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ORIGINAL RESEARCH

Exercise training for people following curative intent treatment for non-small cell lung cancer: a randomized controlled trial☆

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Abstract
Objective: In people following curative intent treatment for non-small cell lung cancer, to investigate the effects of supervised exercise training on exercise capacity, physical activity and sedentary behavior, peripheral muscle force, health-related quality of life, fatigue, feelings of anxiety and depression, and lung function.
Method: This pilot randomized controlled trial included participants 6–10 weeks after lobectomy for non-small cell lung cancer or, for those who required adjuvant chemotherapy, 4–8 weeks after their last cycle. Participants were randomized to either 8 weeks of supervised exercise training (exercise group) or 8 weeks of usual care (control group). Prior to and following the intervention period, both groups completed measurements of exercise capacity, physical activity and sedentary behavior, quadriceps and handgrip force, HRQoL, fatigue, feelings of anxiety and depression, and lung function. Intention-to-treat analysis was undertaken.
Results: Seventeen participants (mean age 67, SD = 9 years; 12 females) were included. Nine and eight participants were randomized to the exercise and control groups, respectively. Four participants (44%) adhered to exercise training. Compared with any change seen in the control

☆ Trial registered the Australian New Zealand Clinical Trials Registry (ACTRN12611000864921). https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=343247.

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group, those in the exercise group demonstrated greater gains in the peak rate of oxygen consumption (mean difference, 95% confidence interval for between-group difference: 0.19 [0.04–0.33] L min^{-1}) and 6-minute walk distance (52 [12–93] m). No other between-group differences were demonstrated.

Conclusions: In people following curative intent treatment for non-small cell lung cancer, 8 weeks of supervised exercise training improved exercise capacity, measured by both laboratory- and field-based exercise tests. These results suggest that this clinical population may benefit from attending exercise training programs.

Introduction

Lung cancer is the leading cause of death for malignancy worldwide.[1] Data from the Australian Institute of Health and Welfare revealed that the 5-year survival of people with lung cancer is 15%.[2] In people diagnosed with lung cancer, 85% of cases are non-small cell lung cancer (NSCLC).[3] Importantly, for people diagnosed with early stage NSCLC, surgical resection of the tumor, with or without adjuvant chemotherapy, is considered to be a curative intent treatment,[4] and the 5-year survival of people following lung resection is up to 80%.[4]

Lung resection is associated with marked reductions in exercise capacity (i.e., peak rate of oxygen consumption [VO_{2peak}])[5–7] and health-related quality of life (HRQoL).[8,9] Although there is strong evidence that exercise training improves exercise capacity and HRQoL in people with chronic respiratory conditions such as chronic obstructive pulmonary disease (COPD)[10] and interstitial lung disease,[11] there are few studies investigating the role of exercise training for people who have recently completed curative intent treatment for NSCLC. Preliminary data suggests that exercise training may play an important role for individuals with a variety of cancer diagnoses.[12,13] A recent Cochrane systematic review, which included three randomized controlled trials (RCT) of exercise training in people following lung resection for NSCLC, demonstrated an increase in six-minute walk distance (6MWD).[14] However, this finding needs to be interpreted with caution due to methodological shortcomings of the included studies, such as lack of computer-generated randomization sequence and blinding of outcome assessors, per-protocol analysis, and selective reporting of results. Further, in the three studies included in the review, outcome measures were limited to exercise capacity, muscle strength, and HRQoL.

Therefore, the aim of this pilot study was to investigate the effects of supervised exercise training on a wide range of outcomes such as exercise capacity, physical activity and sedentary behavior, peripheral muscle force, HRQoL, fatigue, feelings of anxiety and depression, and lung function in people following curative intent treatment for NSCLC. We sought to use a design that would overcome some of the methodological shortcomings evident in earlier work by concealing the computer-generated randomization sequence, blinding the outcome assessor, and analyzing the data according to the intention-to-treat (ITT) principle.

Method

Study design and participants

This study was a pilot single-blinded RCT approved by the Ethics Committees of Sir Charles Gairdner Hospital (SCGH) and Royal Perth Hospital (RPH), Perth, WA, Australia (approval numbers 2011/105 and RA-11/033) and Curtin University, Perth, WA, Australia (approval number HR178/2011). The trial was prospectively registered (15/08/2011) with the Australian New Zealand Clinical Trials Registry (ACTRN12611000864921).

Data collection was performed between February 2012 and April 2014. Measurements were collected in people 6–10 weeks after lobectomy for NSCLC (stages I–IIIA) or, for those who required post-operative chemotherapy, 4–8 weeks after their last chemotherapy cycle. Exclusion criteria comprised: presence of any co-morbid condition that could compromise safety during assessments; severe neuromusculoskeletal limitations; participation in a program of supervised exercise training in the last 3 months; and inability to understand spoken or written English. Participants were recruited from outpatient clinics and referrals to the pulmonary rehabilitation programs at two hospitals and a private thoracic surgery clinic.

Protocol and measurements

After obtaining written informed consent, baseline assessments were undertaken over 2–3 days, with a minimum of 24 h between each assessment day. Participants were then randomized to an exercise group (EG) or a control group (CG). The randomization sequence was generated and managed by an independent researcher using a computer and concealed using sequentially numbered opaque envelopes. The sequence was stratified according to the hospital from which the participant was recruited and for the use (or not) of adjuvant chemotherapy.

Participants were reassessed on completion of the 8-week intervention period. The primary outcome was exercise capacity. Secondary outcomes comprised physical activity and sedentary behavior, peripheral muscle force, HRQoL, fatigue, feelings of anxiety and depression, and lung function. The primary investigator, who was responsible for the baseline and post-intervention period assessments, was not aware of whether a participant had been allocated to the

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