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

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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 to 10 weeks after lobectomy for NSCLC or, for those who received adjuvant chemotherapy, 4 to 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 six-minute 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±7ml·kg^{-1}·min^{-1}; $p<0.001$) and maximum work rate (75±25 *versus* 127±51Watts; $p<0.001$) measured during the CPET, and 6-minute walk distance (494±77 *versus* 649±61m; $p<0.001$). Similarly, impairments were demonstrated in all domains of the SF-36 ($p<0.01$ for all), isometric handgrip force (28±7 *versus* 34±10kg; $p=0.02$), and all measures of lung function ($p\leq0.001$ 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.

Keywords: carcinoma, non-small cell; surgery; exercise capacity

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

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 six-minute 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 to 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.

Materials and Methods

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

Study design and participants

This was a cross-sectional and observational study. People were included if they were 6 to 10 weeks following lobectomy for NSCLC (stage I, II or IIIA) or, for those who required adjuvant chemotherapy following surgery, 4 to 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 to 3 weeks. There was a minimum of 24

hours 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).

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 six-minute 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 15km from either of the hospitals, participants were given the option to decline this assessment.

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 5^{th} 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 $0.57 L \cdot min^{-1}$ ($\alpha=0.05$, $1-\beta=0.8$).

Results

Twenty-three participants in the NSCLC group and 20 healthy controls were included in final analysis (Figure 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.

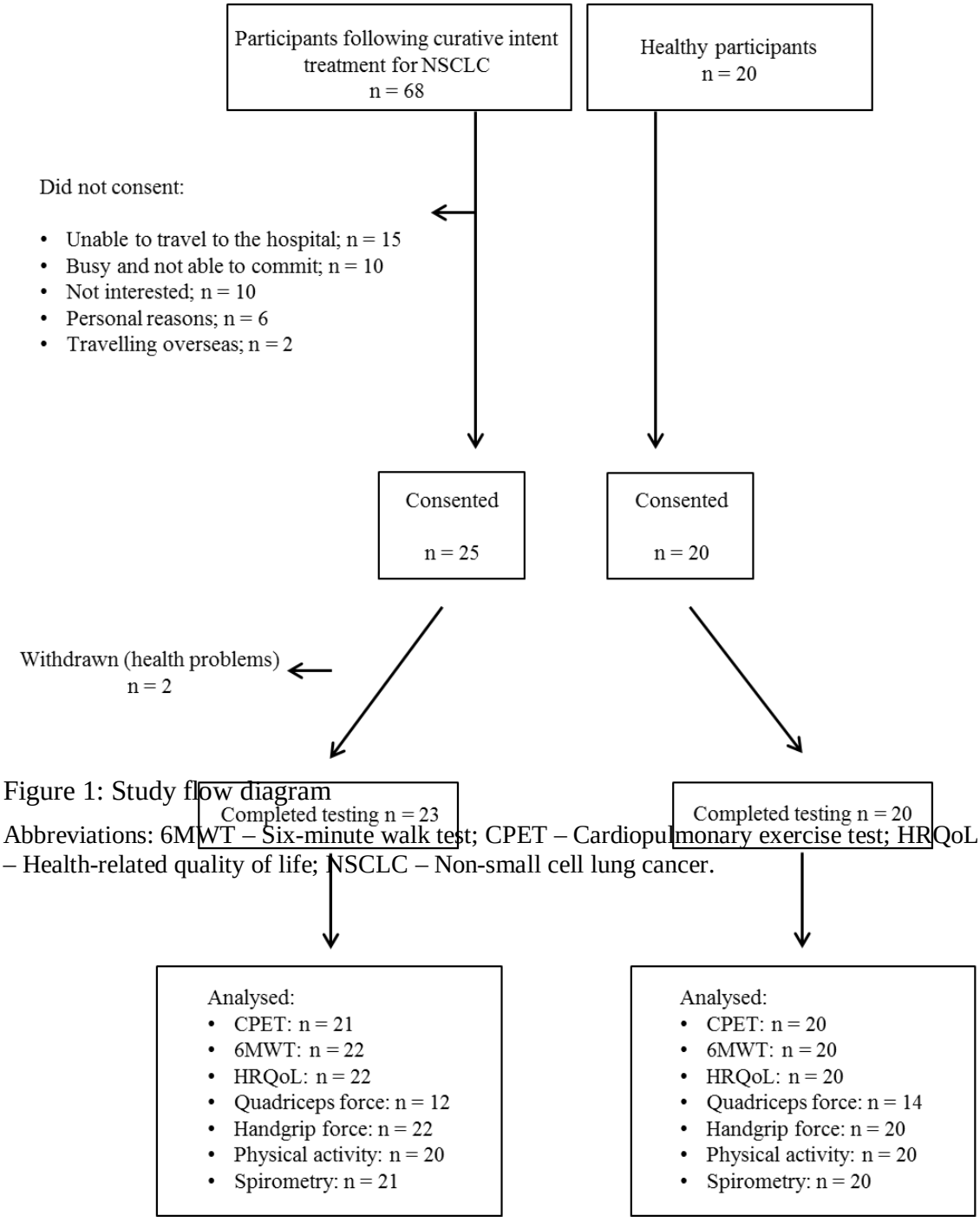

Figure 1: Study flow diagram

Abbreviations: 6MWT – Six-minute walk test; CPET – Cardiopulmonary exercise test; HRQoL – Health-related quality of life; NSCLC – Non-small cell lung cancer.

Table 1: Participant characteristics

Variable	**NSCLC Group (n=23)** *mean ± SD*		**Healthy Controls (n=20)** *mean ± SD*		***p value* (between-group)**
Age (yr)	68 ± 10		69 ± 5		*0.561*
Height (cm)	164 ± 12		167 ± 6		*< 0.001*
Weight (kg)	71 ± 21		71 ± 14		*< 0.001*
BMI ($kg \cdot m^{-2}$)	26 ± 6		25 ± 4		*0.756*
Smoking (pack/years)	39 ± 28		0.3 ± 0.9		*< 0.001*
FEV_1 (L)	1.65 ± 0.48		2.68 ± 0.54		*< 0.001*
FEV_1 (%pred)	67 ± 16		103 ± 15		*< 0.001*
FVC (L)	2.67 ± 0.71		3.44 ± 0.75		*< 0.001*
FVC (%pred)	81 ± 11		99 ± 15		*< 0.001*
FEV_1/FVC (%)	63 ± 12		78 ± 6		*< 0.001*
MVV (L·min)	63 ± 23		78 ± 6		*< 0.001*
MVV (%pred)	66 ± 19		119 ± 16		*< 0.001*
D_LCO ($ml \cdot mmHg^{-1} \cdot min^{-1}$)*	2.67 ± 0.71				
D_LCO (%pred)*	81 ± 11				
TLC (L)*	4.65 ± 1.34				
TLC (%pred)*	84 ± 15				
	n	**%**	**n**	**%**	
Gender, male/female	7/16	30/70	7/13	35/65	*0.750*
Smoking status					
Current smoker	1	5	0	0	*0.345*
Ex-smoker	18	78	2	10	*< 0.001*
Never smoked	4	17	18	90	*< 0.001*
COPD	12	52	0	0	*< 0.001*
Other comorbidities					
Hypertension	13	57	2	10	*0.001*
Stable heart disease	4	17	1	5	*0.206*
Diabetes Mellitus	4	17	1	5	*0.206*
Dyslipidemia	5	22	6	30	*0.334*
GORD	3	13	1	5	*0.365*
Hypothyroidism	3	13	4	20	*0.538*
Other cancers (treated)	6	26	0	0	*< 0.001*
Type of NSCLC					
Adenocarcinoma	15	65			
Squamous cell carcinoma	7	30			
Large cell carcinoma	1	5			
NSCLC stage					
I	18	78			
II	3	13			
IIIA	2	9			
Type of surgery (lobectomy)					
Open	11	48			
VATS	12	52			
Adjuvant chemotherapy	2	9			

Abbreviations: BMI – Body-mass index; COPD – Chronic obstructive pulmonary disease; DLCO – Diffusing capacity for carbon monoxide; FEV_1 – Forced expiratory volume in one second; FVC – Forced vital capacity; GORD - Gastro-oesophageal reflux disease; MVV – Maximum voluntary ventilation; NSCLC – Non-small cell lung cancer; SD – Standard deviation; TLC – Total lung capacity; VATS – Video-assisted thoracoscopic surgery. *Measures only collected in the NSCLC group.

Exercise capacity

Cardiopulmonary exercise test

Compared with healthy controls, participants in the NSCLC group demonstrated a lower VO_{2peak}, maximum work rate (Wmax), nadir arterial oxygen saturation (SpO_2), peak heart rate, breathing reserve, oxygen pulse, and reported greater dyspnoea on test completion (Table 2). The LLN for the VO_{2peak} and Wmax were $1.17 L \cdot min^{-1}$ and 77W, respectively. Fifteen and ten of the 21 participants (71% and 48%) in the NSCLC group had a VO_{2peak} or a Wmax, respectively, below the LLN.

Six-minute walk test

Compared with healthy controls, participants in the NSCLC group demonstrated a lower 6MWD, nadir SpO_2, peak heart rate and reported greater dyspnoea and leg fatigue on test completion (Table 2). The LLN calculated for the 6MWD was 496m. Ten of 22 participants (45%) in the NSCLC group had a 6MWD below the LLN.

Table 2: Measures obtained during the cardiopulmonary exercise test, six-minute walk test and assessments of isometric handgrip force and ismetric quadriceps torque

Variable	**NSCLC Group** *mean ± SD*	**Healthy Controls** *mean ± SD*	**Mean difference (MD)** *MD [95% CI]*	***p value***
CPET	***n = 21***	***n = 20***		
VO_{2peak} ($L \cdot min^{-1}$)	1.03 ± 0.31	1.69 ± 0.63	-0.65 [-0.96 to -0.34]	*< 0.001*
VO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)	15 ± 3	24 ± 7	-8.7 [-12.1 to -5.3]	*< 0.001*
VO_{2peak} (%pred)	64 ± 15	95 ± 23	-32 [-44 to -19]	*< 0.001*
Wmax (W)	75 ± 25	127 ± 51	-52 [-77 to -26]	*< 0.001*
Wmax (%pred)	74 ± 20	122 ± 41	-48 [-69 to -28]	*< 0.001*
BORGd on completion CPET	6.9 ± 2.5	4.6 ± 1.8	2.3 [0.9 to 3.6]	*0.002*
BORGf on completion CPET	6.9 ± 2.4	6.3 ± 2.2	0.6 [-0.9 to 2.0]	*0.443*
Nadir SpO_2 (%)	94 ± 4	96 ± 2	-3 [-5 to -1]	*0.013*
HRmax (bpm)	129 ± 18	149 ± 12	-20 [-29 to -10]	*< 0.001*
BR (%)	31 ± 16	48 ± 12	-17 [-26 to -8]	*< 0.001*
O_2 pulse ($ml \cdot beat^{-1}$)	8 ± 3	11 ± 4	-3 [-5 to -1]	*0.004*
AT (%VO_{2peak})	62 ± 9	60 ± 6	-1.3 [-3.7 to -6.3]	*0.601*
VEmax/MVV (%)	69 ± 16	51 ± 12	18 [9 to 27]	*< 0.001*
RER	1.22 ± 0.10	1.32 ± 0.18	0.10 [0.02 to 0.17]	*0.032*
6MWT	***n = 22***	***n = 20***		
6MWD (m)	494 ± 77	649 ± 61	-155 [-199 to -111]	*< 0.001*
6MWD (%pred)	80 ± 11	104 ± 7	-24 [-29 to -18]	*< 0.001*
BORGd on completion 6MWT	3.2 ± 1.6	1.4 ± 0.9	1.7 [0.9 to 2.6]	*< 0.001*
BORGf on completion 6MWT	2.0 ± 1.9	0.9 ± 0.9	1.1 [0.1 to 2.0]	*0.025*
Nadir SpO_2 (%)	93 ± 3	96 ± 1	-3 [-5 to -2]	*< 0.001*
Peak HR (bpm)	119 ± 14	137 ± 13	-18 [-27 to -10]	*< 0.001*
Isometric handgrip force	***n = 22***	***n = 20***		
Handgrip (kg)	28 ± 7	34 ± 10	-6 [-11 to -1]	*0.023*
Handgrip (%pred)	101 ± 21	123 ± 21	-21 [-35 to -9]	*0.001*
Isometric quadriceps torque	***n = 12***	***n = 14***		
Quadriceps (Nm)	127 ± 64	120 ± 40	8 [-35 to 50]	*0.710*
Quadriceps (%pred)	97 ± 19	104 ± 17	-6 [-21 to 8]	*0.381*

Abbreviations: 6MWT – Six-minute walk test; AT – Anaerobic threshold as a percentage of the VO_{2peak}; BORGd – Dyspnoea; BORGf – Fatigue; BR – Breathing reserve; CI – Confidence interval; CPET – Cardiopulmonary exercise test; HR – Heart rate; HRmax – Maximal heart rate; O_2 pulse – Oxygen pulse; RER – Respiratory exchange ratio; SD – Standard deviation; SpO_2 - Arterial oxygen saturation measured via pulse oximetry; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

Isometric handgrip force and isometric quadriceps torque

Compared with healthy controls, participants in the NSCLC group demonstrated a lower isometric handgrip force (Table 2). The LLN calculated for this outcome measure was 22kg. Five of 22 participants (23%) in the NSCLC group had isometric handgrip force below the LLN.

No between-group difference was demonstrated in isometric quadriceps torque (Table 2).

Health-related quality of life and feelings of anxiety and depression

Compared with healthy controls, participants in the NSCLC group demonstrated a lower physical component score (PCS) and mental component score (MCS) (Table 3). Lower scores were also demonstrated for each of the eight domains assessed using the SF-36 (Table 3).

Pertaining to the HADS, participants in the NSCLC group reported greater score for depression. Nevertheless, mean scores for both anxiety and depression components of the HADS of participants in the NSCLC and healthy control groups were below the threshold used to suspect clinical anxiety or depression (Table 3).

Table 3: Health-related quality of life and feelings of anxiety and depression data

Variable	**NSCLC Group (n=22)** *mean ± SD*	**Healthy Controls (n=20)** *mean ± SD*	**Mean difference (MD)** *MD [95% CI]*	***p value***
SF-36				
PCS	45 ± 5	56 ± 5	-11 [-15 to -8]	*< 0.001*
MCS	51 ± 8	57 ± 7	-6 [-11 to -2]	*0.008*
Physical functioning	62 ± 19	93 ± 8	-31 [-41 to -22]	*< 0.001*
Role physical	60 ± 22	94 ± 9	-34 [-45 to -23]	*< 0.001*
Bodily pain	62 ± 19	81 ± 15	-19 [-29 to -8]	*0.001*
General health	67 ± 18	91 ± 9	-24 [-33 to -15]	*< 0.001*
Vitality	60 ± 18	77 ± 13	-17 [-27 to -7]	*0.001*
Social functioning	76 ± 21	94 ± 12	-19 [-30 to -8]	*< 0.001*
Role emotional	73 ± 23	95 ± 12	-22 [-33 to -10]	*< 0.001*
Mental health	75 ± 16	89 ± 12	-14 [-22 to -5]	*0.003*
HADS				
Anxiety score	4.1 ± 2.4	2.9 ± 2.5	1.2 [-0.3 to 2.8]	*0.112*
Depression score	3.0 ± 2.5	1.5 ± 1.6	1.5 [0.2 to 2.9]	*0.026*

Abbreviations: CI – Confidence interval; HADS – Hospital anxiety and depression scale; MCS – Mental component score; NSCLC – Non-small cell lung cancer; PCS – Physical component score; SD – Standard deviation; SF-36 – Medical outcomes study Short-Form 36 general health survey.

Lung function

Compared with healthy controls, participants in the NSCLC group demonstrated impairments in all measures of lung function (Table 1).

Exploratory subgroup analysis

Results of exploratory subgroup analyses are presented in the online supplementary material.

Discussion

This study has demonstrated that, compared to age and gender-matched healthy controls, people after curative intent treatment for NSCLC have impaired exercise capacity, HRQoL, isometric handgrip force and lung function. Isometric quadriceps torque appears to be preserved; however, only a subgroup of participants attended this assessment. Although those in the NSCLC group reported greater feelings of depression, the mean score for depression in this group was low.

Earlier work that has measured the exercise capacity of people after curative intent treatment for NSCLC reported similar VO_{2peak}, Wmax and 6MWD as the current study [4, 24]. The novel finding of this study is that after curative intent treatment for NSCLC, more than two-thirds (71%) of participants had a VO_{2peak} below the LLN established in healthy controls and almost half achieved a Wmax and 6MWD that were below the LLN. These data suggest that people after curative intent treatment for NSCLC are more likely to present with impairment in maximal exercise capacity (i.e. VO_{2peak}) than in functional exercise capacity (i.e. 6MWD). It is also possible that the smaller between-group difference in 6MWD, compared to measures of exercise capacity obtained during the CPET, reflected the fact that those in the healthy control group were limited from walking further during the 6MWT by mechanical factors such as stride length. This so-called ceiling effect on 6MWD in the healthy control group may have reduced our estimation of differences in 6MWD between the two groups. Of note, the VO_{2peak} of 15±3ml·kg·$^{-1}$·min^{-1} (or 64±15%pred) shown in this study is similar to the VO_{2peak} reported in people with moderate-to-severe COPD [25, 26] in whom

exercise training has been shown to improve exercise capacity [25]. Although exercise training has been established as a treatment option in people with COPD, referral of people following lung resection for lung cancer to exercise training programmes is low [27]. The impairment in VO_{2peak} demonstrated in this study combined with previous work that has shown that VO_{2peak} is an independent predictor of mortality in people with NSCLC [28], supports the need for rehabilitative strategies to optimise exercise capacity in this population.

Compared to healthy controls, both the PCS and the MCS of the SF-36 were decreased in participants in the NSCLC group. Of note, the magnitude of the mean difference in the PCS between the two groups -11[-15 to -8]) was almost twice that seen in the MCS (-6[-11 to -2]). This suggests that people after curative intent treatment for NSCLC perceive their HRQoL to be more affected by physical problems than by mental or emotional problems. This contention is supported by earlier work which has demonstrated a worsening of 14 to 19% in the physical components of HRQoL up to 6 months following lung resection for NSCLC [6, 29, 30], whereas the mental components of HRQoL have been shown to have minimal, if any, change [31-33]. Of note, compared to the Australian population norms [34] (PCS: 50 [50 to 51]; MCS: 53 [52 to 53]), the mean PCS score of the NSCLC group (45±5) was 5 points lower, whereas the mean MCS score (51±8) was only 2 points lower. Minimal impairment in the mental health of the NSCLC group is in keeping with our data showing that feelings of anxiety and depression were within normal ranges (HADS anxiety and depression scores ≤7) in the NSCLC group.

Scores for feelings of anxiety were also reported by Granger et al [35], who followed 50 participants with stage IA to IIIB NSCLC from the time of diagnosis to 6 months following diagnosis. Half of the participants (25 of 50) underwent lung resection (with or without adjuvant chemotherapy) and the remaining 25 participants received chemotherapy, radiotherapy or a combination of both. The study demonstrated no change in anxiety scores from diagnosis to 6 months (5.5±0.7 *versus* 5.5±0.7; p=0.94) [35]. Subgroup analysis comparing changes in the anxiety score of participants who underwent lung resection and those who did not undergo lung resection were not performed, precluding the comparison with findings from the present study.

This is the first study to demonstrate impairment in isometric handgrip force in people after curative intent treatment for stage I, II or IIIA NSCLC. Participants in the NSCLC group were 17% weaker than healthy controls (28±7 *versus* 34±10kg; p=0.02). The relevance of this finding is that handgrip force is related to general muscle strength in older adults [36] and it is also a prognostic factor for mortality in middle-aged and older people [37]. Although the changes in peripheral muscle force after curative intent treatment for NSCLC needs further investigation, the measurement of handgrip force may assist in identifying those who present with impairments in general muscle strength.

Given the impairments in handgrip force, it is somewhat surprising that measures of quadriceps torque were similar between the NSCLC and healthy control groups. However, a previous study of 13 people with thoracic cancers and 13 matched healthy controls has also reported similar quadriceps muscle torque in both groups (median [interquartile range] 65 [27 to 71] *versus* 74 [54 to 84]Nm, respectively; p>0.05) [19].

It also appears that quadriceps force recovers to pre-operative measures within 3 months of surgery. Arbane et al [38] investigated quadriceps twitch force via magnetic stimulation of the femoral nerve in 25 people undergoing lung resection for NSCLC. They demonstrated no change in measures collected 12 weeks following lung resection compared to those collected pre-operatively. However, of the 25 people with NSCLC who were assessed prior to lung resection in that study, only 13 (52%) returned for the 12-week assessment [38]. This was a substantial attrition rate (48%) and it is possible that those people who returned for the 12-week assessment were not representative of the total sample. This is also likely to have occurred in the current study. That is, only 12 of the 23 participants (52%) in the NSCLC group underwent measurement of isometric quadriceps muscle force. Therefore, although further study is needed to determine changes in quadriceps force after curative intent treatment for NSCLC, our data demonstrating reduced hand grip force suggests that peripheral muscle strength is impaired in this group.

Not surprisingly, compared to healthy controls, all variables of lung function were decreased in the NSCLC group. Lung function has consistently been shown to decrease after lung resection for NSCLC [39, 40] and our results corroborate results from these previous studies.

Study strengths and limitations

Compared to previous studies that assessed outcomes in people after lung resection for NSCLC, this study was the first to include a broad range of outcomes measures and compare them with data collected in age and gender-matched healthy controls. The

current study demonstrated that patients were able to tolerate this comprehensive assessment protocol at this time. This increases the rationale to consider referring these patients for rehabilitation as soon as 6 weeks following surgery. This study was also the first to assess exercise capacity of people following lung resection for NSCLC using both a laboratory-based (CPET) and a field-based exercise test (6MWT). The optimal study design to quantify the impact of curative intent treatment for NSCLC on measures such as exercise capacity, HRQoL, peripheral muscle force, lung function and feelings of anxiety and depression would be to collect measures prior to and after treatment in the same sample. Nevertheless, such a design was not possible at our hospitals as the time between the decision to operate and the date of surgery was often less than one week and patients were unable to accommodate the additional visits required for the study assessments. Comparing measures obtained in people after curative intent treatment for NSCLC with those collected in healthy controls, did not delay surgery and was the only feasible study design to quantify impairment in this patient group. Further, rather than use reference equations to estimate measures in a healthy population, comparing measures between those after curative intent treatment for NSCLC with those that have been collected in healthy controls in the same laboratory, by the same investigator, ensures that between-group differences were not due to disparities in testing protocols and equipment.

The main limitation of this study relates to the limited number of healthy controls available to calculate the LLNs. These calculations may have been more robust if a larger sample were available. Nevertheless, in an earlier study which reported impairments in participants with cystic fibrosis the same number of healthy controls were used to derive measures of LLN [21]. Another limitation of the current study was

that people who underwent wedge resection or pneumonectomy for NSCLC were not included, thus our findings cannot be extended to all people undergoing curative intent treatment for NSCLC. Further, although there was no significant difference in the percentage of people in both groups with diabetes mellitus (DM), the NSCLC had three times as much people with DM than the healthy controls group, and this may have contributed to their impairment in exercise capacity. Another limitation of the study was that, although the two groups were balanced for age and gender, we did not seek to balance the groups in terms of participation in daily physical activity. It is possible that the healthy controls participated in greater physical activity and that this factor contributed to the magnitude of between-group difference in maximum exercise capacity. Finally, this study includes a large number of between-group comparisons which increases the risk of type I error. Nevertheless, as the between-group differences for measures of exercise capacity, HRQoL and lung function were large and resulted in p values ≤ 0.001, it unlikely that these results reflect type I errors.

Conclusions

The greatest impairment detected in people after curative intent treatment for NSCLC, compared to healthy controls, was in exercise capacity. The magnitude of difference between groups in variables of exercise was large and 71% of participants after curative intent treatment for NSCLC presented decreased maximal exercise capacity (i.e. VO_{2peak} below the LLN). Compared to age and gender-matched healthy controls, people after curative intent treatment for NSCLC also demonstrated impairments in HRQoL, isometric handgrip force and lung function. Conversely, quadriceps torque and feelings of anxiety were similar to that measured in age and gender-matched healthy controls. Although in those after curative intent treatment for NSCLC greater feelings of depression were reported compared to healthy controls, these levels were below those considered clinically relevant.

These findings provide important information to clinicians working in the field. They highlight impairments in some patient-centred outcomes after curative intent treatment for NSCLC. They also allow health professionals to provide their patients with realistic information regarding the magnitude of these impairments. Further studies are necessary to demonstrate whether impairments exist prior to curative intent treatment and whether rehabilitation strategies are of benefit to improve exercise capacity and HRQoL.

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

Short title: Outcomes following curative intent treatment for non-small cell lung cancer

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SUPPLEMENTARY MATERIAL

1. Study design and participants

1.1 Study exclusion criteria

Exclusion criteria of people following curative intent treatment for non-small cell lung cancer (NSCLC) 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. The rationale for excluding people who had participated in exercise training in the last 3 months was because exercise training has been demonstrated to improve exercise capacity in this population [1] and this would reduce the difference between groups.

1.2 Recruitment

A convenience sample of healthy controls was recruited using stratified sampling. Specifically, once we recruited the first 20 participants in the NSCLC group, we calculated

the mean age and proportion of males vs females. Thereafter, in order to ensure that the healthy control group were similar to the NSCLC, strata were created for age and gender proportion based on the sample characteristics of the NSCLC group. These strata were (i) 4 people aged 55 to 60 yr; 0 males and 4 females (ii) 7 people aged 61 to 70 yr; 3 males and 4 females and (iii) 9 people aged 71 to 80 yr; 4 males and 5 females. Subsequently, 20 healthy controls were recruited into these strata in the order to which they responded to the advertisements. This process was suggested by a statistician in order to ensure that participants in both group were 'balanced' in terms of age and gender proportion.

In order to prevent selection bias of highly active healthy controls, the specific questions of both the advertisement and the radio text were: Are you aged between 55 and 80 years? Are you in good health? Are you a non-smoker? Can you spare some time to do a few tests at Sir Charles Gairdner Hospital? If you have answered "yes" to all these questions, please contact us for more information.

2. Measurements

2.1 Exercise capacity

2.1.1 Cardiopulmonary exercise test (CPET)

A symptom-limited ramp cycle ergometry exercise test was performed on an electronically braked bicycle ergometer (ER 900; Jaeger, Germany) in accordance with published guidelines [2]. Work rate increments during the test were determined using a published equation [3]. Increments varied from 1W every 12 seconds (i.e. 5W per minute) to 1W every 5 seconds (i.e. 12W per minute). The increments in work rate were based on the participants

predicted maximum work rate (Wmax) [4] and chosen based on a 10-minute test duration [2, 3, 5].

Participants rested on the bike for 3 minutes. They then cycled (between 50-60rpm) without any resistance for another 3 minutes. After this time, the resistance on the bike progressively increased until symptom limitation. Breath-by-breath measurements were collected (Medgraphics CardiO2; Medical Graphics Corporation, USA). Blood pressure was measured every 2 minutes by automated sphygmomanometry. Twelve-lead electrocardiography was used and arterial oxygen saturation measured via pulse oximetry (SpO_2) was continuously monitored (Radical; Masimo Corporation, USA). The modified BORG scale (0-10) [6] was used to quantify level of dyspnoea (BORGd) and leg fatigue (BORGf) prior to starting the test, each minute during the test, and on test completion.

Measures of the peak rate of oxygen consumption (VO_{2peak}) and maximum minute ventilation (VEmax) collected during the CPET were averaged over the last 20 seconds of the test [2, 7, 8]. The Wmax and measures of VO_{2peak} were expressed in absolute values and as a percentage of the predicted value in a healthy population [4].

2.1.2 Six-minute walk test (6MWT)

The 6MWT was undertaken according to a protocol based on the American Thoracic Society recommendations [9]. It was performed over a 45-m straight course within an enclosed corridor. Standardised encouragement was given at the end of every minute. Also, at the end of every minute, measures were collected of heart rate (HR) (Polar a1; Polar Electro Oy, Finland) and SpO_2 (finger sensor and handheld pulse oximeter, Rad-57; Masimo Corporation, USA).

Two tests, separated by a 30-minute rest period, were conducted and the best six-minute walk distance (6MWD) achieved was recorded as the test result. The modified BORG scale [6] was used to quantify level of dyspnoea and leg fatigue prior to starting the test and on test completion. The 6MWD was expressed in absolute values and as a percentage of the predicted value in a healthy population [10].

2.2 Health-related quality of life (HRQoL)

The medical outcomes study Short Form 36 general health survey (SF-36) was used to assess HRQoL. It comprises two major components: physical (physical component score [PCS]) and mental (mental component score [MCS]). The responses to items in each component are weighted equally, summed, and transformed to a 0 to 100 scale. Higher scores represent better HRQoL. The SF-36 has been widely used and its reliability and validity has been documented in people with a range of conditions that includes hypertension, diabetes, chronic heart failure and chronic obstructive pulmonary disease (COPD) [11-13].

2.3 Peripheral muscle force

Maximal isometric torque of the quadriceps was measured in an upright seated position using the HUMAC NORM isokinetic dynamometer (CSMi; Stoughton, USA). The dominant leg (i.e. the leg they would kick a soccer ball) was chosen and participants were asked to perform five maximum contractions of the quadriceps at 60º of knee flexion. Each contraction was separated by 60 seconds. The contraction that generated the highest torque, and was within 5% of another effort, was recorded as the test result. Measures were expressed in absolute values and as a percentage of the predicted value in a healthy population [14]. The equipment was calibrated prior to every test in accordance with the manufacturer's recommendations.

Isometric handgrip force was measured using a hydraulic hand dynamometer (Jamar dynamometer; JA Preston Corporation; Jackson, MI, USA). Peak handgrip force was assessed bilaterally, with the elbow at 90° of flexion and the forearm and wrist in a neutral position. Measures were expressed in absolute values and as a percentage of the predicted value in a healthy population [15]. The hand dynamometer was calibrated at time intervals in accordance with the manufacturer's recommendations.

2.4 Lung function

Lung function testing comprised measures made using spirometry (forced vital capacity [FVC] and slow vital capacity [SVC] manoeuvres), body plethysmography and diffusing capacity for carbon monoxide. The healthy controls only underwent the FVC manoeuvre and the maximum voluntary ventilation (MVV) assessment. Inhaled bronchodilator was not administered prior to lung function testing. The Medgraphics Elite Series DX plethysmograph (Medical Graphics Corporation, St Paul, MN, USA) was used to assess lung function and the equipment was calibrated prior to every test in accordance with the manufacturer's recommendations. All the assessments were performed according to published guidelines on standardisation of lung function testing [16-19]. Measurements were expressed in absolute values and, where possible, as a percentage of the predicted value in a healthy population [20-22].

2.5 Feelings of anxiety and depression

Feelings of anxiety and depression measured using the Hospital Anxiety and Depression Scale (HADS) [23]. The HADS has been used to measure depression and generalised anxiety among hospitalised people, people attending outpatient clinics as well as in community settings [24-26]. It comprises 14 statements describing symptoms of depression (7 items) and

anxiety (7 items). Response options for each question range from 0 to 3, with a total range score between 0 and 21 for the depression and anxiety subscales. Higher scores represent greater feelings of depression and/or anxiety. Scores ≤ 7 are considered normal, scores > 7 and < 11 are considered borderline abnormal and scores ≥ 11 are suggestive of a likely clinical diagnosis of depression or anxiety [23].

3. Statistical analyses

3.1 Sample size calculation

Compared with healthy controls, a previous study demonstrated that people with mild COPD had an average reduction in VO_{2peak} of 0.36L·min^{-1} [27]. Although many people with non-NSCLC are likely to also have COPD, there will be a greater difference between the two groups in this study as the systemic effects of cancer as well as its treatment will increase the impairments in exercise capacity over and above those attributed to COPD. Therefore, we increased the magnitude of the between-group difference in VO_{2peak} (i.e. 0.36L·min^{-1} between people with mild COPD and healthy controls) by approximately 50%. That is, we estimated the magnitude of between-group difference in this study to be 0.55L·min^{-1}. The decision to inflate the magnitude of the difference by 50% was arbitrary, but in the absence of any published literature to guide this calculation, this was considered a pragmatic approach. To estimate the standard deviation of the change for our sample size calculation, we averaged the standard deviation in the measurement of VO_{2peak} previously reported in people with mild COPD and healthy controls (i.e. [0.55+0.59L·min^{-1}] / 2 = 0.57L·min^{-1}). Using these estimates, a sample size of 18 participants with NSCLC and 18 healthy controls were needed to detect a between-group difference in VO_{2peak} of 0.55L·min^{-1} with a standard deviation of 0.57L·min^{-1} (α=0.05, 1-β=0.8).

4. Results

Ninety-six people following curative intent treatment for NSCLC were screened to participate in this study, of whom 71% (n=68) were eligible and approached. Of these 68 people, a total of 25 consented to participate (consent rate of 37%). The reasons for declining participation are outlined in **Error! Reference source not found.**. Two of the 25 (8%) were withdrawn due to health issues not related to lung cancer. Specifically, one participant was diagnosed with a primary bowel cancer and the other participant chose not to disclose the nature of the health issue that led to his withdrawal (**Error! Reference source not found.**). During the same time period, 32 healthy people expressed interest in the study after hearing the advertisement on the University radio station. Stratified sampling (strata of age and gender) was used to select the first 20 eligible healthy people who expressed an interest in participating, and those 20 people were included in the study. Twenty-three participants following curative intent treatment for NSCLC (NSCLC group) and 20 healthy controls were included in final analysis (**Error! Reference source not found.**). Baseline characteristics of the two groups are presented in **Error! Reference source not found.**.

The average time between lobectomy and the first day of assessment was 54±17 days. Two participants (9%) received adjuvant chemotherapy. For these participants, the time lapse between the last cycle of adjuvant chemotherapy and first day of assessment was 28 and 55 days.

4.1 Exercise capacity

4.1.1 Cardiopulmonary exercise test

All CPETs results were reviewed by a doctor who interpreted them to be a maximal effort test. The average duration of the CPET in the NSCLC group (9±2 minutes) was similar to that in healthy controls (10±2 minutes) (p=0.19). The average work rate increment during the CPET was smaller for the NSCLC group than for the healthy controls (8±2 *versus* 13±4W/min; p<0.001). The VO_{2peak} of the healthy controls ranged from 1.17 to 2.43 $L \cdot min^{-1}$ and their Wmax ranged from 77 to 301W. The VO_{2peak} of participants in the NSCLC group ranged from 0.56 to 1.48 $L \cdot min^{-1}$ and their Wmax ranged from 37 to 114W. The average VEmax of the participants in the NSCLC group was lower than the healthy controls (42.1±14.3 *versus* 61.1±20.1L/min; p=0.001).

The number of participants who reached the American Thoracic Society/American College of Chest Physicians (ATS/ACCP) criteria for a maximal effort test (i.e. achieved predicted VO_{2peak}, predicted Wmax, predicted HRmax, VEmax/MVV ≥ 0.85 or respiratory exchange ratio [RER] ≥ 1.15) [2] are presented in Table A1.

Regarding the symptoms that limited performance during the CPET, in the NSCLC group, eight participants (38%) were limited by dyspnoea, six (29%) were limited by leg fatigue, and seven (33%) were limited by a combination of dyspnoea and leg fatigue. For the healthy controls, four participants (20%) were limited by dyspnoea, 14 (70%) were limited by leg fatigue and two (10%) were limited by a combination of dyspnoea and leg fatigue.

Table A1: Number of participants who reached the ATS/ACCP criteria of maximal effort

ATS/ACCP criteria for a maximal effort test	**NSCLC Group (n=21)**	**Helthy Controls (n=20)**
Predicted VO_{2peak}	0 (0%)	6 (30%)
Predicted Wmax	2 (10%)	13 (65%)
Predicted HRmax	3 (14%)	10 (50%)
VEmax/MVV ≥ 0.85	4 (19%)	0 (0%)
RER ≥ 1.15	19 (90%)	20 (100%)

Abbreviations: ATS/ACCP – American Thoracic Society/American College of Chest Physicians; HRmax – Maximal heart rate; RER – Respiratory exchange ratio; VEmax/MVV – Maximum minute ventilation, maximum voluntary ventilation ratio; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

4.1.2 Six-minute walk test

A comparison of variables collected during the 6MWT between the groups is presented in **Error! Reference source not found.**. Significant differences were observed in 6MWD, nadir SpO_2, peak HR as well as dyspnoea and leg fatigue measured on test completion. The 6MWD of the healthy controls ranged from 493 to 730m. The 6MWD of participants in the NSCLC group ranged from 335 to 635m.

4.2 Isometric quadriceps torque and isometric handgrip force

Only 12 of 23 (52%) participants in the NSCLC group and 14 of 20 (70%) healthy controls attended Curtin University to undergo the measurement of isometric quadriceps torque (Table 2). No between-group difference was demonstrated in isometric quadriceps torque (Table 2).

The isometric handgrip force of the healthy controls ranged from 20 to 57kg. The isometric handgrip force of participants in the NSCLC group ranged from 18 to 45kg.

4.3 Health-related quality of life and feelings of anxiety and depression

The SF-36 demonstated that the mean difference (MD) [95% confidence interval (CI)] between the groups was greater in the PCS (-11[-15 to -8]) than in the MCS (-6[-11 to -2]) (p=0.001) (Table 3).

Regarding the HADS, only one participant in the NSCLC group had a score >7 for anxiety and the same participant also had a score >7 for depression. Two healthy controls had a score >7 for anxiety, however feelings of depression were all within normal limits (i.e. ≤7).

4.4 Lung function

Comparisons of lung function variables between the two groups are presented in Table 1. Significant differences were observed in all lung function variables.

4.5 Relationships between exercise capacity and isometric quadriceps torque

Isometric quadriceps torque correlated with both Wmax and VO_{2peak} achieved during the CPET (r=0.84 and 0.81; respectively; p=0.001 for both). No correlation was found between isometric quadriceps torque and 6MWD (r=0.29; p=0.36).

4.6 Subgroup analyses of people with COPD *versus* without COPD

Of the 12 participants diagnosed with COPD, seven (58%) were females and five (42%) were males. Four (33%) had mild airway obstruction (i.e. GOLD stage 1), seven (58%) had moderate airway obstruction (i.e. GOLD stage 2) and one (9%) had severe airway obstruction (i.e. GOLD stage 3) following curative intent treatment for NSCLC. People with COPD had lower FEV_1/FVC. No differences were found in any other outcome measures between the subgroup of people with COPD and the subgroup of people not diagnosed with COPD (Table A2).

4.7 Subgroup analyses of video assisted thoracoscopic surgery (VATS) *versus* open thoracotomy

Of the 23 participants in the NSCLC group, 12 (52%) underwent VATS and 11 (48%) underwent open thoracotomy. No differences were found in any outcome between those who underwent VATS and those who underwent open thoracotomy (Table A3).

Table A2: Subgroup analyses comparing people with COPD versus without COPD

Variable	**COPD (n=12)** *mean ± SD*	**Non-COPD (n=11)** *mean ± SD*	***p value***
FEV_1 (L)	1.63 ± 0.51	1.68 ± 0.50	0.21
FEV_1 (%pred)	62 ± 16	70 ± 16	0.16
FEV_1/FVC (%)	56 ± 11	70 ± 8	0.03
VO_{2peak} ($L \cdot min^{-1}$)	15 ± 3	15 ± 3	0.82
6MWD (m)	501 ± 92	506 ± 47	0.53
Isometric hangrip force (kg)	28 ± 6	29 ± 8	0.45
Isometric quadriceps torque (Nm)	125 ± 67	131 ± 67	0.23
PCS	45 ± 6	45 ± 4	0.76
MCS	50 ± 7	52 ± 8	0.42
HADS anxiety	4 ± 2	4 ± 3	0.89
HADS depression	3 ± 2	3 ± 3	0.74

Abbreviations: 6MWD – Six-minute walk distance; COPD – Chronic obstructive pulmonary disease; FEV_1 – Forced expiratory volume in one second; FVC – Force vital capacity; MCS – Mental component score of the Medical outcomes study Short-Form 36 general health survey (SF-36); PCS – Physical component score of the SF-36; SD – Standard deviation; VO_{2peak} – Peak rate of oxygen consumption.

Table A3: Subgroup analyses comparing people who underwent VATS versus open thoracotomy

Variable	**VATS (n=12)** *mean ± SD*	**Open thoracotomy (n=11)** *mean ± SD*	***p value***
FEV_1 (L)	1.68 ± 0.50	1.64 ± 0.39	0.25
FEV_1 (%pred)	68 ± 16	67 ± 18	0.54
FEV_1/FVC (%)	64 ± 11	63 ± 14	0.39
VO_{2peak} ($L \cdot min^{-1}$)	15 ± 3	14 ± 3	0.23
6MWD (m)	515 ± 72	480 ± 78	0.10
Isometric hangrip force (kg)	30 ± 6	27 ± 8	0.36
Isometric quadriceps torque (Nm)	133 ± 71	124 ± 64	0.28
PCS	45 ± 6	44 ± 5	0.66
MCS	52 ± 7	50 ± 9	0.31
HADS anxiety	5 ± 3	4 ± 2	0.58
HADS depression	3 ± 3	3 ± 2	0.72

Abbreviations: 6MWD – Six-minute walk distance; FEV_1 – Forced expiratory volume in one second; FVC – Forced vital capacity; MCS – Mental component score of the Medical outcomes study Short-Form 36 general health survey (SF-36); PCS – Physical component score of the SF-36; SD – Standard deviation; VO_{2peak} – Peak rate of oxygen consumption; VATS – Video-assisted thoracoscopic surgery.

4.8 Subgroup analyses of people who attended the isometric quadriceps strength assessment

Subgroup analyses comparing those who attended (12 participants) with those who did not attend (9 participants) the isometric quadriceps muscle torque assessment have been undertaken (Table A4). However no between-group differences in VO_{2peak}, Wmax, 6MWD, isometric handgrip force, PCS, MCS or FEV_1 ($p>0.05$ for all) were found.

Table A4: Subgroup analyses comparing those who attended with those who did not attend the isometric quadriceps muscle torque assesment

Variable	**Attended quadriceps assessment (n=12)** *mean ± SD*	**Did not attend quadriceps assessment (n=9)** *mean ± SD*	***p value***
FEV_1 (L)	1.65 ± 0.54	1.69 ± 0.37	0.86
FEV_1 (%pred)	66 ± 18	69 ± 15	0.35
FEV_1/FVC (%)	63 ± 13	66 ± 15	0.49
VO_{2peak} ($L \cdot min^{-1}$)	15 ± 3	16 ± 2	0.52
Wmax (W)	79 ± 24	70 ± 26	0.40
6MWD (m)	503 ± 73	480 ± 80	0.20
Isometric hangrip force (kg)	27 ± 6	29 ± 7	0.36
PCS	45 ± 6	44 ± 5	0.72
MCS	51 ± 8	51 ± 7	0.88
HADS anxiety	3 ± 3	4 ± 3	0.33
HADS depression	3 ± 2	3 ± 3	0.89

Abbreviations: 6MWD – Six-minute walk distance; FEV_1 – Forced expiratory volume in one second; FVC – Forced vital capacity; MCS – Mental component score of the Medical outcomes study Short-Form 36 general health survey (SF-36); PCS – Physical component score of the SF-36; SD – Standard deviation; VO_{2peak} – Peak rate of oxygen consumption; Wmax – Maximum work rate.

4. Discussion

No correlation was demonstrated between 6MWD and isometric quadriceps torque. Further, data presented in the manuscript demonstrated that on completion of the 6MWT the average BORG score for leg fatigue of people in the NSCLC group was only 2±2 (Table 2). Therefore, it seems that quadriceps muscle force does not seem to play an important role in the reduction in 6MWD in people following lung resection for early stage NSCLC. Regarding maximal exercise capacity, isometric quadriceps torque correlated with both Wmax and VO_{2peak} achieved during the CPET. These correlations are expected as, in contrast to walking, the quadriceps muscle is the main muscle group recruited during cycling. However, data reported in Table 2 shows that on completion of the CPET, compared with the healthy controls, those in the NSCLC group reported greater dyspnoea and had less ventilatory reserve (VEmax/MVV) and lower stroke volume (O_2 pulse). Therefore, it seems that the impairment in exercise capacity in people following lung resection for early stage NSCLC may also result from cardiopulmonary / central factors rather than simply peripheral muscle issues.

Caution is needed when interpreting the results of the subgroup comparisons due to the small sample size and therefore risk of type II error.

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