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INVITED REVIEW

TITLE: EXERCISE TRAINING AS PART OF LUNG CANCER THERAPY

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ABSTRACT

Exercise training is playing an increasing role in lung cancer care. Lung cancer is associated with significant burden to the individual and healthcare system. There is now substantial evidence that exercise training is safe, feasible and effective at improving several outcomes in people with lung cancer, especially in those with non-small cell lung cancer. Exercise is beneficial across the lung cancer disease and treatment pathway, including in patients with early stage disease before and after surgery, and in patients with advanced disease. This review describes the impact of lung cancer and lung cancer treatment on patient health outcomes and summarises the aims, safety, feasibility and effects of exercise training in the context of both early stage and advanced stage lung cancer. The paper also includes a discussion of current topical discussion areas including the use of exercise in people with bone metastases and the potential effect of exercise on suppression of tumour growth. Finally, seven clinical questions are included, which are a priority to be addressed by future research over the next decade as we strive to progress the field of lung cancer and improve patient outcomes.

Key words:

Exercise; Lung Neoplasms; Rehabilitation; Survivorship; Quality of Life

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ABBREVIATIONS

6MWD: Six-minute walk distance

CI: Confidence interval

COPD: Chronic obstructive pulmonary disease

ERAS: Enhanced recovery after surgery

HRQoL: Health-related quality of life

MD: Mean difference

NK: Natural killer cells

NSCLC: Non-small cell lung cancer

RCT: Randomised controlled trial

RR: Risk ratio

SMD: Standardised mean difference

VO_2peak: Peak rate of oxygen consumption

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1. INTRODUCTION

Exercise training is playing an increasing role in lung cancer care. The past decade has witnessed an exponential increase in the evidence (of varying certainty) that exercise training is safe, feasible and effective at improving several outcomes in people with lung cancer, especially in people with non-small cell lung cancer (NSCLC). A PubMed search, in January 2020, for studies on exercise training for people with lung cancer detected 38 clinical trials and 20 systematic reviews published since 2010. This is a substantial increase in evidence (Figure 1) compared to the very small number of trials and systematic reviews published before this time (6 clinical trials and 1 systematic review from 2000 to 2009, with the first ever trial published in the year 2000).[1] Importantly, the findings of the studies published in the past decade have now informed the recommendations for exercise training in people with lung cancer within several clinical guidelines and position statements worldwide.[2-6]

This review describes the impact of lung cancer and its treatment on patient health outcomes and summarises the aims, safety, feasibility and effects of exercise training in the context of both early and advanced stage lung cancer. The paper also includes a discussion of current topical discussion areas in the field of exercise and lung cancer including exercise in people with bone metastases and the potential effect of exercise on suppression of tumour growth. Lastly, we have included a list of seven clinical questions which we view as a top priority to

be addressed by research over the next decade to progress the field forward. Our take-home messages can be found in Table 1.

2. IMPACT OF LUNG CANCER AND ITS TREATMENT

Lung cancer is estimated to be the leading cause of the burden of disease due to cancer amongst males and the second amongst females. Nearly 90% of patients report symptoms at the time they are diagnosed with lung cancer and, typically, patients present with two or three symptoms at diagnosis.[7] The most frequent symptoms include cough, dyspnoea, chest pain and haemoptysis, with systemic symptoms such as weight loss, anorexia and asthenia also being reported.[8] These symptoms affect patient's health-related quality of life (HRQoL), level of distress and daily physical activity, promoting a cycle of inactivity and decline in exercise capacity and physical function.[9, 10]

Treatment options for people with lung cancer vary according to the type of lung cancer, stage of the disease, and the patient's functional status. Treatments can include surgical resection, chemotherapy, radiotherapy, targeted therapy and immunotherapy. These treatments themselves may also be associated with numerous side effects, and when combined with the symptoms of the cancer itself, result in high patient burden and deterioration in many patient-related outcomes including exercise capacity and physical function.

In people with early stage NSCLC, surgical resection of the tumour is the treatment option that offers the best chance of cure. Although surgical resection offers a chance of cure, postoperative pulmonary complications such as respiratory failure, pneumonia, myocardial

infarction, and arrhythmias are not uncommon.[11, 12] The reported incidence of postoperative pulmonary complications following surgery varies in the literature due to the wide variety of measurement tools utilised, but they are understood to occur more commonly in patients with chronic obstructive pulmonary disease (COPD), those with smoking history or poor lung function[12-15] as well as in patients whose surgery involved a thoracotomy (compared to video assisted thoracic surgery),[12-14] increased use of intraoperative crystalloids,[15] or a surgical procedure of ≥2 hours in duration.[15] Further, following surgery, lung function, exercise capacity and the physical function domain of HRQoL have consistently been shown to immediately decrease,[16-21] with partial to minimal recovery of lung function and exercise capacity at 6 to 12 months following surgery.[16, 18, 20, 21] Lastly, nearly half of patients who are alive two years after surgery continue to experience increased dyspnoea and fatigue when compared with preoperative levels.[19] Adjuvant therapy (such as chemotherapy and radiotherapy) can also exacerbate treatment-related symptoms and impairment.

In people with advanced lung cancer, medical treatment is aimed at prolonging survival and/or improving HRQoL.[22] The most common treatments include chemotherapy, radiotherapy, targeted therapy and immunotherapy. In this population, the direct effects of lung cancer progression, presenting as dyspnoea, fatigue, weight loss, and pain,[10] combined with the indirect effects of cancer treatment (which vary according to the treatment received), can cumulatively lead to further reductions in HRQoL, exercise capacity and physical activity levels.[10, 23-26] It is worth mentioning that data are still pending on the changes in outcome measures related to exercise capacity and physical function following immunotherapy, as this treatment was only recently introduced into clinical practice and the long-term implications

are not yet well understood. In Australia for example, it was only from June 2019, that the Government started covering most of the immunotherapy cost for advanced lung cancer through the Pharmaceutical Benefits Scheme.

3. EXERCISE TRAINING IN PEOPLE WITH EARLY STAGE LUNG CANCER

Exercise training is beneficial as part of the management of early stage operable disease at a number of distinct time points along the surgical treatment pathway (Figure 2). This includes before surgery, in the short-term immediately after surgery (i.e. during the hospital stay), and in the longer-term following surgery. The purpose of exercise, type of exercise training recommended, expected outcomes of exercise, and barriers to exercising at these different time points varies slightly.

3.1 Preoperative exercise

In patients with operable disease, exercise training can be delivered in the time between diagnosis and surgery. It is worth mentioning that, in those deemed 'fit for surgery' by the multidisciplinary team, there is no evidence to delay surgery for exercise. In the lung cancer field, exercise training before surgery is commonly referred to as preoperative exercise or prehabilitation; however, in other clinical areas prehabilitation more commonly refers to a more diverse bundle of care in the pre-treatment setting including exercise, nutrition and psychological support.[27] Preoperative exercise training aims to maximise exercise capacity for the patient and in turn minimise the postoperative burden for both the patient and health system. Prevention of postoperative pulmonary complications in particular is important as they are associated with increased intensive care admissions, length of hospital stay and

hospital re-admissions; as well as early and late mortality in this population.[12, 14, 15] Preoperative exercise programs in published randomised controlled trials (RCTs) were generally short in duration and opportunistically used the time period whilst the patient was awaiting surgery, which was commonly less than 4 weeks.[28] Whilst these programs were short (ranging from 1 to 4 weeks), the exercise sessions occurred frequently during this time (ranging from twice daily to 5 times per week).[28] The focus of exercise prescription in those RCTs was to improve exercise capacity, and the prescription consisted of either moderate intensity continuous aerobic exercise or high intensity interval training,[28] both of which could be achieved using a stationary bike or a treadmill. These types of exercises aimed to increase peak rate of oxygen consumption (VO_2peak), which is an important variable in patients awaiting lung cancer surgery, as it is a predictor of better surgical outcomes.[29] In addition to walking and/or cycling, occasionally programs also included whole body resistance training and/or inspiratory muscle training.[28] The optimal exercise training regime in this setting remains unclear and needs further investigation.

A Cochrane review on preoperative exercise training for people with lung cancer identified five RCT (on 167 participants) published until November 2016.[28] The review has shown that, compared to a control group that did not exercise, patients who exercised had the risk of developing a postoperative pulmonary complication reduced by 67% (risk ratio (RR) [95% confidence interval (CI)] 0.33 [0.17; 0.61]), fewer days needing an intercostal catheter following surgery (mean difference (MD) [95% CI] -3 [-5; -1] days), a shorter postoperative length of hospital stay (MD [95% CI] -4 [-5; -3] days), and improved preoperative six-minute walk distance (6MWD) (MD [95% CI] 18 [9; 28] m).[28] However, caution should be taken in

interpreting these results, as overall the certainty of evidence was rated as low, particularly due to the small sample sizes and significant risk of bias of trials included in the meta-analyses. Since the Cochrane review there have been additional trials published which reported similar findings.[30]

Whilst preoperative exercise may have wide appeal, much work needs to be done before it becomes routine management for patients with lung cancer. Research supporting preoperative exercise in lung cancer has infrequently been implemented into clinical practice worldwide.[31, 32] The limited time frame for training (prior to surgery) means patients need fast access to programs, and high motivation to both commence exercise quickly and adhere to relatively burdensome programs. At this stage the health system in many countries is not set up with routine pathways for patients to be seamlessly enrolled into preoperative exercise programs. This is partly due to lack of data around the longer-term benefits of prehabilitation, as well as lack of data on the cost-effectiveness of preoperative exercise training.[33] With expected reductions in postoperative pulmonary complications and shorter hospital length of stay,[28] we hypothesise cost savings associated with preoperative exercise, but trial data are needed to confirm this. In the future, if we are to see long-term positive outcomes from preoperative exercise clinical trials and cost-effectiveness established, there will be a strong case for preoperative exercise and a major change in the landscape lung cancer management. Until this time, we recommend patients be offered preoperative exercise if feasible in their local setting (for example if there is a program available and the patient is willing), as this is a safe intervention with good short-term benefits for the patient.[28]

3.2 Acute postoperative (in hospital) exercise

Exercise training immediately after lung cancer surgery focuses on early mobilisation, which includes sitting out of bed and walking around the hospital ward, with the aim to achieve fast readiness of discharge to home.[13, 34] Many hospitals follow a clinical pathway for patients following thoracic surgery and key goals of the pathway include sitting out of bed and walking incremental distances commencing from day 0 or day 1 postoperative.[34] The use of Enhanced Recovery After Surgery (ERAS) protocols, which include early mobilisation, are increasingly being implemented in thoracic surgery units.[2, 35] A recent clinical guideline for ERAS in thoracic surgery[2] included the recommendation for early mobilisation and stated that "patients should be mobilised within 24 hours of surgery". This recommendation was graded as 'strong' despite the level of evidence being 'low' in the absence of high-quality trials (with consistent results) demonstrating outcomes of early mobilisation protocols.[2, 36] Instead, the strong recommendation for early mobility stems from the evidence of harm associated with immobilisation, including prolonged hospital length of stay and morbidity following lung resection.[2, 37] Common barriers for patients to not walk early after surgery are low blood pressure and unsteadiness,[14] and patients should be monitored closely to ensure they achieve mobility milestones. There have been a small number of studies investigating the role of postoperative exercise commencing whilst patients are still in hospital after surgery,[38, 39] although the majority of studies commence exercise training once patients are discharged from hospital.[40] It is currently unknown whether early commencement provides added benefits. In addition to early mobilisation, upper limb stretches are also prescribed while patients are in hospital to reduce pain and improve shoulder function.[41]

3.3 Postoperative exercise

Exercise training following hospital discharge after lung cancer surgery focuses on recovery and rehabilitation. Exercise in the weeks to months following surgery for lung cancer is well established as a safe, feasible and effective component in the management of lung cancer.[40] The barriers to exercise at this time point are less evident. For example, when compared to preoperative exercise, there is no time pressure to commence exercise; patients can start exercise when they are ready and when they can access a program. Most postoperative outpatient exercise programs included in published RCTs commenced 5 to 10 weeks following surgery, were usually 6 to 12 weeks in duration (up to 20 weeks), with exercise sessions running 2 to 3 times per week in a supervised environment, often supplemented with home-based exercise to achieve 5 sessions across the week.[40] Exercise prescription included a combination of aerobic exercise (moderate intensity continuous aerobic exercise) or high intensity interval training on a stationary bike or a treadmill, and whole-body resistance training; with or without inspiratory muscle training.[40] These programs were very similar to traditional pulmonary rehabilitation programs for people with COPD and in fact we advocate that all pulmonary rehabilitation programs be open to people following surgery for lung cancer.

A Cochrane review on postoperative exercise training within 12 months of surgery for people with lung cancer identified eight RCTs (on 450 participants) published until February 2019.[40] The review has shown that, compared to a control group that did not exercise, patients who exercised presented improvements in exercise capacity (VO_2peak: MD [95% CI] 3 [2; 4] mL/kg/min; and 6MWD: MD 57 [34; 80] m), HRQoL (physical component of the SF-36) (MD [95% CI] 5.0 [2.3; 7.7] points), quadriceps muscle force (standardised mean difference

(SMD) [95% CI] 0.75 [0.4; 1.1]), and reported less dyspnoea (SMD [95% CI] -0.43 [-0.81; -0.05]). Whilst lack of resources is a major issue and postoperative exercise programs are also uncommon in clinical practice at present, we strongly advocate for the establishment of programs worldwide and for patients to access consultations with health professionals specialising in exercise and cancer, such as physiotherapists or exercise physiologists, if there is not a program in their local area.[31]

4. EXERCISE TRAINING IN PEOPLE WITH ADVANCED STAGE LUNG CANCER

The main aims of exercise training in patients with advanced stage lung cancer (and in those with early stage disease deemed 'unfit' for surgery) are to improve symptoms, prevent the deterioration of exercise capacity and HRQoL and attenuate the side effects of medical treatment. Exercise programs usually comprise moderate intensity aerobic and resistance training, and studies of exercise training in patients with advanced lung cancer have reported few minor musculoskeletal events such as muscle pain; but no serious exercise-related adverse events.[42]

Single group studies on exercise training for people with advanced lung cancer have reported improvements in exercise capacity, functional capacity, anxiety and emotional well-being.[43-45] However, the certainty of the evidence for the effectiveness of exercise to maintain or improve health outcomes in people with advanced lung cancer is lower than that for preoperative or postoperative exercise in people with early stage lung cancer. The very-low to low certainty for the effectiveness of exercise training in people with advanced lung cancer is

mainly due to fewer RCTs, that had small sample sizes and an overall high risk of bias. A Cochrane review on exercise training for people with advanced lung cancer identified six RCTs (on 221 participants) published until July 2018.[42] In those six RCTs, the timing of exercise training commencement was either just before start of medical treatment or during medical treatment. The interventions ranged in length from 6 to 12 weeks and the frequency of supervised exercise varied from 1 to 5 days a week. Findings from five of the six RCTs were included in the meta-analyses. The review has shown that, compared to a control group that did not exercise, patients who exercised had higher 6MWD (MD [95% CI] 63 [4; 123] m) and better HRQoL (SMD [95%CI] 0.51 [0.08; 0.93]).[42] Regarding symptoms, meta-analysis was conducted to investigate the effects of exercise training on dyspnoea. Although the central tendency (i.e. SMD) was in favour of the exercise group (SMD -0.27), the variability around this central tendency was large, and crossed the line of no effect (95% CI -0.64; 0.10). Further, the five studies included in this meta-analysis used four different tools to measure dyspnoea and the statistical heterogeneity was moderate (I^2=47%).[42] Therefore, there is still an uncertainty on the effects of exercise on dyspnoea in this population.

The abovementioned Cochrane review clearly demonstrated the need for larger high-quality RCTs. At present, several RCTs are being conducted all over the world that will shortly assist with confirming and extending the current evidence.[46-48] Since the publication of the Cochrane review, a well-designed RCT conducted in Australia, that investigated the effects of a comprehensive, unsupervised, home-based exercise program combined with nursing-led symptom management on outcomes in people with inoperable NSCLC, has been published.[49] The primary outcome measure of the study was change in 6MWD after the first 8 weeks of

the intervention and a sample size of 92 participants was needed to detect a between group difference in 6MWD of 48 ± 68 m (β=0.8; α=0.05). Of note, the intervention was 6-months long, and several other outcome measures were collected both on completion of the first 8 weeks and on completion of the 6-month intervention. Ninety-two participants were randomised (45 to the intervention group), and there were 14 participants who dropped out in the first 8 weeks (seven in each group). Adherence to the aerobic and resistance training components of the intervention was 65% and 53%, respectively. After the first 8 weeks of the intervention, there was no between-group difference in 6MWD (MD [95% CI] -25 [-64; 13] m). However, exploratory analyses demonstrated that, at 6 months, the intervention group had better HRQoL (MD [95% CI] 13 [4; 22]) and lower symptom severity measured via the MD Anderson Symptom Inventory - Lung Cancer scale (MD [95% CI] -2.2 [-3.6; -0.9]).[49]

The initial evidence that we have for the effects of exercise training in people with advanced/inoperable lung cancer seems to suggest that unsupervised home-based exercise does not confer the same benefits of supervised exercise programs. However, we should agree with the very sensible words from Dr Morten Quist on a recently published commentary, where he stated that: *"In patients with inoperable lung cancer, any improvement (or at least the prevention of deterioration) in physical and/or mental outcomes is of value"*.[50] Exercise training offers low risk of harm, has some evidence of benefit in both physical and mental status outcomes, and therefore should be seen as a potential tool to maximise outcomes in patients with such a devastating disease.

5. TOPICAL DISCUSSION AREAS

This section discusses some areas which are currently topical in the field of exercise and lung cancer. This includes the use of exercise training in people with bone metastases; the potential role of exercise on suppression of tumour growth; and top research clinical questions to be addressed to move the field forward.

5.1. Exercise training in people with bone metastases

Historically, and in many instances still today, health professionals have been concerned about prescribing exercise for patients with bone metastases. Bone metastases occur in approximately 20% to 30% of patients with lung cancer at diagnosis, and an additional 35% to 40% of patients develop bone metastases during the course of their disease.[51] Data collected in men with prostate cancer have shown that those with bone metastases are at risk of developing pathological fractures, nerve or spinal cord compression and other skeletal-related events that result in shorter survival, significant morbidity, limited function and decreased HRQoL.[52]

Over the past two decades, exercise training studies in people with cancer have excluded people with bone metastases due to the potential risk of fractures, spinal compression, or exacerbation of bone pain. However, there is emerging evidence from RCTs (in cancer populations other than lung cancer) that exercise training is safe, well-tolerated and helps with preserving self-reported physical function in men with bone metastases from prostate cancer and no significant bone pain (assessed by their specialist).[53, 54]

Importantly, exercise training programs for patients with bone metastases must be meticulously designed to minimise compressive and shear loads on affected skeletal sites, and executed carefully to avoid associated skeletal complications. The type of aerobic exercise for patients with pelvic, lumbar or proximal femur metastases should be non-weight bearing (i.e. stationary cycling), with weight bearing aerobic exercise (i.e. walking) being safely prescribed for patients with thoracic/ribs metastases.[54] Regarding resistance training, Table 2 (adapted from previous work[54]) provides recommendations for upper limb, trunk and lower limb exercises according to the bone metastasis site. Clinically, we recommend that, in patients with lung cancer, bone metastasis is not seen as an blanket contra-indication, but rather that patients be referred to a health professional specialising in exercise oncology, such as an oncology physiotherapist or exercise physiologist. Then, in collaboration with the treating doctor or general practitioner, an individualised exercise program should be carefully prescribed to meet the patient's needs and keep them as active as able.

5.2 Potential effect of exercise on suppression of tumour growth

Preclinical studies, on a range of experimental animal tumour models, have shown that exercise (i.e. voluntary wheel running) can inhibit tumour growth.[55] A previous study that evaluated the effect of wheel running before and/or during tumour challenge in a melanoma model in female mice, demonstrated an exercise-dependent increase in intratumoral immune cell infiltration.[56] These intratumoral infiltrates included natural killer (NK) cells, which contributed to a reduction in tumour growth. That study demonstrated that 4 weeks of

voluntary wheel running prior to tumour cell inoculation reduced tumour growth by 61%. Wheel running also halved the number of lung metastases after intravenous injection of melanoma cells. Further, in a Lewis Lung carcinoma model, wheel running decreased tumour volume and weight by 58% and 56%, respectively. A mechanistic analysis performed by the authors suggested that suppression of tumour growth was achieved through an epinephrine-dependent mobilisation of NK cells, together with subsequent interleukin-6-induced redistribution and activation of NK cells.[56]

Another mechanism of exercise-induced tumour suppression was described by Higgins and colleagues.[57] The study, in mice after tail vein injections of luciferase-tagged A549 lung adenocarcinoma cells, demonstrated that 4 weeks of wheel running reduced local lung tumour growth. Compared to the lung tumours in the group of mice who did not exercise, the tumours in those who exercised presented an up-regulation of pro-apoptotic proteins such as p53 and Bax (1103% and 179% up-regulation, respectively).[57]

The findings of the abovementioned studies are promising and exciting, but must be interpreted with caution. Although these preclinical studies indicate that exercise might induce intratumoral adaptations with increased immune cell infiltration and up-regulation of pro-apoptotic proteins, future research in humans examining whether the effects of exercise training on lung cancer progression are similar to that in mice are warranted.

5.3 Top questions still to be addressed

This review has addressed many topics related to exercise training across the lung cancer continuum. However, the field of exercise training for people with lung cancer is still in its

infancy and there are many questions still to be addressed. The authors recognise that the questions listed in this section may not be the top questions that clinical and research groups around the world may want to address. However, we believe that several of these questions have the potential to be viewed as critical in the area of exercise training for people with lung cancer. Our main aim is to list questions that, if answered, would fill some of the gaps mentioned in this review, rather than provide a comprehensive review to justify each question. We would like to encourage researchers all around the world to develop international networks/collaborative groups that would develop multicentre studies to address some of these questions.

Question 1: What is the cost-effectiveness of: (i) preoperative exercise training? (ii) postoperative exercise training? (iii) exercise training during treatment for advanced/inoperable lung cancer?

Question 2: In people undergoing treatment for lung cancer, is exercise training delivered via a mobile phone application or telerehabilitation as effective as outpatient supervised exercise training programs to improve health outcomes?

Question 3: What is the optimal length for exercise training programs across all stages of disease?

Question 4: What is the optimal timing to commence exercise training in: (i) people following lung resection for lung cancer; and (ii) in people undergoing treatments other than lung resection?

Question 5: In people with advanced/inoperable lung cancer, what type of exercise training program (i.e. resistance or aerobic) is more effective at improving HRQoL and symptoms?

Question 6: In people with advanced/inoperable lung cancer, is exercise training delivered before treatment commencement feasible and effective at reducing some of the negative impacts of lung cancer treatment?

Question 7: Across the whole lung cancer continuum, does exercise training improve survival?

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TABLES

Table 1: Take-home messages

Number	*Take-home message*
1	The direct effects of lung cancer combined with the indirect effects of cancer treatment can cumulatively lead to reductions in exercise capacity and health-related quality of life
2	Exercise training can play a major role in improving outcomes in patients with lung cancer
3	In patients with operable lung cancer, *preoperative* exercise training improves exercise capacity, and decreases the risk of postoperative pulmonary complications, length of hospital stay and days with an intercostal catheter
4	In patients with operable lung cancer, *postoperative* exercise training improves exercise capacity, health-related quality of life, quadriceps muscle strength and symptoms of dyspnoea
5	In patients with *inoperable* lung cancer, supervised exercise training is safe, feasible and helps maintain or improve exercise capacity and health-related quality of life
6	The field of exercise training for people with lung cancer is still in its infancy and exercise programs for patients with lung cancer are uncommon in clinical practice

7	We encourage researchers globally to develop international networks/collaborative groups to develop and facilitate the conduct of large multicentre/country studies to address important unanswered questions for the field (as listed in this article)

Table 2: Prescription of resistance exercise for patients with bone metastases (recommendations drawn from work in men with metastatic prostate cancer[53,54])

Site	*Upper limb*	*Trunk#*	*Lower limb*
Pelvis	Yes	Yes	Yes**
Lumbar spine	Yes	**No**	Yes
Thorax/ribs	Yes*	**No**	Yes
Proximal femur	Yes	Yes	Yes**
All regions	Yes*	**No**	Yes**

*Exclusion of shoulder flexion/extension/abduction/adduction; inclusion of elbow flexion/extension
**Exclusion of hip extension/flexion; inclusion of knee extension/flexion
#Examples are chest press and abdominal crunches

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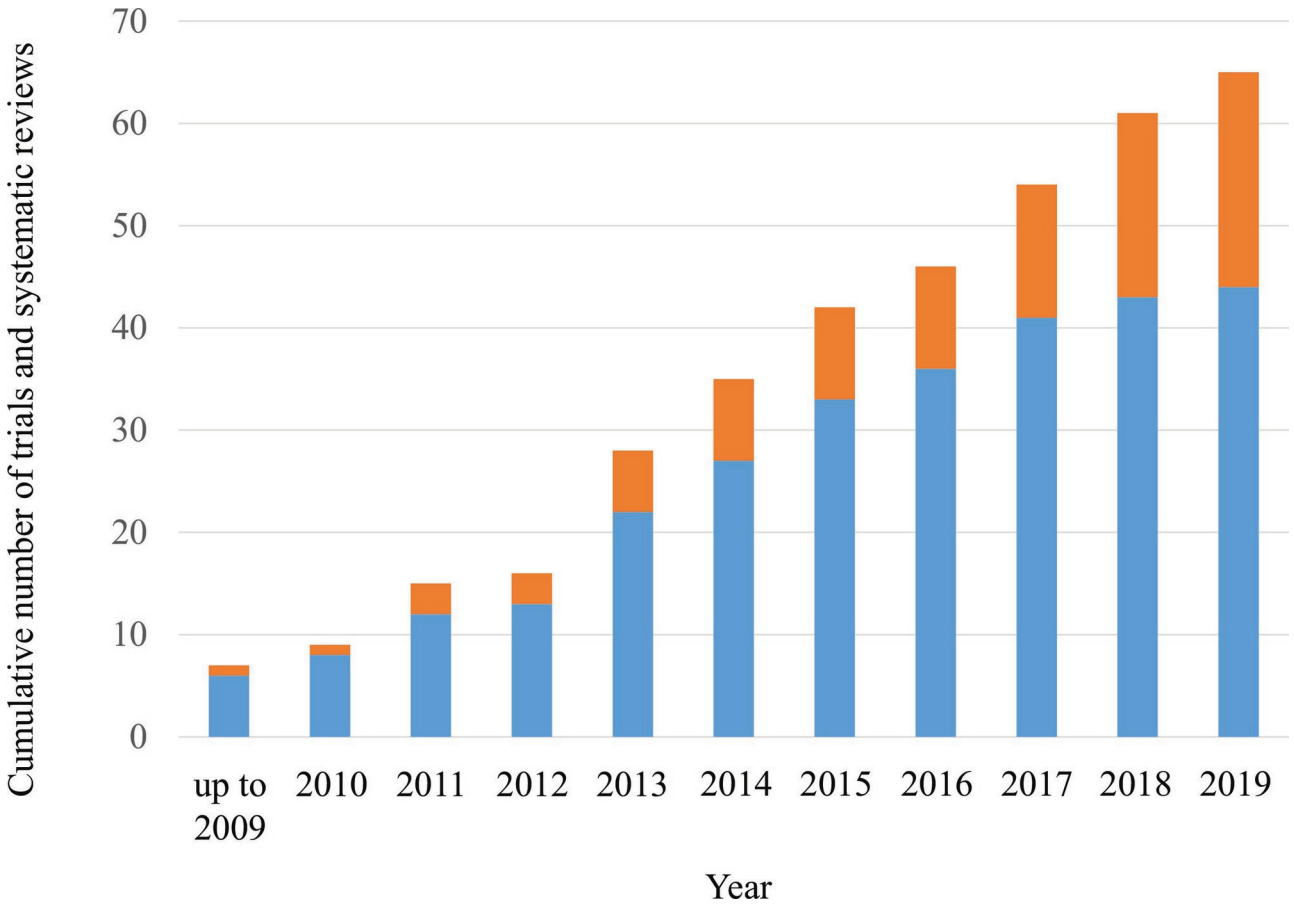
FIGURE LEGENDS

Figure 1: Cumulative number of clinical trials (blue) and systematic reviews (orange) on exercise training for people with lung cancer published until December 2019

Figure 2: Authors' recommendations on timing of exercise training across the disease/treatment pathway following a diagnosis of lung cancer

* Pending research to investigate specific benefits of exercise training

Evidence of benefit from Cochrane systematic reviews that only included randomised controlled trials



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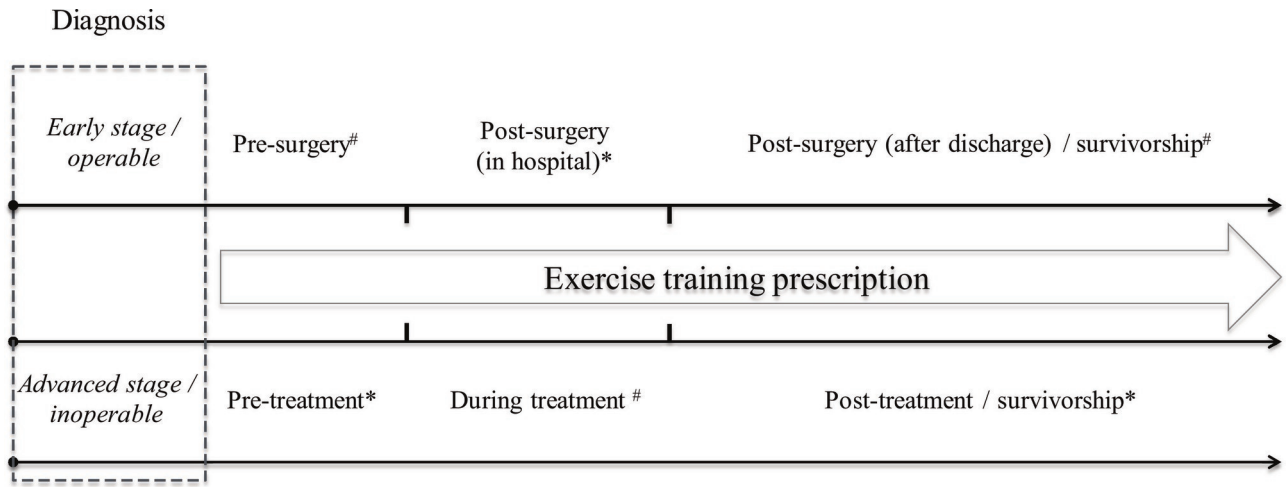

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