher for post-OP-only and pre-and-post-OP interventions. Possibly, the intensive exercise training program had disturbing effects on pain by continually stretching the painful thoracic cage and new scars. Post-OP cardiorespiratory function and complications are highly related to pain [44]. AP van der Ploeg *et al.* [45] analyzed the different surgical types, i.e., robot-assisted, video-assisted, and open thoracic surgery, for resectable NSCLC, and reported no significant differences between age, gender, post-OP Numerical Rating Scale, duration of chest tube drainage, and epidural anesthesia, and hospital length of stay. Stigt *et al.* [28] performed resistance training (RT) combined strength and mobility training in 12-week exercise programs and reported no significant differences in PFT and HRQoL between the groups; moreover,

a significant effect was found in IG, in which significantly more pain was reported than in CG after 3 months ($P = 0.042$) and after 6 months ($P = 0.010$), as assessed using the Dutch version of the McGill Pain Questionnaire. In contrast, Brocki *et al.* [29] performed aerobic RT and strength exercises in a 10-week group-based exercise program and reported no differences in 6WMT performance or lung volume compared with the CG (one individual instruction in exercise training); however, they found a significant effect in SF-36 4 months after OP of the bodily pain domain of the IG ($P = 0.01$). In supervised exercise training that was performed by a therapist, it can be assumed that the attendance rate and exercise harms are lower than those recorded during unsupervised training interventions [46]. Supervised interventions had a more positive effect on quality of life than did unsupervised interventions [47]. Other types of exercise included Qigong, a mind-body exercise that combines meditation, slow physical movements, and controlled breathing with or without visual imagery to promote health for both the mind and body [48], or Baduanjin, a form of traditional Chinese medical practice that is designed to promote physical and psychological health and manage symptoms and stress during illness and has been frequently used by patients with cancer [49]. The effect of a 16-week Tai Chi exercise intervention (60 min, three times per week) yielded significant effects on the proliferation and cytolytic/tumorcidal activities of peripheral blood mononuclear cells [50], the balance between cellular and humoral immunity [51], and the cellular immune responses [52] in patients with NSCLC. The implications for practice were that transdisciplinary (oncologists and oncology exercise specialists) collaborations are urgently needed to develop tailored programs for patients with LC [53].

We found that the 6MWT was one of the most common measures used among the studies examined (10/17; 59%). Among nine studies [13,28-30,32-36], only three [13,29,31] reported no significant differences between groups from the baseline to post-intervention in the IG. Licker *et al.* [37] observed that the distance walked by patients in the CG decreased on average by 2 meters. In contrast, the IG patients increased their walking distance on average by 66 meters (with the lower bound of the 95% confidence interval >0). Cardiorespiratory fitness reflects the ability to carry, transport, and use oxygen, and it is an essential index of functionality, health, and endurance [54]. The 6MWT is the commonly applied assessment of cardiorespiratory fitness in LC and can predict PPCs and survival [55-57]. PPCs are deemed to be strongly correlated with short-and long-term survival after LC surgery [58]. PEF is defined as the maximum flow achieved during expiration delivered with maximal expiratory effort and has been investigated as a risk assessment tool for aging populations [59]. In recent years, several studies have been performed to survey the associations between the PEF and long-term cause-specific mortality, to examine whether it is associated with health status and physical function [60-62]. In this systematic review, a decrease in PPCs was observed in the seven studies that analyzed this variable [13,23,25,26,31,35,37]. Three out of seven studies [25,26,35] also analyzed the PEF, all of which showed

a significant increase in function after exercise training. The PEF reflects airway patency and resistance, respiratory muscle strength, and other aspects of lung function, and its validity as a postexercise measure index has been established.

Patients with LC may experience several tumor-related symptoms that affect their ability to perform daily activities, resulting in decreased independence, and decreased ability to perform societal roles, thereby negatively impacting psychosocial health [63]. In our review, the evidence was very uncertain regarding the advantages of the application of an exercise program in terms of HRQoL. Various studies reported improved cardiorespiratory fitness, decrease hospital stay, and prevention of PPCs. Nevertheless, HRQoL was not re-assessed during the recovery phase, or no improvement of HRQoL was recorded in these studies. Cavalheri *et al.* [32] reported significantly greater gains in VO_2 peak and 6MWT, but no between-group HRQoL differences were noted. Edvardsen *et al.* [24] reported a significant increase in physical capacity and total muscle mass compared with CG, in addition to the SF-36 physical component summary score and the mental HRQoL component summary score. In the study reported by Morano *et al.* [33], patients had lower anxiety and depression levels 1 month after OP. In Sebio García *et al.* [31], the pre-OP exercise including RT and high-intensity interval training, with the progression of volume and intensity after the 10th session, and showed superior scores in the Physical Component Summary of the SF-36 3 months after the OP compared with the IG. Messaggi-Sartor *et al.* [30] reported that, after 8 weeks, combined AE and IMT yielded a significant increase in VO_2 peak and maximal respiratory pressures; however, no differences in the EORTC QLQ-C30 were observed between groups. In patients with LC (and their caregivers), there is a higher risk of experiencing exacerbations of psychosocial distress because of the widely shared stigmatization of this disease based on the close link between LC and smoking [64]. Considering the controversial association between exercise and HRQoL in LC care, further studies with a solid design and an adequate sample size are required to clarify this issue.

CONCLUSION

According to a rigorous quality appraisal, although only four studies were some-concern risk of bias trials [34-37], the results of this systematic review ratify that an exercise program can lead to improvements of cardiorespiratory function, psychological status, and PPCs in LC survivors. Additional research is needed with a similar and randomized design to determine which type of exercise, duration, and intensity are best for improving patients' HRQoL and selecting the most appropriate patient with LC for training. Moreover, the range of heterogeneity of the measurement methods used to evaluate the same field renders it extremely hard to compare the results of different tests. Therefore, additional studies should be performed to standardize the outcome evaluation indicators in the same area.

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Conflicts of interest

There are no conflicts of interest.

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