BMJ Open

Exercise training modalities in patients with lung cancer: a protocol for systematic review and network meta-analysis

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ABSTRACT

Introduction Lung cancer is a common malignancy and a major cause of cancer-related deaths worldwide, ranking high in terms of morbidity and prevalence. Exercise is a well-established recovery aid for many chronic respiratory conditions and lung cancer. However, it is difficult to determine the superiority of different exercise training modalities using randomised controlled trials (RCTs) or pairwise meta-analyses. Our Bayesian network meta-analysis (NMA) aimed to compare the impact of different perioperative exercise training modalities on lung function, exercise capacity, adverse events, health-related quality of life and mortality in patients undergoing lung cancer surgery, including preoperative and postoperative patients.

Methods and analysis We will perform a comprehensive literature search using PubMed, EMBASE, Cochrane Library and Web of Science, from inception to May 2022, to identify studies that potentially provide data regarding exercise training modalities for patients with lung cancer. We will assess the risk of bias according to the Cochrane risk-of-bias tool and certainty of evidence for the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation framework. Pairwise meta-analyses will be conducted using a random effects model and Stata software, and the NMA will be analysed using R software.

Ethics and dissemination Ethical approval and patient consent were not required because this study was a meta-analysis of published RCTs. The results of this study are submitted to a peer-reviewed journal for publication.

PROSPERO registration number CRD42021278923.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This network meta-analysis will assess which exercise training modalities can improve lung function, exercise capacity and health-related quality of life and reduce adverse events and mortality for patients with lung cancer, including preoperative and postoperative patients.

⇒ We will provide more precise information regarding the best type of exercise rehabilitation training for patients with lung cancer.

⇒ We performed a comprehensive search of four primary databases, screened the studies, assessed the risk of bias and extracted the data.

⇒ The quality of the systematic review and meta-analysis will be limited by study heterogeneity, which is influenced by different participant characteristics, study locations and the methodological quality of the included studies.

INTRODUCTION

Lung cancer is a common malignancy and a major cause of cancer-related deaths worldwide, ranking first in terms of morbidity and prevalence.[1 2] According to Global cancer statistics based on 185 national data registries, lung cancer is one of the most commonly diagnosed types of cancer (11.4% of total cases).[3] Non-small cell lung cancer (NSCLC) is the prevalent histological subtype of lung cancer, accounting for 85%–90% of lung cancer cases.[4]

Complete surgical resection is the most effective treatment for stages I and II lung cancer.[5] However, the reduction in postoperative functional capacity due to systemic inflammation, poor physical and nutritional status, and surgical stress[6–8] is a major predictor of morbidity and mortality after lung surgery. An earlier study showed impaired exercise capacity in patients with lung cancer,[9] attributable to underlying anorexia, weight loss and muscle wasting.[10 11] Furthermore, more than half of patients diagnosed with lung cancer have chronic lung disease, which could impair exercise capacity.[12 13]

Exercise has been demonstrated to improve several chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD)[13] and asthma.[14] Results from Cochrane systematic reviews[13 15] have shown that exercise could improve exercise capacity and reduce the symptoms of fatigue and dyspnoea in patients with COPD. According to previous systematic reviews and

meta-analyses,[16 17] exercise training can improve exercise capacity in patients with lung cancer. However, both of these studies investigated the effect of exercise in general rather than the effect of specific types of exercise modalities and the duration and intensity of exercise. Randomised controlled trials (RCTs)[18–23] have been conducted to investigate the impact of breathing, aerobic exercise, resistance exercise, or combined exercise on exercise capacity, health-related quality of life (HRQoL), and lung function in patients with lung cancer. Previous studies have shown that both breathing and aerobic exercises are valid strategies to improve the physical performance of patients with preoperative lung cancer.[22] Chen *et al* also suggested that aerobic exercise could improve anxiety and depression in lung cancer survivors and can be considered an essential component of lung cancer rehabilitation.[23] Furthermore, previous studies[18 19] have proven that combined aerobic and resistance exercise could show some benefits including increased physical capacity and HRQoL for patients following curative surgery for NSCLC. However, it is difficult to determine the superiority of different physical activities using RCTs or pairwise meta-analyses. A network meta-analysis (NMA) makes it possible to assess the comparative effectiveness of all treatments, summarise and explain the wider evidence base and understand a single coherent ranking of treatments.[24]

Our NMA aims to compare the impact of different perioperative exercise training modalities on lung function, exercise capacity, adverse events, HRQoL and mortality in patients undergoing lung cancer surgery using Bayesian NMA.

METHOD

We have reported our protocol for this systematic review following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols checklist.[25] The study protocol has been registered in the International Prospective Register of Systematic Reviews (CRD42021278923).

Data sources and searches

We will perform a comprehensive literature search using the PubMed, EMBASE, Cochrane Library and Web of Science databases from inception to May 2022. The search strategy was developed and tested through an iterative process by an experienced librarian researcher in consultation with a review team. The search terms will include lung neoplasms, lung cancer*, exercise*, rehabilitation*, aerobic*, endurance, resistance, strength*, inspiratory muscle*, respiratory muscle*, walking, cycle*, treadmill and random*. The detailed search strategy is shown in online supplemental appendix 1. The references of relevant systematic reviews and meta-analyses will be manually searched to identify additional studies. There will be no restrictions on the language of publication.

Eligibility criteria

Types of study

RCTs that reported the efficacy of perioperative exercises in patients undergoing lung cancer surgery will be

included. There will be no language or publication status restrictions, and abstracts and unpublished online data will be considered if sufficient data are available.

Participants

We will consider participants who underwent surgery for lung cancer, including preoperative and postoperative patients with lung cancer. Studies that included participants who exclusively underwent radiotherapy and/or chemotherapy will be excluded. There will be no limitations in terms of race or sex.

Interventions

Different exercise training modalities will be considered in our systematic review, including aerobic, strengthening, breathing and combined exercises. Supervised, unsupervised or a combination of both exercise sessions will be considered.

Aerobic exercise will be defined as a regimen that contains aerobic components. Aerobic components include, but are not limited to, walking, cycling, yoga (only yoga that meets the definition of aerobic exercise), jogging and swimming.[26]

Strengthening exercise will be defined as a regimen consisting of some type of progressive resistance to increase muscle strength, endurance or power, which includes, but is not limited to, bench press, seated row, shoulder press, leg press and weight strength.[27]

Breathing exercises will be defined as a broad range of respiratory strategies, including, but not limited to, pursed-lip, abdominal and thoracic breathing exercises.

Combined aerobic and resistance training (combined exercise) will be defined as performing an aerobic training programme plus a resistance training programme to ensure an adequate dose of each type of exercise.

Controls

We will define the control group as those receiving standard care with no exercise.

Outcomes

We will focus on the following outcomes of interest:
► Lung function (eg, volumes and diffusing capacity).
► Exercise capacity (measured either by the 6 min walk test or peak oxygen consumption during a maximal incremental exercise test).
► Adverse events.
► Quality of life, determined using the Medical Outcomes Study Short Form 36 General Health Survey, the European Organization for Research and Treatment of Cancer Quality of Life, the Functional Assessment of Cancer Therapy-Lung scale or HRQoL.
► Mortality.

Study selection

Study selection will be conducted by two reviewers. First, the reviewers involved in the study selection will screen 100 records. The intraclass correlation coefficient (ICC) will be used to assess consistency, and an ICC value over

0.8 will be considered acceptable. When the ICC value exceeds 0.8, the three reviewers will independently examine the studies by reviewing their titles and abstracts to identify possible related studies. The full texts of all potentially relevant studies will be downloaded, and the same reviewers will assess the eligibility of each study according to the inclusion and exclusion criteria. Conflicts will be resolved through discussions among the reviewers.

Data extraction and quality assessment

Three researchers will independently extract relevant information and assess the methodological quality of the included RCTs. The data of interest will include authors, year of publication, study design, study location, type of lung cancer, cancer staging, sample size, age, sex distribution, type of exercise, frequency of exercise, intensity of exercise, duration of exercise, adherence to exercise, extent of exercise supervision, whether the patient underwent radiotherapy and/or chemotherapy and outcomes. We will assess the risk of bias according to the Cochrane risk-of-bias tool,[28] which consists of random sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete data, selective reporting and other biases. Each item will be classified as low, high or unclear. Disagreements regarding data extraction and the by-item rating of quality will be resolved by consensus or third-party adjudication if a consensus cannot be reached.

Statistical analysis

Pairwise meta-analyses will be conducted using a random effects model and Stata software. Pooled ORs with 95% CIs will be used for dichotomous variables. Mean differences and standardised mean differences with 95% CIs will be used for continuous variables. The heterogeneity between head-to-head trials will be estimated using I^2 statistics and p values. I^2 values of 25%, 50% and 75% will indicate low, moderate and high statistical heterogeneity, respectively. We will explore the sources of heterogeneity using subgroup analysis and meta-regression. Publication bias will be evaluated using the Egger's test and funnel plots if the number of studies exceeds 10.[29] A two-tailed p value<0.05 will be considered statistically significant.

We will use the 'networkplot' function of STATA to generate network plots to describe and present the geometry of different forms of exercise. The NMA will be conducted on both direct and indirect evidence in a Bayesian framework using the gemtc R package of R software. We will use the deviance information criterion to compare model fit and parsimony. Convergence will be assessed using the Brooks-Gelman-Rubin plot method. We will assess global heterogeneity for all comparisons from the NMA models using the I^2 statistic in the gemtc R package. The node splitting method will be used to examine inconsistency between direct and indirect comparisons if a loop connecting three or more arms exists.[30] When inconsistency exists, we will use higher-certainty evidence or direct evidence as our best estimate of the treatment effects. The rank probabilities of the treatment formats will be evaluated on the basis of the surface under the cumulative ranking curve.[31] Comparison-adjusted funnel plots will be generated to explore the presence of small-sample effects among the networks.[32] Analyses will be performed using Stata and R software. We will assess the certainty of evidence for the main outcomes using the Grading of Recommendations Assessment, Development and Evaluation framework, which contains five domains: study limitations, imprecision, heterogeneity and inconsistency, indirectness and publication bias.[33]

Where sufficient data are available, we will conduct subgroup analyses based on the sample size, sex, mean age, number of sessions, cancer stage, type of exercise and subtype of lung cancer. Exercise intensity and duration have been proven to be potential modifiers of outcomes, and pairwise meta-analyses will be performed to investigate the impact of duration and intensity as covariates on the magnitude and direction of the estimates. We will also conduct sensitivity analyses to explore the influence of variables on the main outcomes. Planned sensitivity analyses will exclude trials with a high risk of bias, significant levels of missing data or low numbers of participants. We will conduct a sensitivity analysis using a fixed effects model to assess the consistency of the results.

Ethics and dissemination

As this study involved only a protocol for a systematic review, ethical approval was not required. The results of this study will be published in peer-reviewed journals and distributed electronically or in print form.

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