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Impairments after curative intent treatment for non-small cell lung cancer: A comparison with age and gender-matched healthy controls

Vinicius Cavalheri [a, b], Sue Jenkins [a, b, c], Nola Cecins [b, c, d], Kevin Gain [e, f], Martin Phillips [g], Lucas H. Sanders [h], Kylie Hill [a, b, i, *]

[a] School of Physiotherapy and Exercise Science, Curtin University, GPO Box U1987, Perth, WA 6845, Australia
[b] Institute for Respiratory Health, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA 6009, Australia
[c] Physiotherapy Department, Sir Charles Gairdner Hospital, Western Australia, Hospital Avenue, Nedlands, WA 6009, Australia
[d] Community Physiotherapy Services, 151 Wellington Street, Perth, WA 6000, Australia
[e] Department of Respiratory Medicine, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia
[f] School of Medicine and Pharmacology, University of Western Australia, GPO Box X2213 Perth, WA 6847, Australia
[g] Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA 6009, Australia
[h] Department of Cardiothoracic Surgery, Sir Charles Gairdner Hospital, Hospital Avenue, Nedlands, WA 6009, Australia
[i] Physiotherapy Department, Royal Perth Hospital, GPO Box X2213, Perth, WA 6001, Australia

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ABSTRACT

Background: The aim of this study was to compare measures of exercise capacity, health-related quality of life (HRQoL), muscle force, lung function and feelings of anxiety and depression in people after curative intent treatment for NSCLC with age and gender-matched healthy controls.
Methods: This cross-sectional study included 23 participants (68 ± 10yr; 16 females), 6–10 weeks after lobectomy for NSCLC or, for those who received adjuvant chemotherapy, 4–8 weeks after their last cycle. The study also included 20 age and gender-matched healthy controls (69 ± 5yr; 13 females). All participants underwent measurements of exercise capacity (cycle-ergometry test [CPET] and 6-min walk test [6MWT]), HRQoL (Short-Form 36 general health survey [SF-36]), handgrip force, quadriceps torque, lung function and feelings of anxiety and depression.
Results: When compared with data collected in healthy controls, those in the NSCLC group demonstrated impairments in the peak rate of oxygen consumption (15 ± 3 *versus* 24 ± 7 ml $kg^{-1} \cdot min^{-1}$; $p < 0.001$) and maximum work rate (75 ± 25 *versus* 127 ± 51Watts; $p < 0.001$) measured during the CPET, and 6-min walk distance (494 ± 77 *versus* 649 ± 61 m; $p < 0.001$). Similarly, impairments were demonstrated in all domains of the SF-36 ($p < 0.01$ for all), isometric handgrip force (28 ± 7 *versus* 34 ± 10 kg; $p = 0.02$), and all measures of lung function ($p \leq 0.001$ for all). A higher score for depression was also seen (3.0 ± 2.5 *versus* 1.5 ± 1.6; $p = 0.03$). There was no difference between the groups in isometric quadriceps torque or feelings of anxiety.
Conclusions: After curative intent treatment for NSCLC, compared to healthy controls, impairments were demonstrated in laboratory and field-based measures of exercise capacity, HRQoL, isometric handgrip force and lung function. Although people after curative intent treatment for NSCLC reported greater feelings of depression, these levels were below those considered clinically relevant. These findings suggest that people after curative intent treatment for NSCLC may benefit from rehabilitative strategies to optimise exercise capacity and HRQoL.

Abbreviations: 6MWD, Six-minute walk distance; 6MWT, Six-minute walk test; CI, Confidence interval; CPET, Cardiopulmonary exercise test; HADS, Hospital Anxiety and Depression Scale; HRQoL, Health-related quality of life; LLN, Lower limit of normal; MD, Mean difference; MCS, Mental component score; NSCLC, Non-small cell lung cancer; PCS, Physical component score; SF-36, Medical outcomes study Short-Form 36 general health survey; VO_{2peak}, Peak rate of oxygen consumption; Wmax, Maximum work rate.

* Corresponding author. School of Physiotherapy and Exercise Science, Curtin University, GPO Box U1987, Perth, WA, 6845.
E-mail addresses: vinicius.cavalher@curtin.edu.au (V. Cavalheri), s.jenkins@curtin.edu.au (S. Jenkins), nola.cecins@health.wa.gov.au (N. Cecins), kevin.gain@health.wa.gov.au (K. Gain), martin.phillips@health.wa.gov.au (M. Phillips), lucas.sanders@health.wa.gov.au (L.H. Sanders), K.Hill@curtin.edu.au (K. Hill).

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1. Introduction

For people diagnosed with early stage non-small cell lung cancer (NSCLC), lung resection, with or without adjuvant chemotherapy, is considered curative intent treatment [1]. Although lung resection is associated with post-operative pulmonary complications such as lung collapse, pneumonia and prolonged mechanical ventilation, people with lung cancer perceive the likelihood of a physical debility as more important and undesirable [2].

There is a dearth of studies exploring the impact curative intent treatment has on functional outcomes. Earlier work that has attempted to quantify impairments in people after curative intent treatment for NSCLC has focused exclusively on measures of lung function, maximal exercise capacity and health-related quality of life (HRQoL) [3–6]. It is unknown whether people after curative intent treatment for NSCLC present with impairments in other measures that are likely to be important, such as 6-min walk distance (6MWD), peripheral muscle force, and feelings of anxiety and depression. Such data would allow healthcare professionals to provide their patients who have been diagnosed with early stage NSCLC with realistic information regarding the magnitude of impairments they may experience after curative intent treatment. It may also provide a target for rehabilitation strategies, such as exercise training. Further, although studies have demonstrated that lung function and maximal exercise capacity are expected to decrease after curative intent treatment for NSCLC [3–6], these data were published 10–20 years ago, when the surgical techniques were considerably different to those used at present [7]. Data on impairments in lung function and exercise capacity that follow current surgical management and techniques are warranted.

The aim of this study was to compare measures of exercise capacity, HRQoL, peripheral muscle force, lung function and feelings of anxiety and depression made in people after curative intent treatment for NSCLC, with those made in age and gender-matched healthy controls. The hypothesis was that, compared to age and gender-matched healthy controls, all outcomes will be impaired in those who have completed curative intent treatment for NSCLC.

2. Materials and methods

See Online supplement for more details on study exclusion criteria, recruitment, sample size calculation and measurements.

2.1. Study design and participants

This was a cross-sectional and observational study. People were included if they were 6–10 weeks following lobectomy for NSCLC (stage I, II or IIIA) or, for those who required adjuvant chemotherapy following surgery, 4–8 weeks following their last cycle. Exclusion criteria comprised: presence of co-morbid conditions thought to compromise safety during the assessments such as uncontrolled hypertension; severe neuromusculoskeletal limitations; participation in exercise training in the last 3 months and; inability to understand spoken or written English. People with NSCLC were recruited from outpatient clinics and from referrals to the exercise training programmes at two tertiary hospitals in Perth. Regarding the healthy controls, Perth residents, with normal spirometry, aged between 55 and 80 years were eligible to participate. Exclusion criteria comprised the presence of any cardiac or neuromusculoskeletal condition thought to adversely influence performance during the assessments and the inability to understand spoken or written English. Stratified sampling was used to select healthy people who responded to the advertisements on the Curtin University radio station and in a community newspaper.

Assessments were initiated after participants gave written informed consent and were undertaken over 2 or 3 days, over a period of 2–3 weeks. There was a minimum of 24 h between assessment days. The study was approved by the Human Research Ethics Committees of two tertiary hospitals (approval numbers 2011/105 and RA-11/033) and Curtin University (HR 178/2011).

2.2. Protocol and measurements

For those with NSCLC (NSCLC group), the first two assessment days took place at the hospital at which they had received their treatment. The first two assessment days for the healthy controls took place at one of these hospitals. On the first assessment day, all participants performed two 6-min walk tests (6MWTs) [8–10], completed the medical outcomes study Short-Form 36 general health survey (SF-36) [11–13], the Hospital Anxiety and Depression Scale (HADS) [14] and had their isometric handgrip force measured [15]. On the second assessment day, all participants completed spirometry [16] and a symptom-limited ramp cycle-ergometry cardiopulmonary exercise test (CPET) [17]. The third assessment day took place at Curtin University, during which a measure was collected of isometric quadriceps muscle torque [18,19]. As the university is approximately 15 km from either of the hospitals, participants were given the option to decline this assessment.

2.3. Statistical analyses

Statistical analyses were performed using SPSS® (Statistical Package for Social Sciences, version 22.0). The distribution of data was examined by the Shapiro–Wilk test and all data were normally distributed. Between-group comparisons of continuous data were undertaken using independent-samples *t*-tests. Pearson Chi-square was used for comparison of categorical data. Differences between groups are reported as mean difference (MD) and 95% confidence interval (CI). For measures of function (e.g. exercise capacity and peripheral muscle force) that demonstrated a significant difference between the groups, data from the healthy controls were used to calculate the lower limit of normal (LLN). The LLN was defined as the 5th percentile, that is, the value above which 95% of the measures obtained in the healthy control group were situated [20,21]. For the NSCLC group, exploratory subgroup analyses were undertaken using independent *t*-tests to compare outcome measures between (i) in people with vs. without chronic obstructive pulmonary disease COPD [22] and (ii) people who underwent video assisted thoracoscopic surgery (VATS) vs. people who underwent open thoracotomy. For all analyses, a p value ≤ 0.05 was considered significant. All data are expressed as mean ± standard deviation unless otherwise stated.

Using published data on people with COPD [23], a sample size of 18 participants with NSCLC and 18 healthy controls was needed to detect a between-group difference in peak rate of oxygen consumption (VO_{2peak}) of 0.55 $L \cdot min^{-1}$ with a standard deviation of 0.57 $L \cdot min^{-1}$ ($\alpha = 0.05$, $1-\beta = 0.8$).

3. Results

Twenty-three participants in the NSCLC group and 20 healthy controls were included in final analysis (Fig. 1). Baseline characteristics of the two groups are presented in Table 1. The average time between lobectomy and the first day of assessment was 54 ± 17 days. Two participants received adjuvant chemotherapy. For these, the time between the last cycle of adjuvant chemotherapy and first day of assessment was 28 and 55 days. The average time between the first and second day of assessment and between the second and third day of assessment were 9 ± 3 and 3 ± 2 days, respectively.