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Master of Philosophy Thesis

Prehabilitation for individuals having lung cancer surgery

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Abstract

Non-small cell lung cancer (NSCLC) is the fourth most commonly diagnosed cancer in males and the fourth most commonly diagnosed cancer in females in Australia. It is the leading cause of cancer-related mortality, being responsible for more deaths than breast, colorectal and prostate cancer combined. Pulmonary resection provides the best chance of a cure for patients with early stage lung cancer. However, pulmonary resection is associated with significant impairment in functional capacity along with a moderate risk of postoperative morbidity, particularly in frail or deconditioned patients.

Prehabilitation is defined as *“a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment that, in the perioperative setting, aims to enhance functional capacity of the individuals to enable them to withstand the stress associated with a procedure”* (Julie K. Silver & Baima, 2013). Prehabilitation can include a care bundle incorporating smoking cessation, diet optimization, psychosocial support and exercise, and aims to identify impairments and deliver targeted interventions that improve patient outcomes. It provides an opportunity to decrease treatment-related morbidity, increase available treatment options for patients who would not otherwise be surgical candidates and facilitate return of patients to the highest possible functional level. There is a growing body of evidence that supports prehabilitation as a means of preparing patients with newly diagnosed cancer for surgery by optimizing their health preoperatively. Enhancing a patient’s preoperative condition may help them withstand the stressors of surgery. Evidence supports the implementation of prehabilitation in the preoperative care pathway of other cancer cohorts, for example colorectal, breast and prostate cancers. Unfortunately, the evidence for the effects of prehabilitation in lung cancer has lagged behind and the use of prehabilitation (specifically the exercise component) for patients with lung cancer is now an emerging area. To date, exercise prior to lung cancer surgery has been shown to be safe and associated with improvements in functional capacity as well as postoperative morbidity (hospital length of stay) and rates of postoperative

pulmonary complications), however the feasibility and acceptability of prehabilitation for patients with lung cancer is still unclear.

The two studies within this thesis focus on the exercise component of prehabilitation in the context of surgical management of lung cancer in Australia.

Study 1, a pilot randomized controlled trial (RCT), primarily examined the feasibility of a prehabilitation program for individuals with early stage NSCLC. The primary aims of this trial were to investigate the feasibility and safety of a pre-surgical exercise intervention (prehabilitation) for individuals with stage I-IIIa NSCLC. The primary hypotheses were that prehabilitation would be deemed to be feasible and safe in this population (determined as >50% of eligible participants consenting to participate;; >70% of participants randomized to the intervention group completing the prehabilitation program;; and no serious adverse events). Patients were eligible if they were: adults aged ≥ 18 years, who had suspected stage I-IIIa NSCLC presenting for surgical consult, and primary treating surgeon approval for enrolment into the trial. Twenty-four participants were recruited (13 in the control group and 11 in the intervention group). Participants were aged between 52-83 years old and underwent their surgical treatment in both the public and private settings. Participants in both groups were similar in terms of extent of respiratory disease and comorbidities. Intervention group participants underwent 1-4 weeks of personalized exercise training prior to surgery, which consisted of aerobic and resistance exercise 3-5 times per week. Each program was individualized to the participant and included a mix of both hospital-based supervised sessions (ideally 2 times per week) and home-based unsupervised exercise (ideally 3 times per week). The control group received usual care which did not involve preoperative exercise or physiotherapy. The primary outcome of feasibility was measured via consent rate, adherence to the program, ability to deliver the program within the pre-surgery timeframe, patient satisfaction and safety (absence of adverse events). Secondary outcomes focused on patient related outcomes (HRQoL, anxiety/depression and self-reported physical activity levels) as well as measures of change in physical activity parameters (walking exercise capacity and strength).

The completed follow-up testing consent rate for this study was 75% and adherence within the intervention group was high with 82% of participants completing their prescribed prehabilitation program. Follow-up of participants was challenging throughout the trial, 71% of participants completed follow-up testing at T1 (pre-op), while only 58% completed follow-up testing at T2 (30-days post-surgery). Results demonstrated that prehabilitation in lung cancer is safe, partly acceptable to patients, and that the exercise program was feasible for some participants to undertake before surgery. However, our results also showed that participant attrition throughout the trial, both before and after surgery, was high. This suggests that a future scaled-up version of this pilot trial (as an adequately powered RCT) is not appropriate in its current form. Instead further research is required to explore why participants are withdrawing/dropping out to be able to effectively address this before conducting an RCT. Additionally research is required to explore the ideal target population who would benefit from prehabilitation. It may be that future trials should focus on the high-risk surgical patients who may not have surgery unless they are fitter. No adverse events occurred, and this concurs with previous trials which have concluded that preoperative exercise intervention is safe within the lung cancer population.

Study 2 consisted of an online survey examining the perceptions and attitudes of cardiothoracic surgeons in Australia and New Zealand to prehabilitation in lung cancer. As surgeons are often seen as the gatekeepers to prehabilitation referral, it is important to understand their beliefs about prehabilitation in order to determine how prehabilitation could be implemented, promoted and utilized in the lung cancer model of care. This study consisted of an online survey of 24 questions administered via SurveyMonkey. An email invitation was sent to the 198 cardiothoracic fellows registered with the Royal Australasian College of Surgeons. The initial email invitation was followed by a subsequent email invitation as well as promotion of the survey in college newsletter material in an effort to increase the response rate. Paper versions of the survey were also distributed at the annual scientific meeting of the Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS). Despite this, the response rate for the survey was 14% (n = 28). This is in line with

other studies conducted involving medical professionals, specifically surgeons, who cite limited time and/or resources as reasons for not responding to research survey requests. Results from the survey demonstrated a clear interest in prehabilitation amongst cardiothoracic surgeons, with 91% of surgeons willing to delay surgery to allow sufficient time for prehabilitation. The main reasons for preoperative referral were; borderline fitness for surgery, standard practice in the unit and high-risk patients. Many of the sample were able to identify more than one benefit of prehabilitation for their patients. In terms of referral to preoperative physiotherapy, only 32% of the sample reported that they do refer their thoracic surgery patients preoperatively and only 17% of surgeons reported that preoperative exercise intervention delivered by Allied health professionals is readily available. This study adds to the current knowledge in lung cancer prehabilitation by uncovering the perceived acceptability of prehabilitation and referral practices amongst surgeons working within the lung cancer population.

The findings from the studies included within this thesis demonstrate that prehabilitation in lung cancer is safe, potentially feasible (albeit with changes required to the current format) and perceived to be of benefit by both patients and thoracic surgeons. However, in order to recommend prehabilitation for patients with lung cancer further research in this area is warranted prior to wide-spread implementation. Research is required to determine the optimal preoperative exercise program, in terms of mode of exercise, timing and duration of programs. Additionally, the most suitable patient sub-type for prehabilitation in lung cancer needs to be determined, as our findings show that although many patients consented there was a large dropout rate once enrolled in the program. For example, if surgery was dependent upon improving fitness for patients it would be reasonable to assume the dropout rate may be lower. Future larger randomized trials are then required to assess efficacy, preferably multicentre, before implementation of this service more generally could be scaled up to improve outcomes in this vulnerable population.

To conclude, the work in this thesis adds to the knowledge that we currently have regarding the role of exercise for individuals after a cancer diagnosis. The overall results from the included studies highlight a keen interest in lung cancer prehabilitation both from patients as well as surgeons, indicating that more work needs to occur in order for this important intervention to become part of the standard preoperative care for patients with lung cancer.

Declaration

This is to certify that;

- i. this thesis comprises only my original work and has not been published elsewhere (except as indicated in the preface) or submitted for the award of another degree
- ii. due acknowledgement has been made in the text to all other materials used,
- iii. the thesis is less than 50,000 words in length, inclusive of footnotes but exclusive of tables, references and appendices

A Shukla
2020

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Dissemination of Research Findings

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Glossary and Abbreviations

6MWT	Six minute walk test
ACSM	American College of Sports Medicine
ACTRN	Australian Clinical Trials Registration Network
AIHW	Australian Institute of Health and Welfare
ALK	Anaplastic Lymphoma Kinase
ANZSCTS	Australian and New Zealand Society of Cardiothoracic Surgery
ARDS	Acute Respiratory Distress Syndrome
AT	Anaerobic Threshold
BMI	Body Mass Index
CCV	Cancer Council Victoria
CI	Confidence Interval
CO₂	Carbon Dioxide
COPD	Chronic obstructive pulmonary disease
CPET	Cardiopulmonary Exercise Test
CT	Computed tomography
CXR	Chest x-ray
DLCO	Diffusing capacity for carbon monoxide
DNA	Deoxyribonucleic Acid
Dx	Diagnosis
EBUS	Endobronchial ultrasound
ECG	Electrocardiogram
ECHO	Echocardiography
EGFR	Epidermal Growth Factor Receptor
EORTC-QLQ	European Organisation for the research and treatment of cancer – Quality of life questionnaire
ERAS	Enhanced recovery after surgery
ESWT	Endurance shuttle walk test
FACT-L	Functional Assessment of Cancer Therapy - Lung
FEV1	Forced expiratory volume in one second
FiO₂	Fraction of Inspired Oxygen

FNA	Fine Needle Aspirate
FT	Full Time
FVC	Forced vital capacity
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HIIT	High Intensity Interval Training
HRQoL	Health related quality of life
IMT	Inspiratory Muscle Training
IPAQ	International Physical Activity Questionnaire
IQR	Interquartile Range
ISWT	Incremental shuttle walk test
Kg	Kilogram
K-RAS	Kirsten Rat Sarcoma gene
LBS	Pounds
LDCT	Low Dose Computed Tomography
LOS	Length of stay
MD	Mean Difference
MDM	Multidisciplinary meeting
METS	Metabolic Equivalents
MRI	Magnetic resonance imaging
Mx	Management
NGS	Next Generation sequencing
NHMRC	National Health & Medical Research Council
NICE	National Institute for Clinical Excellence
NSCLC	Non-small cell lung cancer
PA	Physical activity
PEF	Peak Expiratory Flow
PET scan	Positron emission tomography scan
PFT	Pulmonary Function Test
PO	Post-Operative
POY	Post-Operative Year
PPC	Postoperative pulmonary complication

PPO	Predicted Postoperative
PPV	Positive Predictive Value
pt	Patient
PT	Part Time
QoL	Quality of Life
RCT	Randomized Controlled Trial
RIB	Resting in Bed
RPE	Rate of Perceived Exertion
RR	Risk Ratio
SCLC	Small Cell Lung Cancer
SD	Standard deviation
SF-36	Short Form-36
SMD	Standardized Mean Difference
SOB	Shortness of Breath
SpO₂	Saturation of Oxygen
Sx	Surgery
TNM	Tumour Node Metastases
TSANZ	Thoracic Society of Australia and New Zealand
UK	United Kingdom
VATS	Video Assisted Thorascopic Surgery
VO₂Max	Maximal oxygen consumption
W_{Max}	Work Rate Maximum

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CHAPTER 1 INTRODUCTION

1.1 STATEMENT OF THE PROBLEM

Non-small cell lung cancer (NSCLC) is the fifth most common cancer in Australians and the leading cause of cancer-related mortality accounting for nearly 18% of all cancer deaths (AIHW, 2019). Globally, lung cancer accounts for approximately 13% of total cancer diagnoses (Torre et al., 2015). Patients with lung cancer experience a range of symptoms including: fatigue, breathlessness, cough, pain, psychological distress and depression (Iyer, Roughley, Rider, & Taylor-Stokes, 2014; Walker et al., 2017). These symptoms can occur as complex clusters and contribute to significant burden for the patient.

The high symptom burden in lung cancer frequently leads to a vicious cycle of inactivity and functional decline. An observational study by Granger et al highlights the extent of this problem in Australia: Sixty percent of patients with NSCLC did not meet the recommended physical activity guidelines at time of diagnosis (prior to treatment) (Granger, 2013). Additionally, patients had reduced functional exercise capacity, muscle strength and greater levels of depression at the time of diagnosis compared to healthy aged-matched peers. Low physical activity levels are often compounded by poor respiratory reserve which can significantly limit the options available for cancer treatment and can render patients with early stage lung cancer inoperable. This is not desirable, as pulmonary resection of the tumour offers the best chance of survival for patients with early stage lung cancer. Poor fitness prior to surgery also increases the likelihood of longer postoperative hospital stay, higher incidence of surgical complications and increased morbidity (Brunelli, Belardinelli, et al., 2009; Ismail et al., 2018; D. Z. Levett, Edwards, Grocott, & Mythen, 2016; Licker et al., 2011). Improving physical activity levels and enhancing functional exercise capacity prior to lung cancer surgery may have beneficial effects on the complex symptom burden experienced by these patients, as well as optimise this cohort to withstand the demands of cancer treatment and reduce post-treatment morbidity and mortality (L. W. Jones et al., 2012; L. W. Jones et al., 2007; Myers, 2016).

In the general cancer population, numerous high quality randomized controlled trials (RCTs) exist demonstrating the positive effects of exercise across the continuum of cancer treatment in different tumour streams. The benefits of exercise include, but are not limited to, improvements in functional exercise capacity, fatigue, health-related quality of life (HRQoL), mood and dyspnoea (Ben-Aharon, Gafer-Gvili, Leibovici, & Stemmer, 2012; Chen, Tsai, Wu, Lin, & Lin, 2015; Mishra, 2012; Mustian et al., 2017; Quist et al., 2015; Speck, Courneya, Masse, Duval, & Schmitz, 2010). Specifically, in lung cancer, exercise prior to lung resection surgery can increase functional exercise capacity and pulmonary function (A. Bradley et al., 2013), and reduce postoperative morbidity (Rosero et al., 2019). A Cochrane review of preoperative exercise in lung cancer, including four RCTs, demonstrated that patients who exercise prior to lung cancer surgery have a 67% reduced risk of developing a postoperative pulmonary complication (PPC). However this Cochrane review found the quality of the evidence to be 'low' and that trials were of a small sample size (Cavalheri & Granger, 2017). Additionally, none of these trials were conducted in Australia and the feasibility of delivering prehabilitation in our local setting is unknown.

Optimal care pathways, such as those published by Cancer Council Victoria in Australia (Cancer Council Victoria, 2014), provide clinicians with cancer pathway guidelines for various cancer streams. Within the lung cancer pathway, it is recommended that multidisciplinary teams be involved in the preoperative work-up and postoperative follow-up of the patient via lung cancer specific multidisciplinary meetings (MDM's). Despite growing evidence about the benefits of exercise for those diagnosed with lung cancer, exercise is not routinely embedded into these pathways nor services accessible for patients with lung cancer. There is currently no standard pathway or model of care for exercise intervention in patients with lung cancer prior to undergoing lung resection surgery in Australia. Research investigating the feasibility and acceptability of prehabilitation for patients with lung cancer in Australia would help address this issue and take steps towards implementing exercise into the model of care.

Prehabilitation may be delivered in a multimodal format, however the focus of prehabilitation research in the context of lung cancer has almost exclusively been on the exercise component of prehabilitation. This is also the case within this thesis, where the term 'prehabilitation' will refer to preoperative exercise.

1.2 SIGNIFICANCE OF THE RESEARCH

Evidence supporting the feasibility of prehabilitation in lung cancer is still emerging. Although prehabilitation has proven to be safe and feasible in other cancer cohorts (Faithfull et al., 2019; Treanor, Kyaw, & Donnelly, 2018), the complex and unique symptom cluster (dyspnoea, fatigue, pain) specific to lung cancer as well as the limited time available for preoperative intervention prior to lung cancer surgery makes this a challenging intervention to implement into current clinical practice. Since 2011, one Cochrane Review (Cavalheri & Granger 2017) and fourteen reviews (refer to chapter 4 for a summary of narrative/systematic reviews) have already been published within the topic area of exercise and lung cancer, therefore another systematic review on this topic is currently not required. The most recent evidence, including the Cochrane Review published by Cavalheri and Granger in 2017 and two systematic reviews (Driessen et al., 2017; Rosero et al., 2019), have addressed some aspects of feasibility but have not examined feasibility exclusively. Future research should instead focus on the feasibility of prehabilitation for patients undergoing lung resection surgery, to understand how we can implement this intervention into clinical practice. This is the key focus of the studies within this thesis.

In order to deliver effective prehabilitation programs in lung cancer, support and early referral from the multi-disciplinary team, most notably thoracic surgeons, is essential. A previous survey of lung cancer multidisciplinary team members in the United Kingdom (UK) examining referral patterns and barriers to pre and post-treatment exercise for lung cancer patients, provides a starting point to help us learn the best means of improving referral pathways. In this study it was identified that rehabilitation needs of lung cancer patients were inadequately recognised and managed, in fact only 39% of responders considered rehabilitation services adequate (Nwosu, Bayly, Gaunt, & Mayland, 2012). This study concluded that there

are two main factors that prevent patients with lung cancer from being offered rehabilitation: these include long waiting times and lack of knowledge of services by health professionals (Nwosu et al., 2012). As no current literature exists examining the attitudes and perceptions of Thoracic surgeons to prehabilitation in lung cancer, the survey within Study 2 of this thesis allows us to further understand the barriers to prehabilitation referral, determine current referral practices, and provide insight into the views of these important referrers to and advocates for prehabilitation in Australia.

The studies within this thesis, consisting of a pilot RCT and survey, further contribute to both our understanding of 1) the feasibility of prehabilitation in this complex cancer population in Australia, specifically whether the method of prehabilitation implemented within the pilot RCT is feasible and acceptable for patients with lung cancer undergoing lung resection surgery; and 2) barriers to prehabilitation from a medical/treating surgeon point of view. These research studies provide important information relating to the next steps in understanding prehabilitation in lung cancer clinical practice in Australia.

1.3 RESEARCH AIMS OF THESIS

The specific aims and hypothesis of the studies are noted below.

1.3.1 Study 1: “Prehabilitation for individuals having lung cancer surgery: a pilot RCT”

The primary aims of this trial were to investigate the feasibility and safety of a pre-surgical exercise intervention (prehabilitation) for individuals with stage I-IIIa NSCLC. The primary hypotheses were that prehabilitation would be deemed to be feasible and safe in this population (determined as >50% of eligible participants consenting to participate: >70% of participants randomized to the intervention group completing the prehabilitation program and no serious adverse events).

The secondary aims were to descriptively explore the benefit of prehabilitation on exercise capacity, physical activity levels, muscle strength, HRQoL, anxiety and

depression compared to a control of standard care and to explore the views and experiences of participants in both the prehabilitation and usual care group with regards to preoperative care and prehabilitation.

1.3.2 Study 2: “Attitudes and perceptions to prehabilitation”: an online survey

The primary aim of this study was to gain insight into the perceptions and attitudes of Thoracic surgeons throughout Australia and New Zealand on the area of prehabilitation.

The specific aims of this study were:

- 1) To explore the acceptability of prehabilitation before lung cancer resection amongst Thoracic surgeons
- 2) To explore the perceived benefit of prehabilitation amongst Thoracic surgeons
- 3) To understand the thoracic surgeon’s view on the optimal timing of preoperative interventions

The primary hypotheses were that the survey response rate from thoracic surgeons would be between 20-30%. Thoracic surgeons within Australia and New Zealand would have mixed responses in their attitudes and perceptions to prehabilitation and this would depend on a number of factors such as: place of training, years of experience, work in a dedicated thoracic unit vs mixed cardiothoracic unit and access to and knowledge/interest of prehabilitation.

1.4 THESIS OVERVIEW

An overview of the chapters within this thesis is presented in Table 1.1.

The next chapter within this thesis, Chapter 2, provides information on lung cancer in Australia, which is the patient population of investigation within the studies of this thesis.

Table 1.1: Thesis overview

Chapter 1	Introduction to the thesis
Chapter 2	This background chapter provides information on lung cancer in Australia. It focuses on the risk factors for developing lung cancer along with the classification, diagnosis, staging and medical treatment of NSCLC. The chapter ends with information on survival.
Chapter 3	This background chapter explores the surgical management of lung cancer. It begins with the indications for surgery and assessment of fitness for surgery and then details the types of surgical access and pulmonary resection. The main focus is on VATS surgery as this was the primary technique used for surgical access in the NSCLC patients within the studies of this thesis. The chapter finishes with common surgical complications along with recovery and postoperative physiotherapy.
Chapter 4	This background chapter introduces the concept of prehabilitation in the surgical oncology population. This chapter outlines the components of prehabilitation with a particular emphasis on exercise as this was the intervention utilized in the studies within this thesis. From analysis of research previously completed in this area, gaps in the literature have been identified – particularly within the lung cancer population. The chapter finishes by highlighting the need for further high-quality research into prehabilitation in the lung cancer population and how the studies included in this thesis will contribute to this expanding evidence base.
Chapter 5	This chapter reports on Study 1, a pilot RCT, investigating the feasibility and safety of a pre-surgical exercise intervention (prehabilitation) for individuals with stage I-IIIa NSCLC.
Chapter 6	This chapter reports on Study 2, an online survey, which provides insight into the attitudes and perceptions of Thoracic surgeons within Australia and New Zealand to exercise prehabilitation within the lung cancer population.
Chapter 7	This conclusion chapter provides a detailed summary and conclusion of the main findings of the thesis and discusses future directions of research for the field of exercise and lung cancer.

CHAPTER 2 LUNG CANCER IN AUSTRALIA

2.1 INTRODUCTION

This chapter provides an introduction to lung cancer in Australia. The chapter will provide a summary of the incidence and burden of lung cancer in Australia. The risk factors, early symptoms, diagnostic process and classification will then be outlined, followed by a description of the current staging classification. The chapter will finish by describing the medical treatment options for patients with lung cancer. Information within the chapter relates to lung cancer generally, however specific focus on the non-small cell classification is given in certain sections of the chapter as this is the type of lung cancer which is the focus of the studies within this thesis.

2.2 BURDEN OF LUNG CANCER

Globally, lung cancer remains the most commonly diagnosed cancer and is the leading cause of cancer death worldwide, responsible for nearly one cancer death in five (Ferlay et al., 2015). In Australia, lung cancer is the leading cause of cancer death representing 18.9% of all cancer deaths (AIHW, 2019). The incidence of lung cancer increases with age (figure 2.1). In 2018, it was estimated that 12,741 new cases of lung cancer would be diagnosed, 7,212 males and 5529 females, this accounts for 9.2% of all new cancer cases diagnosed (Cancer Australia, 2019). The 5-year survival for lung cancer is currently 17% (AIHW, 2019), figure 2.2 shows the relative 5-year survival of lung cancer by stage at diagnosis and highlights the importance of early detection to improve survival.

Some of the main factors impacting on the low improvements seen in survival rates in lung cancer have been identified as: delays to diagnosis, diagnosis occurring in late stages of disease and lack of access to multi-disciplinary teams and appropriate treatment. National strategies to address these issues are currently underway and aim to improve cancer outcomes in Australia (Cancer Australia, 2014a).

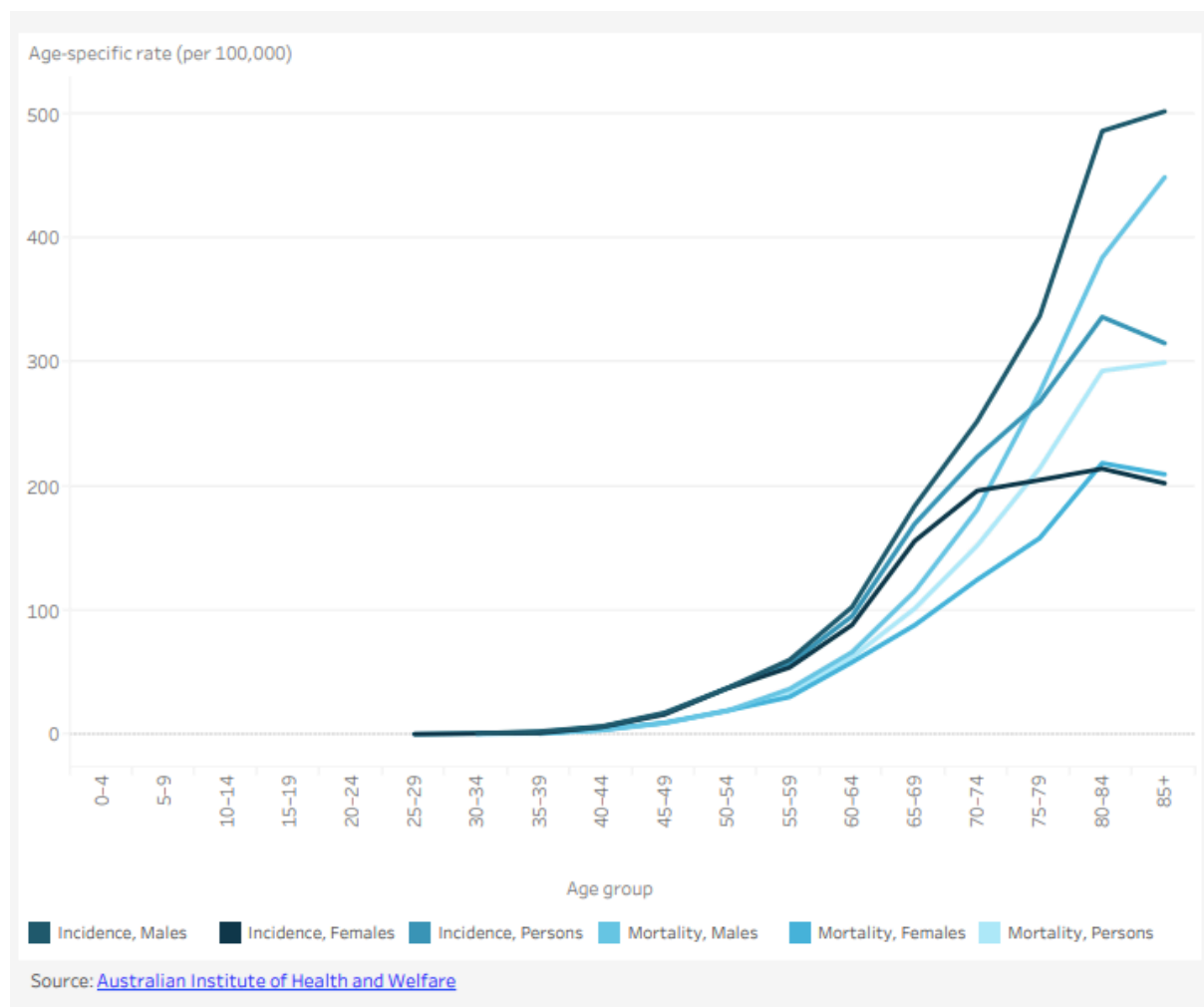
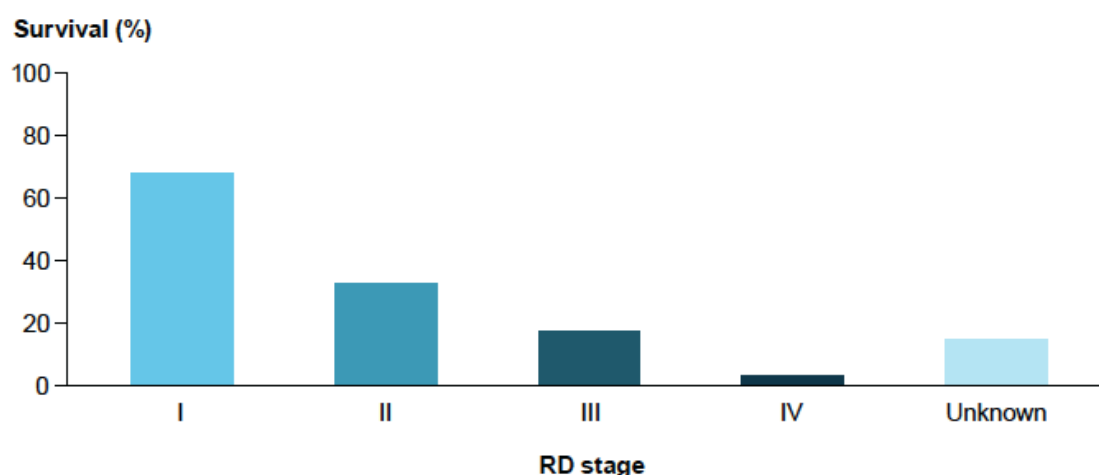


Figure 2.1: Estimated age-specific incidence and mortality rates for lung cancer in Australia, by sex, 2018

(AIHW, 2011)



Note: Data for this figure are in online Table S3.1.

Source: AIHW ACD 2014.

Figure 2.2: Relative 5-year survival for lung cancer by stage at diagnosis in Australia

(AIHW, Cancer in Australia 2019)

FOOTNOTE: Registry-derived stage (RD Stage) – this data is used to report cancer stage at diagnosis. The higher the number, the further the cancer has spread. In lung cancer stage at diagnosis was unable to be derived in nearly a quarter of cases (unknown).

2.3 RISK FACTORS FOR LUNG CANCER

Tobacco smoking is the predominant risk factor for developing lung cancer. Approximately 75-90% of lung cancer cases can be attributed to active tobacco smoking (Brenner, Yannitsos, Farris, Johansson, & Friedenreich, 2016). The highest risk remains with tobacco smoking, however pipe and cigar smoking are comparable to light cigarette smoking (Molina, 2008).

The risk of developing lung cancer in non-smokers or passive smokers is also significant. Passive smokers have a relative risk for developing lung cancer which is 20-30% higher than that of non-smokers/non-passive smokers (Hunt, 2009). Passive smoking during childhood increases the risk in adulthood of developing lung cancer 3.6-fold (Molina, 2008). Unintentional workplace exposure to silica dust, asbestos fiber and cooking oils heightens the risk of developing lung cancer. There is also an increasing incidence of lung cancer amongst lifelong non-smokers, accounting for about 10% of all cases (Hunt, 2009),

a family history of cancer also increases the risk. Genetic mutations may also contribute to the development of lung cancer in non-smokers, this is particularly prevalent in women, individuals from Asian or Hispanic backgrounds (Wakelee, 2016).

Individuals with chronic obstructive pulmonary disease (COPD) are also at increased risk of developing lung cancer, the direct causative factors remain unknown. The Table 2.1 below outlines other risk factors associated with developing lung cancer.

Table 2.1: Lung Cancer risk factors

(Cancer Australia, 2014b)

Factor	Relative Risk (RR)
TOBACCO SMOKING	
Active smoking	9.0
Passive smoking	1.2 – 2.0
ENVIRONMENTAL / OCCUPATIONAL EXPOSURE	
Radon	1.6 – 3.8
Polycyclic hydrocarbons	1.2 – 2.0
Cadmium	2.1
Asbestos	1.3 – 2.0
Silica	1.2 – 1.3
Iron + Steel founding	1.3 – 1.4
Nickel	1.6
Beryllium	1.0 – 1.5
Painting	1.3
Chromium	1.2
Air pollution	1.2
FAMILY HISTORY	2.0

A systematic review and meta-analysis conducted by Brenner in 2016 also identified physical inactivity as a contributor to lung cancer risk. Previous systematic reviews had demonstrated an association between physical activity and reduced lung cancer risk, indicating that higher levels of physical activity were protective against the development of lung cancer, however this review further evaluated the impact of smoking status and histological subtype on this association. The results indicate that there is an inverse

association between recreational physical activity and lung cancer risk – relative risk (RR) 0.76 (95% confidence interval (CI) 0.69 – 0.85, $p = < 0.001$) with this association noted for all histological subtypes: adenocarcinoma (RR 0.80, 95% CI 0.72-0.88), squamous (RR 0.80, 95% CI 0.71-0.90) and small cell (RR 0.79, 95% CI 0.66-0.94). Examining the effect of smoking status, there were no associations between recreational physical activity and lung cancer risk in never smokers (RR 0.96, 95% CI 0.79-1.18), however inverse associations between recreational physical activity and lung cancer risk were observed in former smokers (RR 0.77, 95% CI 0.69 – 0.85) and current smokers (RR 0.77, 95% CI 0.72 – 0.83) (Brenner et al., 2016). This means that current or former smokers who have higher levels of physical activity have a reduced risk of developing lung cancer compared with those who are inactive.

2.4 DIAGNOSIS

Increased awareness of lung cancer risk factors, along with advances in screening and investigation, have contributed to earlier detection of lung cancers. The streamlining of lung cancer pathways via multi-disciplinary teams, which help to coordinate patient care, has also enhanced diagnosis. This has been aided by the development of evidence-based recommendations and international guidelines, such as the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) guidelines for the diagnosis and screening of lung cancer (NICE, 2019). The Cancer Council in Australia have also published clinical practice guidelines for the treatment of lung cancer specific to Australia and they are currently developing guidelines for the prevention and diagnosis of lung cancer as well (Cancer Council Australia, 2018).

In a USA-based national lung cancer screening trial examining the effect of low-dose CT (LDCT) screening for individuals at high-risk of developing lung cancer it was found that the use of regular LDCT contributed to a 20% relative reduction in lung cancer mortality and 6.7% reduction in all-cause mortality for screened participants (Aberle et al., 2013). Further to this, pooling of UK and European trial results has also demonstrated a 19% reduction in mortality with the use of LDCT (De Koning, Van Der Aalst, Ten Haaf, &

Oudkerk, 2018; Field, Hansell, Duffy, & Baldwin, 2013). Despite this evidence, there are currently no recommendations in Australia to support population-based lung cancer screening with CT scanning. The current evidence-based recommendation is that CT scans for the early detection of lung cancer in asymptomatic individuals should only be considered in those at high-risk of lung cancer who meet the minimum criteria: aged 55-74 with heavy smoking history (at least 30 pack years, current or former smokers who have quit within the prior 15 years) (Cancer Council Australia, 2018). These recommendations are based on the insufficient evidence base for routine CT scanning along with the potential problems of false-positive results, over-diagnosis and unnecessary invasive follow-up testing that occurs with non-selective screening.

Once a nodule or lesion is detected on imaging, pathologic diagnosis based on tissue biopsy remains the gold standard assessment procedure. Radiologic surveillance may be the preferred option for slow-growing or low-risk profile patients and may include chest x-ray or LDCT. LDCT has been shown to be superior to chest x-ray in terms of detection of positive lung cancer cases and has been shown to reduce the rate of death from any cause by 6.7% (95% CI 1.2 – 13.6, $p = 0.02$) (The.National.Lung.Screening.Trial.Research.Team, 2011).

Recently, there has been increasing interest in the use of DNA profiling and next-generation sequencing (NGS) for the screening of lung cancer. Circulating tumor DNA (cell-free DNA in an individual's blood) is a biomarker that can be used to facilitate early detection and localization of disease as well as the assessment of post-surgical minimal residual disease (Abbosh, Birkbak, & Swanton, 2018). As this is a relatively new area, no clear guidelines exist for the use of NGS or DNA profiling in NSCLC, further technical improvements and research is required to make definitive conclusions about the value of its use in lung cancer screening.

Patients often experience symptoms for an extended period before presenting for assessment, many patients with existing chronic airways disease dismiss a persistent cough as a natural symptom of their airways disease. At the time of diagnosis, up to 61%

of patients presenting with lung cancer already have locally advanced or metastatic disease (Walters et al., 2013). Lung cancer diagnosis is typically triaged through primary general practitioners who manage patients with suggestive symptoms and/or a significant smoking history. Cases are also discovered as incidental findings following investigations such as chest x-rays or scans, performed for example following trauma, where ground-glass opacities or pulmonary nodules are detected. Once a lesion is detected, further investigation is carried out to determine the extent of disease and how a tissue/biopsy sample may be safely obtained in order to guide targeted treatment. Figure 2.3 outlines the process of investigations for diagnosis of lung cancer. Investigations commonly carried out during the investigation/diagnosis phase of lung cancer are:

- Chest x-ray
- Blood tests and sputum cultures
- CT scan or MRI
- PET scan
- Bronchoscopy – for central tumors
- CT guided biopsy – for peripheral tumors
- Endobronchial ultrasound (EBUS) or navigational bronchoscopy
- Intra-operative frozen section – used when histology has failed to detect cancer but there is a high suspicion based on history and radiological evidence

Once investigation and workup has been completed, the individual will be referred to an oncologist, respiratory physician or thoracic surgeon. Current best practice in Australia (Cancer Council Australia, 2018) suggests that all cases should be discussed at a lung specific multi-disciplinary meeting (MDM) to ensure holistic and evidence-based care is delivered to the individual in a timely manner. These MDMs are a potential opportunity for screening and identification of patients who may benefit from prehabilitation, and this is discussed in further detail in subsequent chapters.

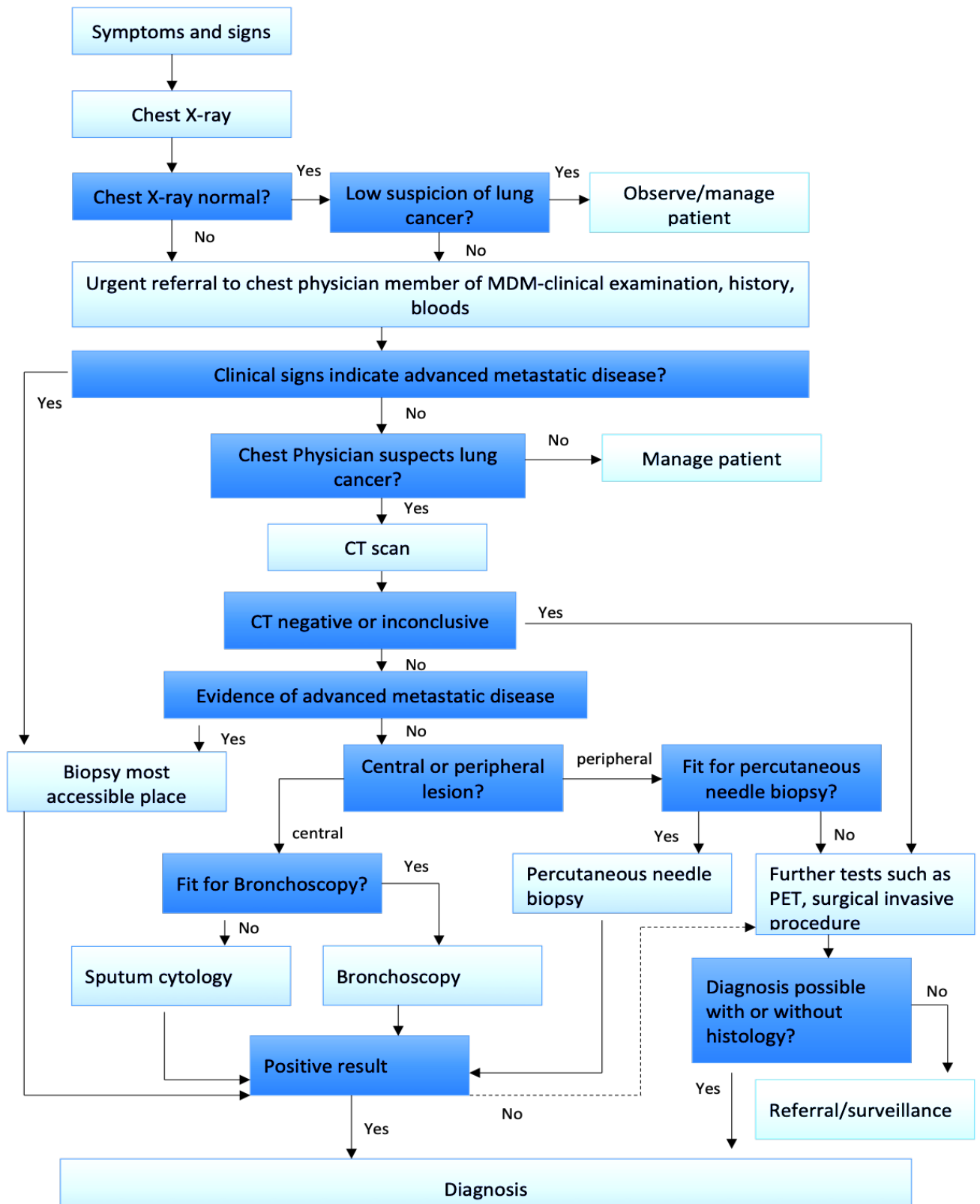


Figure 2.3: Diagnosis of Lung cancer

(Hunt, 2009)

2.5 CLASSIFICATION

Lung cancer can be classified histologically into small-cell and non-small cell types. Small-cell lung cancer (SCLC), accounts for 15% of all lung cancer diagnoses, grows rapidly and is associated with poorer prognosis when compared to non-small cell lung cancer (NSCLC). Non-small cell lung cancer comprises 85% of all lung cancer diagnoses, this thesis focuses on NSCLC as this was the patient population for prehabilitation within this research.

NSCLC can further be classified histologically into adenocarcinoma, squamous cell carcinoma and large cell carcinoma. Figure 2.4 provides a pictorial representation of the proportions of the different subtypes of NSCLC. In more recent years, oncogenic driver mutations for each of these subgroups have been identified. These mutations present as protein kinases or mutations in receptors, the result of these mutations is upregulation of signaling pathways which lead to uncontrolled tumor growth, proliferation and survival (Chan & Hughes, 2015). The main mutations which have been identified within NSCLC adenocarcinoma include the Epidermal growth factor receptor (EGFR) mutation, Kirsten rat sarcoma 2 viral oncogene homolog (K-RAS) and Anaplastic lymphoma kinase (ALK) gene rearrangement. Identification of driver mutations for NSCLC squamous cell carcinoma is the focus of many current studies. Detection of these biomarkers is aimed at ensuring delivery of personalized and targeted cancer treatment as well as better prognostication.

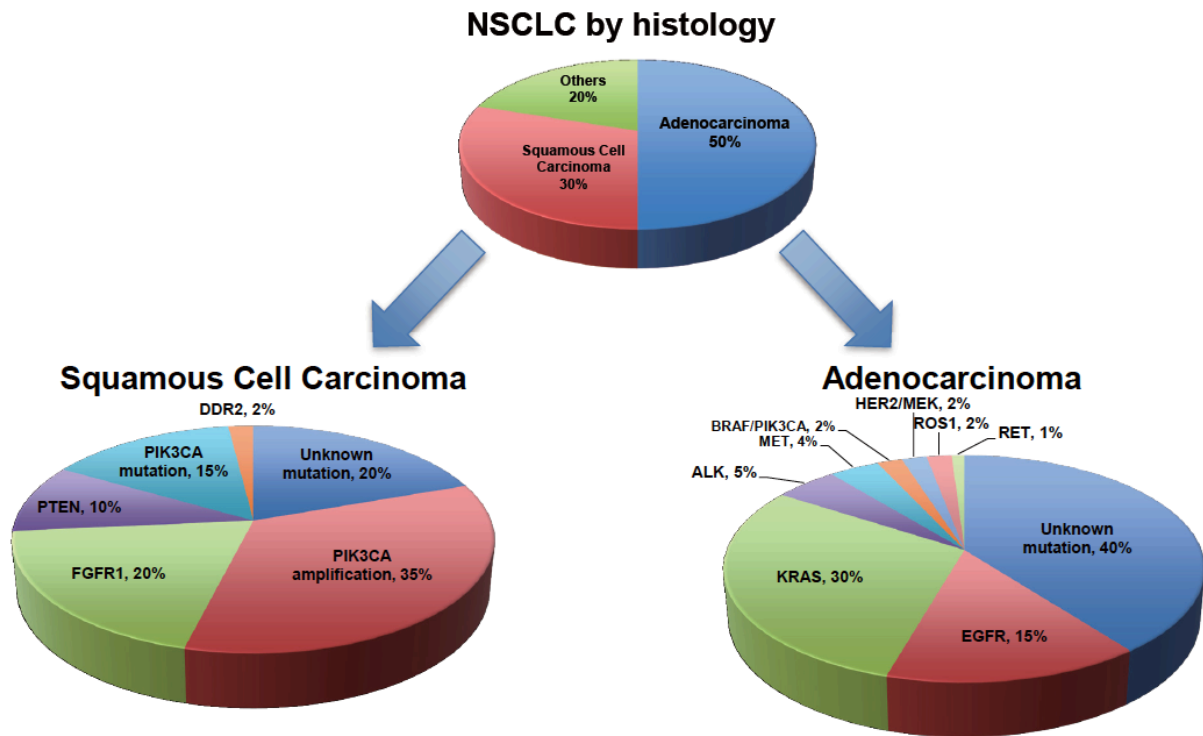


Figure 2.4: NSCLC by histology and mutations

(Chan & Hughes, 2015)

2.6 STAGING

Initial clinical staging for lung cancer is achieved via Computed tomography (CT) and/or positron emission tomography (PET) scan to establish the extent of disease. These modalities provide a gross assessment of disease burden, however, are not specific enough to detect microscopic metastatic disease and may not accurately represent lymph node involvement (Molina, 2008). Invasive biopsy and tissue sampling of both lung and lymph nodes by either mediastinoscopy, EBUS or frozen section during surgery enables precise histopathology assessment to be performed and is therefore considered an essential component of staging in order to define optimal treatment. Gaining a tissue sample also allows the pathologist to grade the tumor to determine if it is well differentiated (low grade) or poorly differentiated (high grade) which will also influence the treatment options available.

Anatomic staging of lung cancer follows the TNM staging classification; T representing tumor, N representing nodal involvement and M representing the presence of metastases. Table 2.2 below outlines the definitions of each category within the TNM classification and how these relate to each stage. Stages I and II represent early stage lung cancer, Stage III locally advanced lung cancer and Stage IV advanced or metastatic lung cancer. Figure 2.5 provides further insight into lung cancer stage classification by visually demonstrating the difference between early stage (0-I) and late stage (IV) disease.

Staging of lung cancer is essential and once established it is used to guide effective targeted treatment. Staging may vary during the course of an individual's treatment, for example if the tumor has rapidly progressed or if more extensive disease is discovered during invasive surgical biopsy. Providing the best evidenced-based treatment for the stage of disease is of key importance in effectively managing lung cancer once it is diagnosed (Cancer Council Australia, 2020).

Table 2.2: Definitions for TNM classifications

(International Association for the Study of Lung Cancer – 8th Edition of the TMN classification for lung cancer, (Detterbeck, Boffa, Kim, & Tanoue, 2017))

T (Primary Tumor)		Label
T0	No primary tumor	
Tis	Carcinoma in situ (Squamous or Adenocarcinoma)	Tis
T1	Tumor ≤3 cm,	
T1a(mi)	Minimally Invasive Adenocarcinoma	T1a(mi)
T1a	Superficial spreading tumor in central airways ^a	T1a _{ss}
T1a	Tumor ≤1 cm	T1a _{≤1}
T1b	Tumor >1 but ≤2 cm	T1b _{>1-2}
T1c	Tumor >2 but ≤3 cm	T1c _{>2-3}
T2	Tumor >3 but ≤5 cm or tumor involving: visceral pleura ^b , main bronchus (not carina), atelectasis to hilum ^b	T2 _{Visc Pl} T2 _{Centr}
T2a	Tumor >3 but ≤4 cm	T2a _{>3-4}
T2b	Tumor >4 but ≤5 cm	T2b _{>4-5}
T3	Tumor >5 but ≤7 cm or invading chest wall, pericardium, phrenic nerve or separate tumor nodule(s) in the same lobe	T3 _{>5-7} T3 _{Inv} T3 _{Satell}
T4	Tumor >7 cm or tumor invading: mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine; or tumor nodule(s) in a different ipsilateral lobe	T4 _{>7} T4 _{Inv} T4 _{Ipsi Nod}
N (Regional Lymph Nodes)		
N0	No regional node metastasis	
N1	Metastasis in ipsilateral pulmonary or hilar nodes	
N2	Metastasis in ipsilateral mediastinal/subcarinal nodes	
N3	Metastasis in contralateral mediastinal/hilar, or supraclavicular nodes	
M (Distant Metastasis)		
M0	No distant metastasis	
M1a	Malignant pleural/pericardial effusion ^c or pleural /pericardial nodules or separate tumor nodule(s) in a contralateral lobe;	M1a _{Pl Dissem} M1a _{Contr Nod}
M1b	Single extrathoracic metastasis	M1b _{Single}
M1c	Multiple extrathoracic metastases (1 or >1 organ)	M1c _{Multi}

TX, NX: T or N status not able to be assessed

^a Superficial spreading tumor of any size but confined to the tracheal or bronchial wall

^b such tumors are classified as T2a if >3≤4 cm, T2b if >4≤5 cm.

^c Pleural effusions are excluded that are cytologically negative, non-bloody, transudative, and clinically judged not to be due to cancer.

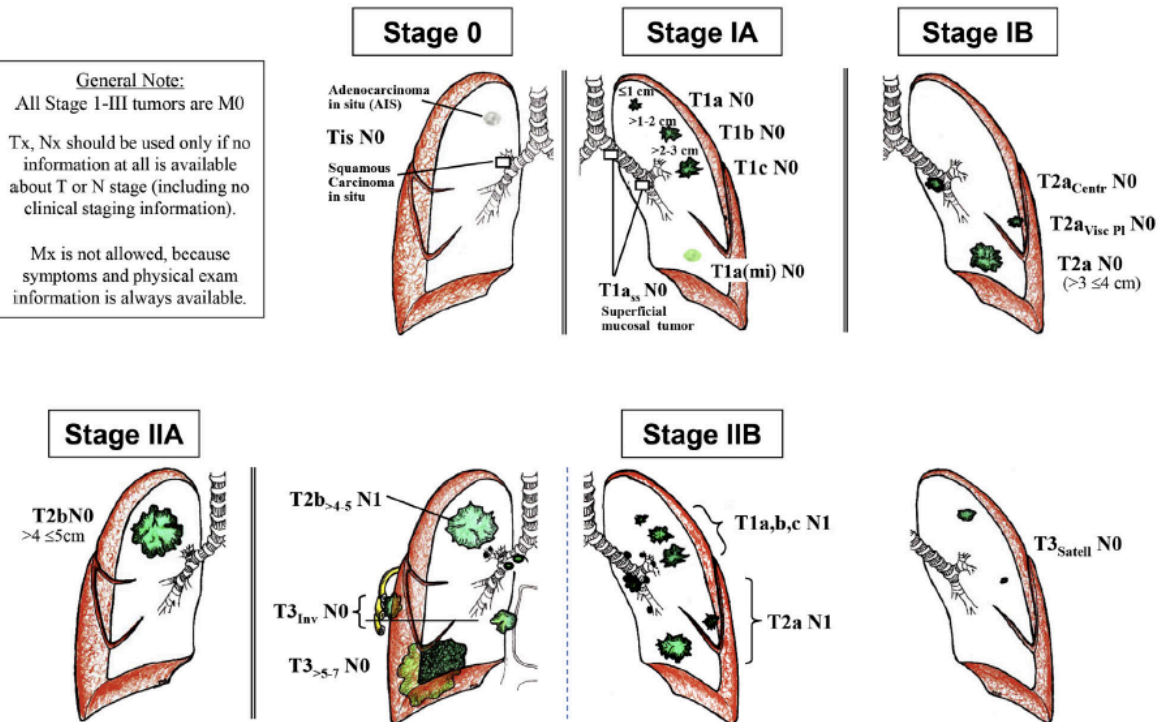
a)

Lung Cancer Stage Classification (8th Edition)

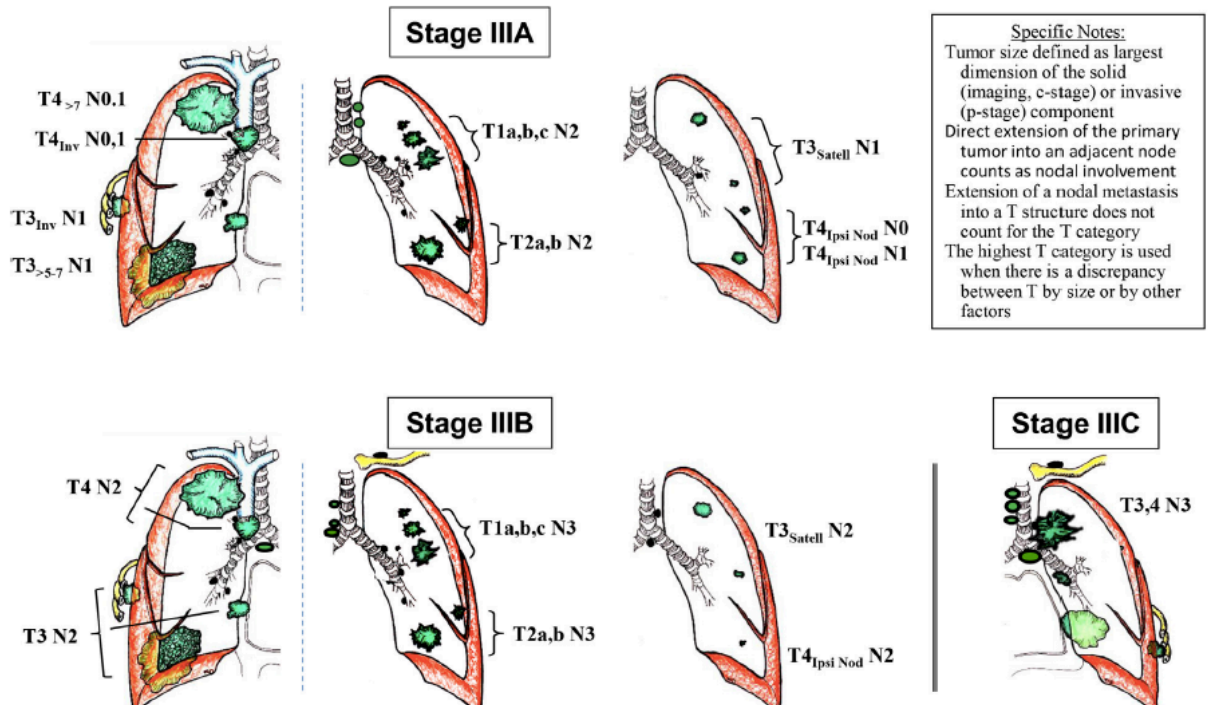
General Note:
All Stage I-III tumors are M0

T_x, N_x should be used only if no information at all is available about T or N stage (including no clinical staging information).

M_x is not allowed, because symptoms and physical exam information is always available.



b)



c)

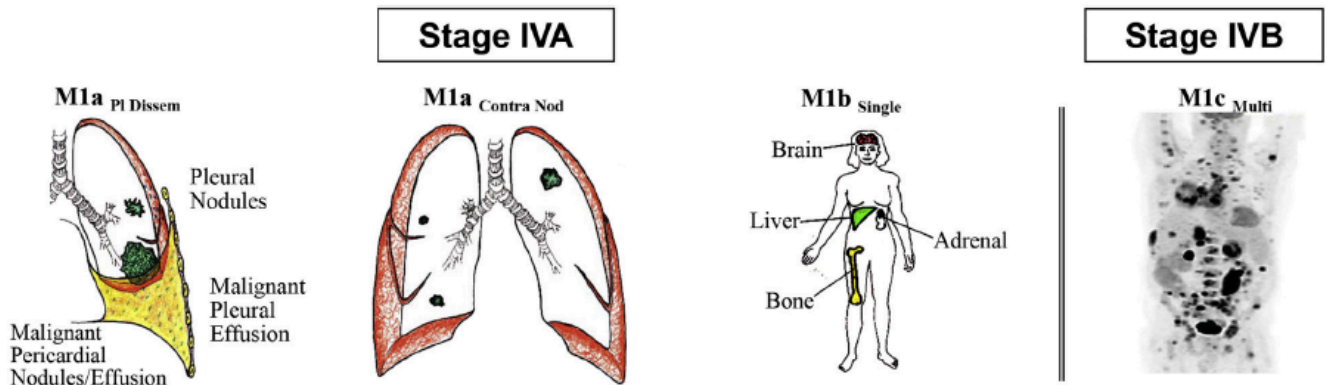


Figure 2.5: Lung cancer stage Classification (8th Ed)

(Detterbeck et al., 2017)

a) Stages I and II, b) Stage III, c) Stage IV

Key: T (T1, T2, T3, T4) – tumour, M – metastases, N (N0, N1, N2, N3) – node
Refer to Table 2.3 for expansion of abbreviations

2.7 SYMPTOMS

Symptoms experienced by individuals with lung cancer can be pulmonary or systemic depending on the stage of disease and whether the cancer has metastasized. Pulmonary symptoms include; persistent cough, shortness of breath, chest or shoulder pain, hoarseness of voice, haemoptysis and dyspnea which are related to the pathophysiology within the lung parenchyma, conducting airways and local intrathoracic spread. Intrathoracic spread may be indicated by one or more of the following symptoms; chest wall invasion, esophageal/swallowing problems, Horner syndrome, phrenic nerve paralysis, pleural effusion, recurrent laryngeal nerve paralysis and superior vena cava obstruction. Early stage symptoms tend to be vague or non-specific and may be mistaken for co-existing respiratory disease, however other systemic symptoms typically present in later stages of disease. These symptoms include; weight loss, fatigue, confusion, headaches and bone pain, these features are related to disease which has metastasized from the lung to other sites within the body. Because these symptoms are more obvious, patients are more likely to seek medical attention at this point (i.e. later in the disease process) and are often diagnosed many months to years after the onset of their symptoms.

The symptoms experienced by individuals with lung cancer have low discriminative utility in isolation (S. H. Bradley, Kennedy, & Neal, 2019). Figure 2.6 presents the positive predictive values (PPV %) for different symptoms of lung cancer, comparing them alone and in combination. It is worth noting that smokers and those of 70 years of age have higher PPV's for each symptom and that haemoptysis (with the highest PPV of between 2.4 -7%) is only present in about a fifth of all lung cancers.

Cough	Fatigue	Dyspnoea	Chest pain	Loss of weight	Loss of appetite	Thrombocytosis	Abnormal spirometry	Haemoptysis	
0.40 0.3, 0.5	0.43 0.3, 0.6	0.66 0.5, 0.8	0.82 0.6, 1.1	1.1 0.8, 1.6	0.87 0.6, 1.3	1.6 0.8, 3.1	1.6 0.9, 2.9	2.4 1.4, 4.1	PPV as a single symptom
0.58 0.4, 0.8	0.63 0.5, 0.9	0.79 0.6, 1.0	0.76 0.6, 1.0	1.8 1.1, 2.9	1.6 0.9, 2.7	2.0 1.1, 3.5	1.2 0.6, 2.6	2.0 1.1, 3.5	Cough
	0.57 0.4, 0.9	0.89 0.6, 0.3	0.84 0.5, 1.3	1.0 0.6, 1.7	1.2 0.7, 2.1	1.8	4.0	3.3	Fatigue
		0.88	1.2 0.9, 1.8	2.0 1.2, 3.8	2.0 1.2, 3.8	2.0	2.3	4.9	Dyspnoea
			0.95 0.7, 1.4	1.8 1.0, 3.4	1.8 0.9, 3.9	2.0	1.4	5.0	Chest pain
				1.2 0.7, 2.3	2.3 1.2, 4.4	6.1	1.5	9.2	Loss of weight
					1.7	0.9	2.7	>10	Loss of appetite
							3.6	>10	Thrombocytosis
								>10	Abnormal spirometry
								17	Haemoptysis

Figure 2.6: Positive predictive values (%) for lung cancer individual risk factors

(S. H. Bradley et al., 2019)

Key: bold type indicated the Positive Predictive Value (PPV) for an individual symptom. Figures beneath bold type indicate the 95% confidence interval (CI) for the PPV.

Yellow square indicates PPV above 1%, orange squares indicate PPV above 2%, red squares indicate PPV above 5%

2.8 MEDICAL TREATMENT

Medical treatment for lung cancer is dependent on disease related factors as well as individual patient related factors (for example comorbidities, functional capacity, patient preferences and social circumstances). Treatment options include pulmonary resection, chemotherapy, radiotherapy and newer targeted immunotherapies. Treatment options vary with stage of disease and take into account the histological type, stage (TNM classification) and extent of systemic disease (metastases). In early stage NSCLC (stages I-IIIa) complete resection via lobectomy is the treatment choice for curative intent in patients with low cardiopulmonary risk, minimally invasive and/or sub lobar resections are suitable for a subset of patients with higher cardiopulmonary risk (McDonald et al., 2017). Chapter 3 of this thesis details the surgical treatment options available for early stage NSCLC. Stages IIIB and IV may be considered for surgery depending on the performance status and resectability of disease (Lang-Lazdunski, 2013), whether the disease is oligometastatic (limited systemic metastases) or widely advanced will also determine suitability for pulmonary resection. Advances in surgical techniques and minimally invasive approaches have provided better surgical treatment options to thoracic surgeons for older patients, patients with poor pulmonary function or significant comorbidities. Surgery may also be used in advanced-stage disease, where palliative procedures have been used to improve symptom burden and quality of life. The 5-year survival for patients undergoing pulmonary resection ranges from 75% for stage IA to 25% for stage IIIA (Le Chevalier, 2011).

Neoadjuvant (delivered before primary treatment) or adjuvant (delivered after primary treatment) chemotherapy and or radiotherapy may also be used in the treatment of lung cancer. In early stage I-III NSCLC where surgery is considered the primary treatment, the addition of adjuvant cisplatin-based chemotherapy after lung resection can improve overall survival by 5.3% and disease-free survival by 5.2% at 5 years for individuals with tumors >4cm (stage IIA) (McDonald et al., 2017). For later-stage disease (stages IIA – IIIA), where the disease burden is more extensive, treatment is often related to patient performance status. For those with good performance status, chemotherapy and radiotherapy (concurrent chemo-radiotherapy) are typically offered as first line

treatment where it is considered that surgery provides no survival benefit or is too risk averse. For those with poor performance status, radiotherapy is considered the treatment choice for inoperable lung cancer that is widely advanced or for individuals considered unfit for surgery due to co-morbidities (McDonald et al., 2017), providing a median survival benefit of 10 months and 5-year survival of 5% (Molina, 2008). More recently, current trials are suggesting that radiotherapy combined with chemotherapy for late stage NSCLC may provide greater survival benefit compared with radiotherapy alone. Conclusions regarding treatment in advanced disease will become clearer once the results of these trials are published. Stereotactic radiotherapy, delivering high-dose radiotherapy in a limited number of fractions, may be used as an alternative to conventional radiotherapy to treat those with limited disease who are not surgical candidates or for those with solitary metastases. This is generally well tolerated by the patient and one advantage is that patients are required to attend only a few hospital appointments for treatment.

Systemic therapies including targeted agents, immunotherapy and anti-angiogenic agents, provide greater scope for patients with varying stages of disease. There are currently a number of large phase III clinical trials taking place internationally exploring the use of these therapies in NSCLC. It is hoped that better understanding of tumor biology, biomarkers, mutations and testing of targeted therapies will improve treatment options and therefore improve prognosis for patients with lung cancer in the future (Lang-Lazdunski, 2013).

2.9 SURVIVAL

The five-year survival for primary lung cancer is 17% (AIHW, 2019) (Figure 2.7). Compared with other cancer cohorts, lung cancer survival statistics have not improved greatly over the past three decades and international inequalities in survival continue to exist (Coleman et al., 2008; Walters et al., 2013). In an international population-based study by Walters et al, the age-standardized one-year net survival for NSCLC ranged from 30% in the UK to 46% in Sweden with survival being reported as relatively low in

Denmark, intermediate in Norway and high in Australia and Canada (Walters et al., 2013). Part of this discrepancy can be explained by a difference in the stage at diagnosis in different countries. At diagnosis, the proportion of patients with metastatic disease (TNM stage IV) varied between countries ranging from: 46.8% in Sweden, 47.5% in Australia and 61.2% in Denmark (Walters et al., 2013).

Within the Australian setting, survival may also be influenced by geographical confines. Many of the specialist thoracic cancer centers within Australia are located in the metropolitan regions making access to those who live rurally difficult. In a study examining the impact of distance from thoracic specialist centers on survival, it was found that distance from the nearest accessible specialist hospital affected NSCLC outcomes. The results of this data linkage study found that there was substantial variation in survival of NSCLC depending on the type of hospital and distance from the nearest accessible specialist hospital. Two factors were identified which strongly influenced the hazard of death; attendance at a specialist hospital and having a pulmonary resection of the lung cancer, both of which lowered risk. Patients at greater distance from specialist hospitals are less likely to attend specialist hospitals and therefore less likely to undergo pulmonary resection in a timely fashion. Patients admitted for resection at 2-12 months after diagnosis had a hazard of death at 5 years that was more than double patients admitted for resection within 1 month of diagnosis (Tracey, McCaughan, Badgery-Parker, Young, & Armstrong, 2015). The study concluded that NSCLC survival outcomes are best when patients are treated in specialist thoracic centers and that distance from specialist treatment centers can negatively affect survival.

Recurrence of primary lung cancer, even after curative treatment, remains a problem. Survivors of lung cancer require long-term follow-up as recurrence of disease has been reported as late as 10 years after treatment. Early studies demonstrated that the cumulative risk of developing subsequent primary lung cancer or other smoking-related lung cancers at 6-8 years reaches 13-20% (Molina, 2008).

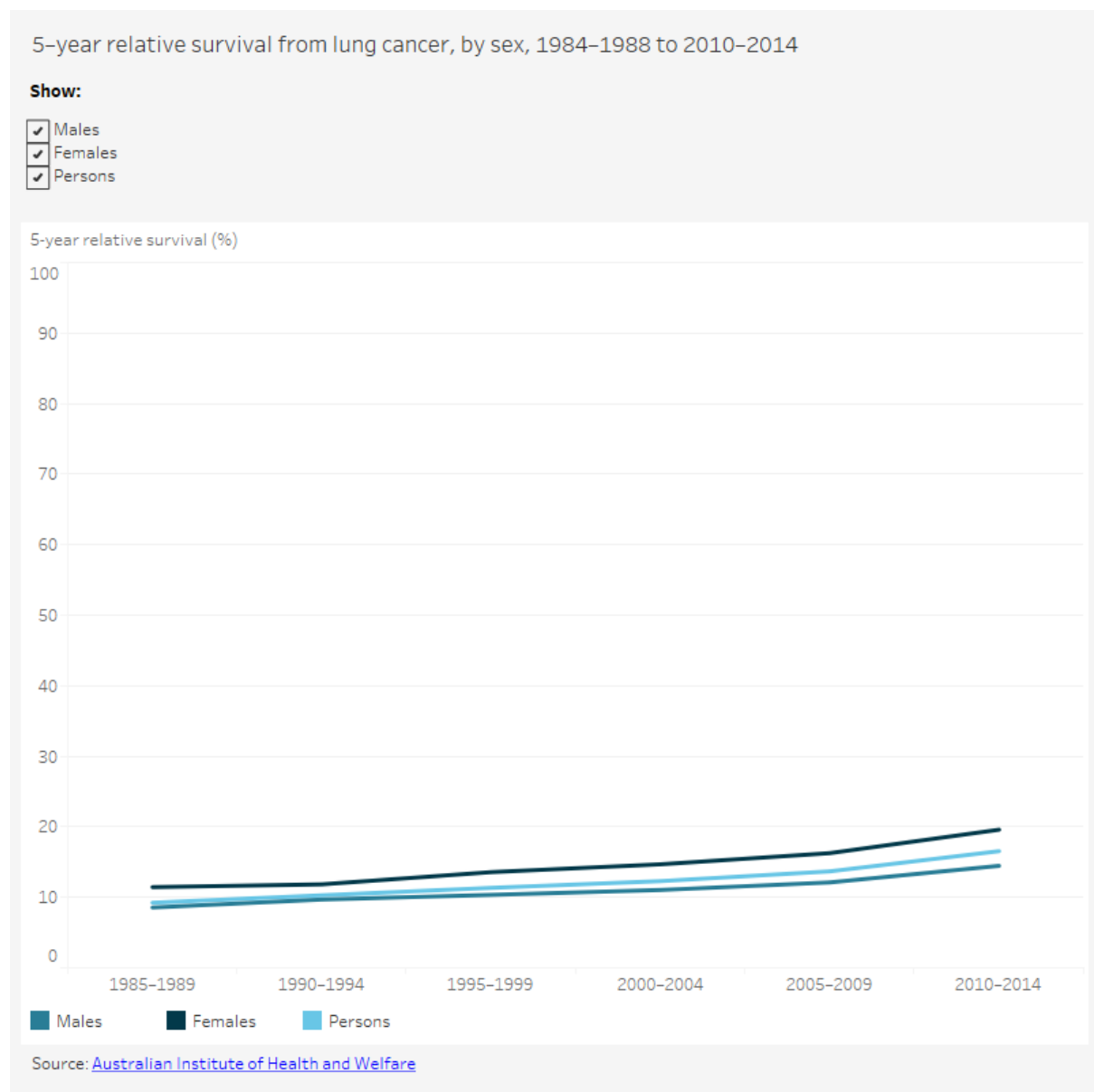


Figure 2.7: 5-year survival for lung Cancer in Australia
(<https://lung-cancer.canceraustralia.gov.au>)

2.10 SUMMARY

This chapter has discussed the burden of lung cancer and provided insight into its incidence and influence on mortality within the Australian setting. Despite enhanced awareness and education campaigns about the risk factors and behaviors (such as smoking) that have been directly associated with the development of lung cancer, delays to diagnosis still exist. Until there is further robust evidence regarding the routine use of low-dose CT scanning in the screening and detection of lung cancer, early detection will rely on primary care physicians identifying and risk stratifying those individuals most at risk of developing lung cancer and referring them to centers with lung cancer multidisciplinary teams for assessment and treatment. Although the 5-year survival for lung cancer has been slower to improve in comparison to other cancer cohorts, it has shown slow progress over time and will hopefully continue to improve with ongoing research and development into lung cancer detection and treatment. The next chapter of this thesis will specifically focus on the surgical treatment of NSCLC.

CHAPTER 3 THORACIC SURGERY

3.1 INTRODUCTION

This chapter introduces the surgical options available for the treatment of early stage lung cancer. Common thoracic surgical access incisions and specific pulmonary resection types will then be outlined, with a focus on video-assisted thorascopic surgery (VATS) as this is the minimally invasive technique used in all the patients within the studies of this thesis. The chapter will finish with details of the recovery after thoracic surgery including the role of postoperative physiotherapy.

3.2 LUNG CANCER SURGERY

Pulmonary resection is considered the best treatment option with curative intent for individuals with resectable early stage NSCLC (Osarogiagbon et al., 2019). Surgery is usually performed as soon as possible after diagnosis, and the type and extent of pulmonary resection depends on the size and stage of disease (figure 3.1 outlines the patient flow from diagnosis to surgery).

Surgical options for lung cancer include pneumonectomy, lobectomy or limited pulmonary resection (sub lobar) performed either via a thoracotomy or more recently through minimally-invasive video-assisted access. Lobectomy is the gold standard approach for resectable early stage NSCLC as this approach has been shown to have lower rates of loco-regional recurrence and improved survival compared with limited pulmonary resection (De Zoysa, Hamed, Routledge, & Scarci, 2012). In cases where lobectomy would be poorly tolerated (severe lung disease, multi-morbidities, high anaesthetic risk), limited pulmonary resection provides an option that preserves a greater amount of lung parenchyma and therefore limits physiological insult, leading to fewer postoperative complications and shorter length of stay (De Zoysa et al., 2012).

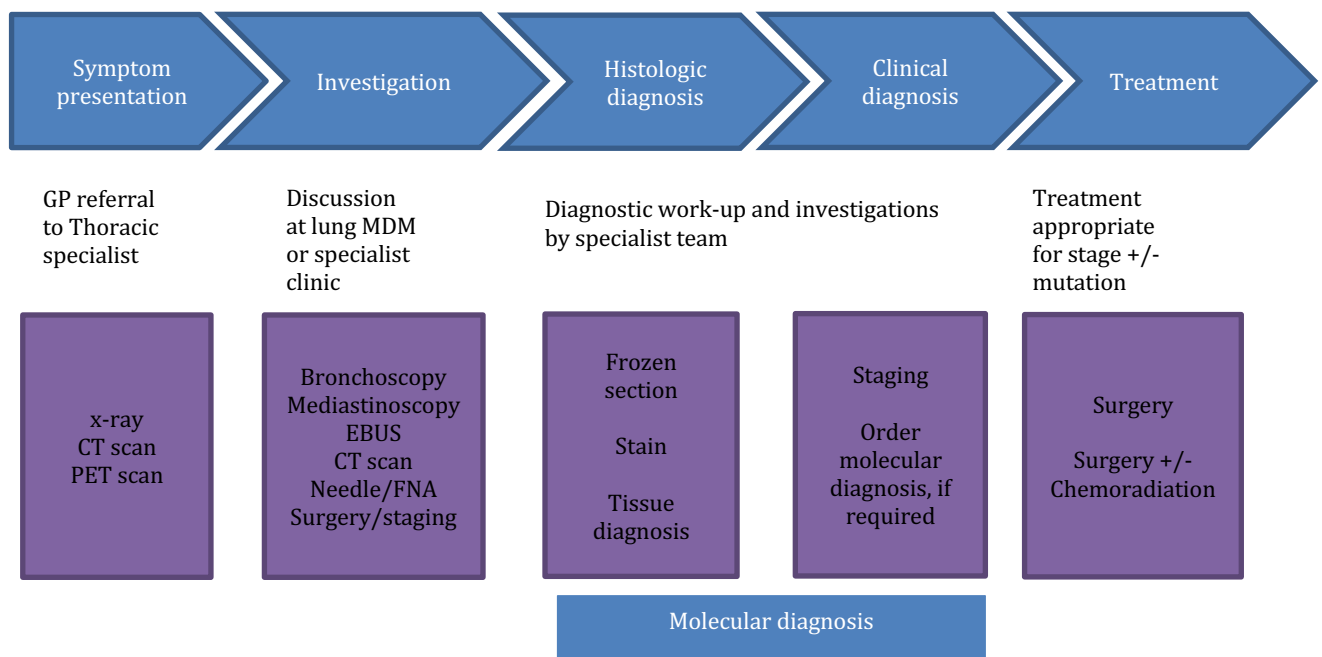


Figure 3.1: Diagnosis to surgery flow chart

Advances in lung cancer screening and detection have led to an increased rate of detection of ground-glass nodules and/or small solid lesions which may be amenable to pulmonary resection. This can create a treatment dilemma in deciding whether to continue with radiological surveillance or perform an invasive sub lobar resection to remove a potentially non-malignant lesion. Guidelines such as those developed in 2017 by the Fleischner Society, which recommend extended follow-up for individuals with smaller ground-glass nodules, assist in determining the size of lesion at which point surgery is indicated for the best treatment outcome (Bueno, Landeras, & Chung, 2018). Prognosis following surgery is based on completeness of oncological resection and individual lung cancer characteristics (e.g. genetic mutations, histological type and stage) as well as patient-related factors such as comorbidities, frailty, functional capacity and psychosocial factors.

3.3 INDICATIONS FOR SURGERY

Advances in imaging modalities (CT and PET scans) and diagnostic techniques (such as endobronchial ultrasound (EBUS) and navigational bronchoscopy) have improved screening for lung cancer and have contributed to earlier rates of detection as highlighted in the previous chapter. Diagnosis of lung cancer earlier in the disease process allows for better work-up and planning of treatment thus improving the chances of disease-free survival. The classification system used for staging NSCLC also assists in determining an individual's suitability for surgery. Lung cancer with multiple mediastinal lymph node involvement (N2 and above) demonstrates that the cancer has advanced beyond the hilar (lung) nodes, therefore surgery alone is unlikely to be of curative intent.

Surgery remains the best treatment option for patients with resectable stages I-II NSCLC (Wright, Manser, Byrnes, Hart, & Campbell, 2006) where the primary tumour can be anatomically resected with clear margins. Stage IIIA NSCLC may be considered for surgery, however adjuvant chemotherapy must be considered prior to or following pulmonary resection. Figure 3.2 depicts suitability for surgery based on stage of disease. The 5-year survival for all patients undergoing lung resection surgery with curative intent for NSCLC with stage I and II disease is between 50-70% (Hunt, 2009).

T/N	T1	T2	T3	T4
N0	IA	IB	IIB	IIIB
N1	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIB
N3	IIIB	IIIB	IIIB	IIIB

Figure 3.2: Suitability for surgery according to stage of disease

(Hunt 2009 - ABC of Lung Cancer p31)

FOOTNOTE: Lung cancer stages as derived from T (tumour) and N (nodal) status. Green squares = suitable for surgery with curative intent. Red boxes = surgery considered futile and offers no survival benefit. Orange squares = may be suitable for surgery, cautious consideration required

Surgical options for patients with lung cancer have rapidly grown in recent years. The emergence of VATS procedures, which are considered safer and less invasive, has improved the risk-benefit ratio of surgery as well as provided a more palatable option to patients for which the more invasive procedures, such as thoracotomy, would not be well tolerated (Hennon & Yendamuri, 2012). In a systematic review examining the differences in oncological outcomes (based on satisfactory lymph node dissection or lymph node sampling, systemic or loco-regional recurrence and survival) between VATS and thoracotomy for early stage NSCLC, no statistically significant difference was found in the number of total lymph node dissections or lymph node sampling procedures (MD: -0.63, 95% CI: -1.47 to 0.21, $P = 0.14$) between groups. Recurrence rates were significantly lower in the VATS group; systemic recurrence (RR: 0.61, 95% CI: 0.48 to 0.78, $P < 0.01$) and loco-regional recurrence (RR: 0.66, 95% CI: 0.46 to 0.95, $P = 0.03$), and survival rates were also higher in the VATS group (RR: 1.09, 95% CI 1.03 to 1.15, $P < 0.01$). These results provide evidence that for patients with early stage NSCLC, VATS lobectomy may be a suitable alternative to thoracotomy and result in reduced cancer recurrence and improved survival rates (Zhang et al., 2013). Similarly, the emergence of robotic surgical platforms offers a less invasive approach to pulmonary resection of lung lesions compared to video-assisted lobectomy approaches. Recent studies suggest comparable results for the two approaches in terms of: conversion-to-open rates, median length of stay and 5-year survival (Cerfolio et al., 2018).

3.4 ASSESSMENT OF FITNESS FOR LUNG CANCER SURGERY

Unfortunately, 70% of people who present with lung cancer have advanced inoperable disease, and of those with operable disease 25% are unfit for surgery (C. L. Granger, 2016). It is known that patients with lung cancer experience high symptom burden (pain, dyspnoea, cough, cachexia, fatigue) and have lower levels of physical activity at the time of diagnosis (C. L. Granger, Parry, Edbrooke, & Denehy, 2016). Of the cohort of patients that are eligible for lung cancer surgery, adequate pre-surgical workup is paramount to operative success. Low fitness levels have been shown to be an independent marker of risk for cardiovascular and all-cause mortality (Myers, 2016). Thorough functional assessment, frailty screening and identification of risk factors will assist pre-surgical

planning of appropriate treatment/care and ultimately lead to better postoperative outcomes.

3.4.1 Preoperative assessment

Preoperative assessment must consider each patient on an individual basis, despite the association between physiologic exercise measures and clinical outcomes, decisions regarding surgery are often complex and multifaceted. “No single variable or algorithm involving exercise testing should be used in the decision making process. Instead, an individualised/patient-oriented and multidisciplinary approach is likely to lead to better clinical outcomes” (Ha, Mazzone, Ries, Malhotra, & Fuster, 2016). A variety of preoperative tests/ assessments are used to risk stratify patients. Table 3.1 compares the characteristics of the most commonly used exercise tests used clinically, figure 3.3 demonstrates the risk stratification algorithms for these tests. Depending on the available resources and expertise, preoperative assessment may include one or more of the following;

Exercise Tests

Cardiopulmonary exercise testing (CPET) is the gold standard method of assessing an individuals' cardiorespiratory reserve as well as determining the limitation to maximal or submaximal exercise. During this test, patients undergo an incremental exercise test (cycle or treadmill) whilst cardiac (12-lead ECG) and respiratory measures (breath by breath analysis of oxygen uptake and carbon dioxide excretion) are continually recorded. Two important outputs are VO_2 peak (oxygen consumption at maximal exercise) and anaerobic threshold (AT) which is the point at which an individual's blood lactate levels start to rise during exercise. CPET has been used over the last two decades to risk-stratify patients prior to surgery as it has been found that low preoperative peak VO_2 is predictive of postoperative complications and poorer outcomes (Myers, 2016). In 2009 the European Respiratory Society published guidelines on the preoperative evaluation of fitness for radical therapy (including surgery) in lung cancer. These guidelines recommend that CPET cut-off values be considered: 75% of predicted values or $20\text{mL.kg}^{-1}.\text{min}^{-1}$ for pneumonectomy and 35% of predicted values or $10\text{mL.kg}^{-1}.\text{min}^{-1}$ for any type of resection. Due to limited evidence, cut-off values for lobectomy could not be recommended (Brunelli, Charloux, et al., 2009).

A subsequent study by Brunelli et al in 2009 of 204 patients undergoing lung resection surgery for cancer examined the results of CPET as a risk-stratification tool. They found that those with a peak $\text{VO}_2 < 12\text{mL.kg}^{-1}.\text{min}^{-1}$ had a five- to eight-fold risk of cardiac or pulmonary complications and a thirteen-fold higher risk of mortality. Within this cohort, in all deaths that occurred, patients were found to have a peak $\text{VO}_2 < 20\text{mL.kg}^{-1}.\text{min}^{-1}$ (Brunelli, Belardinelli, et al., 2009). Since this time, numerous studies have been published in relation to CPET and surgical outcomes within the general surgical and lung resection populations. The literature in relation to lung cancer surgery identifies reduced physical fitness (defined by CPET variables) as a predictor of increased postoperative morbidity and mortality and recommends CPET testing as a screening measure for all high-risk surgical patients (Benzo, Kelley, Recchi, Hofman, & Sciurba, 2007; Gao et al., 2015; D. Z. Levett & Grocott, 2015; Older & Levett, 2017). For current practice in Australia, high-risk surgical patients undergo CPET testing in the work-up for lung cancer surgery, whereas all patients (high or low risk) are recommended to undergo a field walking test.

Field walking and exercise tests

These tests, such as the six-minute walk test (6MWT) and incremental shuttle walk test (ISWT), offer a less invasive version of an exercise test compared to CPET and have been extensively used to assess patient's preoperative functional status.

During the 6MWT patients are asked to walk at their own pace along a 25 or 30m corridor for 6 minutes with the number of 'laps' or distance measured over time. Guidelines for conducting the test in a standardised manner have been published by the American Thoracic Society & European Respiratory Society (Casanova et al., 2011; Holland et al., 2014). During the ISWT patients are asked to walk a distance of 10m between two marked out shuttles keeping pace with the timed beeps on an audiocassette/CD. It is an externally paced test where the participant is required to keep up with the progressively shorter time intervals on shuttles in order to continue the test (initial starting speed is 0.50m/s and final speed is 2.37 m/s and the maximal distance able to be achieved is 1020 m). In a study comparing the validity of three field walking tests to assess functional exercise capacity in lung cancer, Granger et al found that the ISWT had the greatest criterion validity and demonstrated a moderate relationship with VO_2 peak oxygen

consumption whereas the 6MWT and Endurance shuttle walk test (ESWT) had a poorer relationships with VO₂ peak. The study concluded that field walking tests are clinically applicable as they are quick (taking < 16minutes to complete), safe and require only one assessor (C. L. Granger et al., 2015) but they do measure slightly different constructs to information obtained from CPET.

Table 3.1: Characteristics of common exercise tests

Exercise test	Pacing	End point	Measurement	Intensity	Complexity	Relationship to VO₂ peak/max
CPET	Externally paced	Prohibitive symptoms or plateau of VO ₂	VO ₂ AT HR, BP, O ₂ saturation, work	+++	+++	
6MWT	Self-paced	6-min duration	Distance HR, BP, O ₂ saturation	++	+	Moderate-strong
ISWT	Externally paced	Prohibitive symptoms or 12 total stages	Distance HR, O ₂ saturation	++	++	Strong

CPET – cardiopulmonary exercise testing, AT – anaerobic threshold, VO₂ – oxygen consumption, HR – heart rate, BP – blood pressure, O₂ saturation – oxygen saturation, 6MWT – six minute walk test, ISWT – incremental shuttle walk test (Ha, 2016)

Pulmonary function tests

Pulmonary function tests/spirometry measures (forced expiratory volume in 1 second – FEV₁, forced vital capacity – FVC and diffusing capacity of the lung for carbon monoxide – DLCO) are used early in the diagnosis of lung cancer as a means to quantify the extent of respiratory disease or dysfunction. Results of these tests allow risk-stratification of patients with operable lung cancer and cut-off targets are often used to determine

optimal surgical procedure. Predicted postoperative (PPO) lung function should also be calculated to estimate the impact of the intended resection. Current evidence-based clinical practice guidelines are outlined in the Table 3.2 below.

Table 3.2: Risk stratification based on spirometry results

(Brunelli, Kim, Berger, & Addrizzo-Harris, 2013)

Spirometry measure	Risk	Recommendation
%PPO FEV ₁ > 60% %PPO DLCO	Low risk	No further tests required
%PPO FEV ₁ 30-60% %PPO DLCO	Moderate risk	Low technology test required (stair climbing test or ISWT)
%PPO FEV ₁ < 30% %PPO DLCO	High risk	CPET testing required

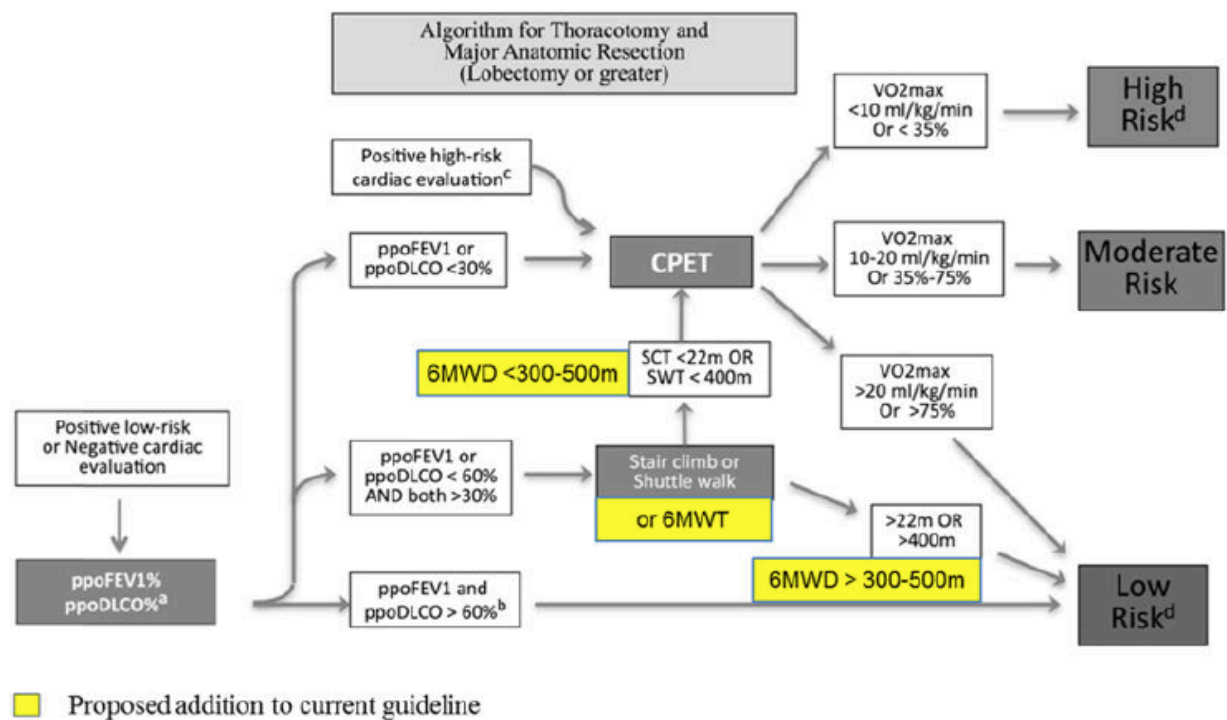


Figure 3.3: Algorithm for thoracotomy and major anatomic resection

6MWD – 6-minute walk distance, 6MWT – 60minute walk test, DLCO – diffusion capacity of the lung for carbon monoxide, FEV₁ – forced expiratory volume in 1 second, ppoDLCO – predicted postoperative, ppoFEV₁ – predicted postoperative forced expiratory volume in 1 second, SCT – stair climbing test, SWT – shuttle walk test, VO₂ Max – maximal oxygen consumption (Ha, 2016)

3.4.2 Assessment of risk factors

Some patient related factors, such as age, sex and lung cancer stage/type are not modifiable, however screening for modifiable risk factors preoperatively allows for timely optimization prior to lung surgery, which may have positive effects on postoperative recovery. Modifiable risk factors include (McIsaac et al., 2018):

- Anaemia
- Chronic obstructive pulmonary disease (COPD)
- Smoking
- Malnutrition
- Alcohol consumption

Individual patient risk factor assessment is also important when specific target outcomes are required. For example, choosing to reduce the risk of postoperative pulmonary complications (PPCs) requires knowledge of the factors that put individuals at highest risk of these complications so that resources can be targeted to these cases. Agostini et al report specific patient attributes in thoracic surgery patients associated with the highest risk of developing PPCs. These include; aged > 75 years, BMI > 30 kg/m², an American Society of Anaesthesiologist (ASA) score of > 3, current smoking history and COPD diagnosis (P. Agostini et al., 2010).

Careful consideration of all the above-mentioned points needs to take place prior to consenting a patient for lung cancer surgery. The risk-to-benefit of each measure should be assessed on an individual basis and in consultation with patient or advocate to ensure shared decision making and patient-centred care.

3.5 TYPE OF SURGICAL ACCESS

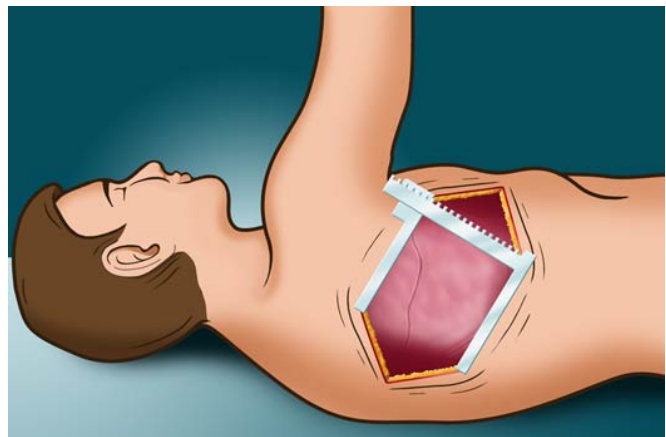
The optimal incision site is determined by the site which offers optimal exposure and provides the greatest access to the intra-thoracic structures of interest: the lung, mediastinum and lymph nodes. Choice of surgical incision will depend on the anatomical location of the tumour (central/hilar lung tumour vs superior sulcus tumour), surgeon

experience as well as the aim to minimize pain and reduce postoperative dysfunction (Ferguson, 2007).

Traditionally, thoracic resection procedures have been performed via an open posterolateral approach (thoracotomy). Posterior, anterior, subcostal and supraclavicular incisions may also be used (Figure 3.4).

Posterolateral thoracotomy

Posterolateral thoracotomy is the most traditional of the thoracotomy incisions. It is universal in the fact that it allows access to the lung and posterior mediastinum on the chosen side for a variety of procedures, it can also be extended anteriorly for access to the diaphragm/abdomen or posteriorly where greater exposure is required (Martin-Ucar & Socci, 2017). Disadvantages of this procedure include: significant postoperative pain, compromised respiratory function due to the large incision and shoulder movement dysfunction (Martin-Ucar 2017).



Muscle sparing thoracotomy

The muscle sparing thoracotomy is performed in the same position to the posterolateral thoracotomy however the incision preserves the lateral chest wall muscles. This is achieved by reducing the size of the incision which lessens the risk of adhesions (Martin-Ucar 2017).

Anterolateral thoracotomy

Anterolateral thoracotomy has limited use in thoracic surgery due to the restricted exposure from this type of incision (Martin-Ucar 2017). To perform an anterolateral thoracotomy, the patient is positioned supine, the incision starts at the anterior axillary line and curves under the breast towards the sternum. This type of incision may be useful as a procedure for staging of lung cancer, as a means of gaining lung biopsy or invasive assessment of mediastinal lymph node invasion (Martin-Ucar 2017).

Figure 3.4: Thoracotomy incisions

Modified from (Simoglou, 2017)

Over the past two decades video-assisted thorascopic surgery (VATS) has become more widely used as a minimally invasive alternative to traditional thoracotomy for pulmonary resection. Initially VATS was performed via a four-port set-up, however with increased use and progression in surgeon skill levels, VATS has advanced to uni-portal (see figure 3.5) as well as subxiphoid approach. Evidence suggests that the advantages of VATS on post-surgical recovery include: improved return to function in the early postoperative period, better shoulder range of motion, fewer postoperative complications, decreased risk of intensive care re-admission, shorter hospital length of stay and reduced requirement for inpatient rehabilitation (W. W. Li et al., 2003; Port et al., 2011). In a recent randomized controlled trial comparing VATS versus anterolateral thoracotomy lobectomy for early stage lung cancer, VATS was found to be associated with less postoperative pain and better quality of life for the first year after surgery (Bendixen, Jørgensen, Kronborg, Andersen, & Licht, 2016).

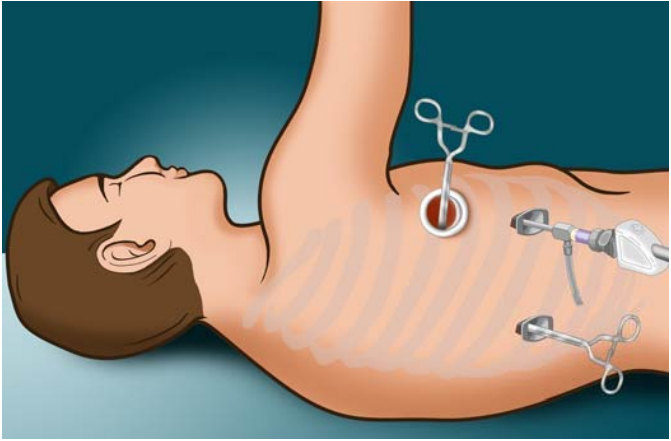
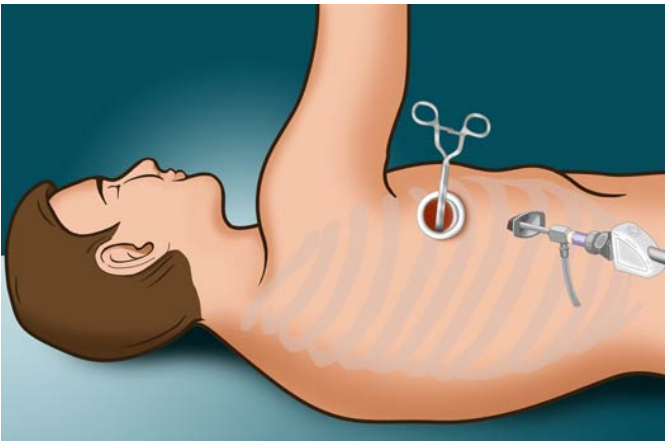
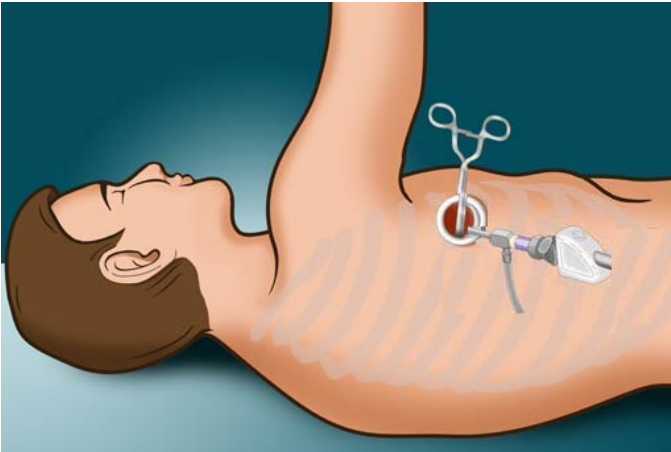
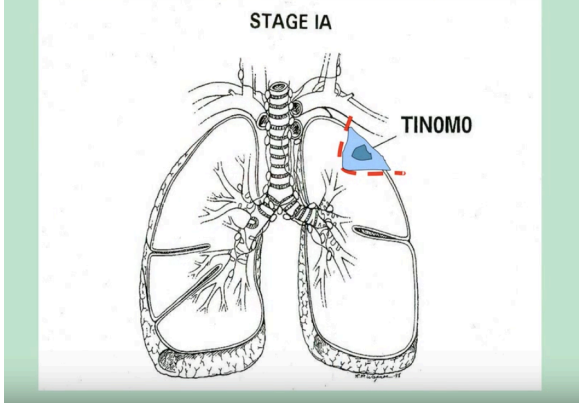
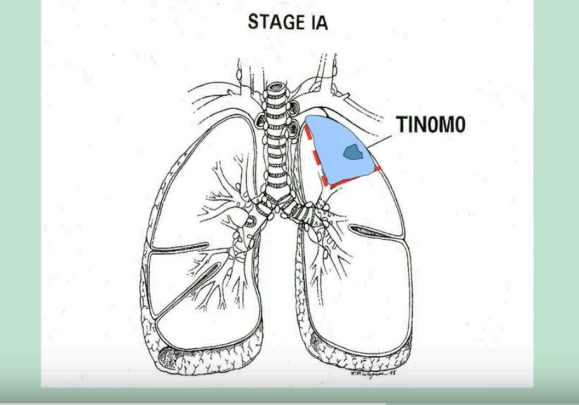
VATS incision	Diagram
Three-port VATS	
Two-port VATS	
Uni-port VATS	

Figure 3.5: VATS incisions

Modified from (Simoglou et al 2017)

3.6 TYPES OF PULMONARY RESECTION

The different types of pulmonary resection are summarised in Figure 3.6 below.

Type of resection	Indication	Diagram
Wedge resection Wedge resection refers to the removal of a limited section of the lung (sub-lobar resection or limited pulmonary resection). The purpose of removing a small wedge is to target small peripheral nodules whilst also preserving lung tissue.	Procedure of choice for small (<1cm) peripheral lung nodules Early stage small size peripheral tumours (T1a) and/or a compromised approach in patients with poor performance status (Harrison, Stiles, & Altorki, 2018)	Wedge Resection 
Segmentectomy Segmentectomy involves removal of one or more pulmonary segments of the lobe within the lung. Each pulmonary segment has its own bronchial, pulmonary arterial and venous supply (the right lung consists of 10 pulmonary segments and the left lung 8). Due to the close relationship of structures, a detailed knowledge of segmental anatomy as well as potential anatomical arterial anomalies, is required making this a technically complex procedure (Kato et al., 2017).	Utilized for small lung nodules with ground-glass opacity that may not be appropriate for lobectomy. Considered the preferred procedure where sparing of lung parenchyma, reduced morbidity and disability are important considerations (Villamizar & Swanson, 2014).	Segmentectomy 

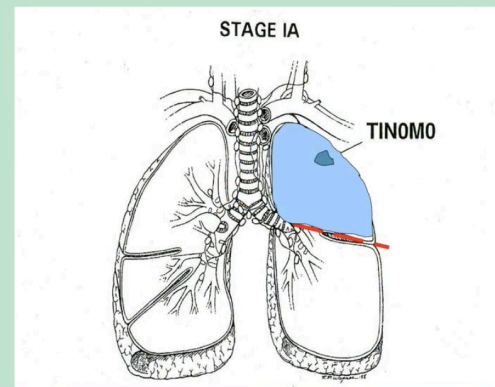
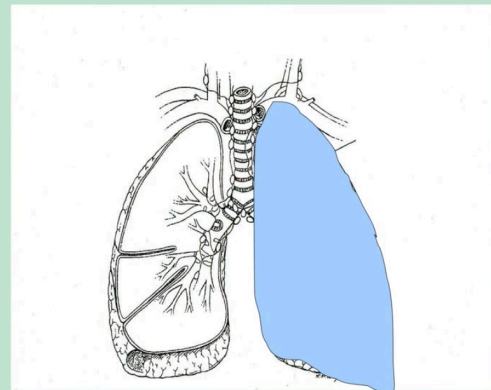
Type of resection	Indication	Diagram
Lobectomy Lobectomy involves complete removal of one or more lobes of the lung.	Lobectomy may be unsuitable for particular patient populations (including older adults and individuals with limited pulmonary reserve) or where the size of the nodule (< 2cm) can be adequately treated with sub-lobar resection resulting in shorter operating times and reduced morbidity (Dai et al., 2016).	 The diagram illustrates a lobectomy procedure. It shows a frontal view of the human thorax with the lungs. The right lung is highlighted in blue. A red line indicates the resection plane, removing the upper lobe. A small blue nodule is labeled 'TINOMO' and 'STAGE IA'.
Pneumonectomy Involves removal of one entire lung, the remaining lung remains as the sole means of ventilation.	In cases of advanced disease, or where a lobectomy is inadequate for curative treatment. Pneumonectomy may also be considered in cases of loco-regional recurrence of lung cancer where previous lobectomy have been performed.	 The diagram illustrates a pneumonectomy procedure. It shows a frontal view of the human thorax with the lungs. The right lung is highlighted in blue and is shown being removed, leaving the left lung in place.

Figure 3.6: Types of pulmonary resection

Taken from online resource: (Global resource for the advancing cancer education (GRACE), 2019)

3.7 FUNCTIONAL LUNG LOSS

Functional loss post pulmonary resection is an inevitable consequence of removal of lung parenchyma. The extent of dysfunction depends on the type of resection (i.e. the volume of functional lung units removed), the condition of remaining lung units, as well as patient related factors. Consideration of the postoperative outcomes resulting from this functional lung loss need to be considered in the planning and work-up of patients in order to achieve the best treatment outcome. This involves calculation of the predicted postoperative pulmonary function parameters (predicted postoperative forced expiratory volume in 1 second - PPOFEV₁ and predicted postoperative forced expiratory volume -PPOFVC) in relation to the anticipated number of functional lung units required for resection along with consultation and functional evaluation of the patient.

A recent study examining the long term (5 year) outcomes of surgery on pulmonary function, demonstrated that pulmonary function declines with time regardless of surgical procedure (Kobayashi et al., 2017). In this retrospective study, the results of respiratory function parameters (%FEV₁ and %FVC) were compared at postoperative year 1 (POY 1) and postoperative year 5 (POY 5). The results indicated that respiratory function declined with pulmonary resection up to postoperative year 5 regardless of type of procedure (no significant differences were observed in 'rate of decline' between groups). However, lobectomy decreased pulmonary function to a greater extent than either segmentectomy or partial resection. This result highlights the long-term effects of functional lung loss post resection which is compounded by the known decline in pulmonary function due to the reduced elastic properties of the lung and decreases in respiratory muscle strength that occur with ageing.

3.8 SURGICAL COMPLICATIONS

Complications in thoracic surgery can be classified as intra-operative or postoperative. Complications differ with the type of surgical approach (thoracotomy versus minimally invasive) and the extent of pulmonary resection. The Clavien-Dindo Classification Score is often used to quantify the severity of postoperative complications in a range of surgical

specialties (see Table 3.3) and has been used extensively in research as it objectively ranks complications in a valid and reproducible manner (Clavien et al., 2009).

Table 3.3: Classification of surgical complications by Clavien-Dindo

Grade I	Non-life threatening, not requiring used of drugs, treated only with bedside intervention and does not lengthen hospital stay longer than twice the median
Grade II	Potentially life-threatening, requiring only drug therapy, total parenteral nutrition or transfusion
Grade III	Life-threatening, requiring therapeutic imaging or endoscopic procedure or reoperation
Grade IV	Complication with residual or lasting disability or objective signs of life-threatening disease
Grade V	Death

3.2.1 Intra-operative complications

Intra-operative complications in thoracic surgery can be broadly categorized into: injury/disruption to the surgical lung field, vascular injuries, unexpected patient-related factors (cardiac arrhythmias, myocardial infarction, renal failure) and conversion to open procedures. Rare intraoperative complications include: cardiac arrhythmias (atrial fibrillation, ventricular tachycardia), lobar torsion and, specific to robotic surgery, complications arising from CO₂ insufflation (CO₂ embolus, compromised venous return, severe bradycardia or progressive arterial desaturation/acid-base disturbance due to hypercarbia (Louie, 2017).

3.2.2 Postoperative complications

Postoperative complications which are common after thoracic surgery include: atelectasis, bleeding, pulmonary oedema, infection (wound or lung), atrial fibrillation, persistent air leak, pneumothorax, chylothorax and respiratory failure. The incidence of developing one or more postoperative complications after surgery is around 20%, with a 2% mortality (Myles, 2015). Other postoperative complications which occur less frequently include: empyema, bronchopleural fistula, anastomotic dehiscence, cardiac

herniation, pulmonary embolism, right ventricle failure and neurological injury. Rare but serious complications include lung torsion (occurring in less than 0.4% of cases) and development of Acute Respiratory Distress Syndrome (ARDS) (occurring in approximately 5% of cases, most commonly pneumonectomy).

3.2.3 Postoperative pulmonary complications

One of the most common complications in the early postoperative period, particularly relevant for physiotherapists, is the development of postoperative pulmonary complications (PPC's). These occur in approximately 3-15% of thoracic cases, and are associated with increased length of stay, intensive care readmission and mortality (P. Agostini et al., 2010). PPC's are caused by retained secretions and lack of aeration of the alveoli (atelectasis) with subsequent loss of volume causing collapse of lung parenchyma. Resolution of the collapsed portion of the lung is assisted by postoperative interventions aimed to increase lung volume and/or secretion clearance such as postoperative physiotherapy and early mobilization. Preventing PPCs has been a focus of much of the prehabilitation literature in lung cancer over recent years.

3.9 RECOVERY and POSTOPERATIVE PHYSIOTHERAPY

Postoperative recovery after pulmonary resection involves the medical management of potential early postoperative complications (i.e. air leak, pain, wound healing) along with multidisciplinary allied health, in particular physiotherapy for respiratory therapy (as indicated) and early mobilization. Thoracic surgery pathways, incorporating evidence-based practice guidelines to deliver the best standard care, have become more commonplace (see Table 3.4). These clinical pathways provide clear milestones that enable organized and efficient care of the patient under a particular surgical specialty or after a specific surgical procedure. Deviation from the pathway can therefore be recorded and appropriate intervention delivered. The main aims of these pathways are to minimize recovery time, decrease the physical impact of the operation to the patient, minimize complications from the operation and evaluate/treat complications that do

occur (Wei & Cerfolio, 2016). Ultimately this leads to a reduced hospital length of stay and improved quality of care for the patient.

Physiotherapy interventions after thoracic surgery aim to prevent or treat postoperative pulmonary complications (PPC) and enhance early postoperative function to facilitate fast discharge from hospital. Postoperative physiotherapy (during the inpatient hospital stay) for most patients after pulmonary resection for lung cancer is part of routine clinical practice in Australia and most countries globally. Routine post-operative physiotherapy treatments include early mobilization (from postoperative day 1), sitting out of bed and supported coughing and are utilized within the short postoperative stay (generally < 7 days). Additionally, once chest tubes/intercostal catheters are removed, gentle shoulder range of motion exercises can be prescribed to improve function (C. L. Granger, 2016). Table 3.4 outlines a standard postoperative clinical pathway post thoracic surgery.

Additional prophylactic postoperative targeted respiratory/chest physiotherapy such as breathing exercises for routine thoracic surgery patients on a clinical pathway is not recommended and currently the evidence suggests that the addition of prophylactic targeted respiratory physiotherapy (deep breathing and coughing) to usual care (consisting of clinical pathways and early mobilization) provides no benefit in terms of PPC rate or hospital length of stay (Reeve et al., 2010). Further evidence also suggests that respiratory therapies such as incentive spirometry, intermittent positive pressure breathing, flutter, positive pressure devices or breathing and coughing exercises provide no additional benefit on development of PPCs or length of stay (Rodriguez-Larrad, Lascurain-Aguirrebena, Abecia-Inchaurregui, & Seco, 2014). Enhanced minimally invasive surgical techniques as well as improved perioperative care (pre-admission clinic, pain management, use of clinical pathways and advanced intercostal catheter design) have contributed to a lower rate of PPCs, therefore the need to direct physiotherapy resources to early assessment of patients (both pre and postoperatively) and to identify patients at high risk of PPCs will lead to better recovery and surgical outcomes.

Lastly, postoperative physiotherapy aims to prepare the patient for discharge from hospital, ultimately at the most functionally independent state possible. The

physiotherapy interventions mentioned above in the acute postoperative recovery, along with thorough functional assessment and progressive return to normal activities of daily living/mobility levels, highlight the important role played by the physiotherapist in the recovery phase to ensure timely discharge.

Table 3.4: Standard clinical thoracic surgery pathway

(C. L. Granger, 2016)

Box 2. Example clinical pathway for patients after thoracotomy.
Day 1 postoperative • Sit out of bed in ward chair • Ambulate ≥ 20 m on ward $\pm$ portable supplemental oxygen if required to keep $\text{SpO}_2 \geq 95\%$ $\pm$ portable suction if large air leak present $\pm$ assistance from one person if required $\pm$ gait aid if patient is unable to ambulate despite assistance from one person • Teach supported cough with towel wrap • Commence respiratory physiotherapy if indicated (high-risk patient or presence of PPC) Day 2 postoperative • Ambulate ≥ 50 m on ward $\pm$ portable supplemental oxygen if required to keep $\text{SpO}_2 \geq 95\%$ $\pm$ portable suction if large air leak present $\pm$ assistance from one person if required $\pm$ gait aid if patient unable to ambulate despite assistance from one person • Encourage supported cough • Commence or continue respiratory physiotherapy if indicated (high risk or presence of PPC) Day 3+ postoperative • Review by physiotherapist only if patient requires ongoing mobility assistance or respiratory physiotherapy Once intercostal catheters are removed • Teach upper limb and thoracic mobility range of motion exercises • Physiotherapy completes a discharge mobility assessment and provides any discharge planning as required for safety

3.10 SUMMARY

Surgery is the first line treatment for resectable early stage NSCLC, the type and extent of surgery required is dependent on the location and stage of disease. Due to the inherent risks of surgery, thorough preoperative assessment must be performed to determine patient suitability and ensure optimal outcomes. Other factors to consider in thoracic surgery which have been covered in this chapter include: functional lung loss, potential complications, postoperative recovery and the role of physiotherapy after surgery. The next chapter will discuss the role of prehabilitation prior to surgery for lung cancer.

CHAPTER 4 PREHABILITATION

4.1 INTRODUCTION

This chapter begins with a general background on the concept of prehabilitation, looking at the components, target populations and outcomes. The focus will then shift to prehabilitation in lung cancer specifically with greater detail about the research to date on this topic.

Preoperative optimisation of the surgical patient is not a new concept. A plethora of literature has been published within the general surgical population, which demonstrates that enhancing cardiorespiratory fitness and functional capacity prior to surgery, particularly in high-risk patients, accelerates postoperative recovery and reduces postoperative morbidity (Levy, Grocott, & Carli, 2019; O'Doherty, West, Jack, & Grocott, 2013; Valkenet, 2011). Within recent years, the importance of this preoperative optimisation has been widely recognised and has resulted in the concept of prehabilitation, which encompasses more than preoperative physical conditioning. In the period between diagnosis and definitive treatment, prehabilitation provides the ideal time to improve cardiometabolic risk (Myers, 2016). As one of the key aims of prehabilitation is to reduce the risks and complications of planned procedures, it has also been more widely incorporated into other medical specialties, for example there is emerging evidence for its efficacy in stem cell transplant and non-surgical prostate cancer treatments. Its potential to reduce the postoperative morbidity and mortality associated with surgery remains the focus of much of the work that is currently being conducted in the field of prehabilitation.

Internationally, three recent reports have recommended that prehabilitation be included as a component of the cancer care pathway (MacMillan Cancer Support, 2018; National Academies of Sciences, 2018; Stout et al., 2016), however these recommendations have been slow to translate into the Australian setting and robust evidence within the lung cancer population has lagged behind other cancer cohorts. This chapter will introduce general prehabilitation and then focus specifically on prehabilitation for individuals with lung cancer prior to lung resection surgery. It will address primarily the physical pre-

conditioning (exercise) of patients as this was the major focus of the studies included in this research.

4.2 PREHABILITATION IN ONCOLOGY

4.2.1 Components of prehabilitation

Within the oncology setting, prehabilitation has been described as *“a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment that, in the perioperative setting, aims to enhance functional capacity of the individuals to enable them to withstand the stress associated with a procedure. It includes a care bundle involving smoking cessation, diet optimization, psychosocial support and exercise that identify impairments and provide targeted interventions that improve patient outcomes.”* (Julie K. Silver & Baima, 2013). Within the general surgical oncology population, prehabilitation offers a means of: enhancing the patient’s physical status, buffering treatment-related deconditioning, managing comorbidities (Faithfull et al., 2019), enhancing longer term HRQoL and reducing anxiety (Tsimopoulou et al., 2015) and improving postoperative outcomes such as hospital length of stay and postoperative complications (Piriaux, Caty, & Reychler, 2018; Treanor et al., 2018).

Prehabilitation has evolved into a multi-modal assessment and treatment process delivering a variety of different preoperative interventions to enhance postoperative morbidity and mortality. These are summarised in Table 4.1. There is the opportunity to assess and intervene in multiple components and hence optimize many aspects of a patient’s preoperative work-up, the effect being enhanced quality of cancer care and improved outcomes for the patient with cancer (figure 4.1). Despite all the work on prehabilitation to date, *which* components produce the greatest effect and in *what* combination remains unknown. Research in lung cancer, which is covered in subsequent sections, have focused specifically on the exercise component of prehabilitation, which is the focus of this thesis.

Table 4.1: Components of multimodal prehabilitation

Prehabilitation component	Description (evidence)	Recommendation
Exercise training	<i>“Diminished cardiopulmonary exercise testing (CPET) scores and low walking capacity levels are identified as risk factors for increased postoperative morbidity and mortality after major surgery” (Snowden et al., 2010).</i> Epidemiological evidence consistently indicates that individuals with positive exercise behaviours demonstrate improved cancer-free survival and reduced all-cause mortality (Ismail 2018). Exercise has also been shown to minimize physical decline, fatigue, psychological distress and reduced quality of life caused by cancer and its treatment (Ismail et al., 2018).	• Aerobic and resistance exercise, plus flexibility/stretching exercises (Scheede-Bergdahl, Minnella, & Carli, 2019; Tew, Ayyash, Durrand, & Danjoux, 2018) • Follow the current physical activity for cancer survivor guidelines (i.e. moderate intensity physical activity at least 3 times per week for 30 minutes (program duration 8-12 weeks) and muscle strengthening activities 2 or more days per week involving major muscle groups) (Campbell et al., 2019) • Be of moderate intensity (measured either via BORG scale, 12-14 on Rating of Perceived Exertion Scale (RPE) or 50-70% of heart rate reserve (HRR) Karvonen formula) (Banugo & Amoako, 2017) • Tailored and individualized to the individual (Tew et al., 2018) • Supervised, delivered and progressed by professionals with relevant expertise (Tew et al., 2018) • Consider inclusion of inspiratory muscle training or incentive spirometry in specific surgical cohorts (Tew et al., 2018)
Nutrition	<i>Diet modification and/or supplementation. Malnutrition has been detected in up to 50% of patients with cancer. Strong associations have been shown between malnutrition and poorer postoperative outcome (Ismail et al., 2018)</i>	• Ensure adequate protein consumption to achieve anabolism • Enhance immunity • Support normal blood sugar levels

		• Ensure adequate energy levels to maintain normal body weight • Promote gastrointestinal tolerance (decrease incidence of nausea and vomiting) • Ensure adequate nutrient intake and providing supplementation where deficits exist • Improve appetite recovery
Smoking cessation	<i>The systemic effects of smoking lead to an increased incidence of postoperative complications, delayed wound healing, increased risk of wound infection and cardiorespiratory complications (D. Z. Levett et al., 2016). Cessation of smoking prior to surgery has been associated with reduced risk of postoperative complications, improved performance status and higher quality of life measures (Sorensen, 2012).</i>	• Counselling of current smokers prior to surgery in an attempt to reduce or cease smoking • Offer of nicotine replacement therapy • Cessation of smoking at least 4 weeks prior to surgery (shorter timeframes increase the relative risk (RR) of developing a PPC: < 2 weeks RR 1.20 (95% CI 0.96,1.50), 2-4 weeks RR 1.14 (95% C.I 0.90, 1.45) and > 8 weeks RR 0.53 (95% C.I 0.37, 0.76) (Wong, Lam, Abrishami, Chan, & Chung, 2012) • Reinforcing abstinence post-surgery
Alcohol cessation	<i>Safe long-term alcohol levels and the effect this has on postoperative outcomes has not been extensively studied. The known effects of excess alcohol consumption include: chronic immune dysfunction, cardiac insufficiency and arrhythmias, increased bleeding time and exaggerated neurohumoral response to surgery (Tonnesen, Nielsen, Lauritzen, & Moller, 2009).</i>	• Counselling regarding reduction or cessation of alcohol prior to surgery • Objective quantification of alcohol intake pre-admission • Support for alcohol withdrawal (e.g. vitamin supplementation) as indicated
Psychological	<i>Psychological distress is not uncommon in patients undergoing major surgery and may be related to a number of factors such as diagnosis, the actual treatment or disability related to the disease or surgery itself (D. Z. Levett et al., 2016). Qualities such as</i>	• Screening of psychological distress prior to cancer treatment or surgery • In consultation with the patient, referral to psychologist or counsellor where known preoperative psychological risk factors are identified

	<i>depression, anxiety, health beliefs, expectations, coping strategies and past experience play a huge role in the preparation and recovery after surgery. Even after known psychological factors are accounted for, presence of anxiety and depression can predict surgical outcomes (Rosenberger, 2006). Which psychological factors are modifiable is highly variable and outcomes after surgery may be partly related to 'fixed' personality type/traits (Contrada et al., 2008)</i>	• Trial of cognitive behavioural therapy • Anxiety reduction strategies such as relaxation training, deep breathing exercises, visualization, yoga and music therapy
Identification of anaemia	Screen for anaemia and the need for iron therapy. <i>Perioperative anaemia occurs in up to 76% of patients with cancer and may lead to adverse outcomes following major surgery (Ismail et al., 2018).</i>	• Preoperative assessment and correction of low haemoglobin • Treatment with iron therapy when anaemia is identified • Treatment with erythropoietin has not been extensively studied therefore its effect on postoperative outcomes are unknown
Education/expectations	Clarify patient and family understanding of care. <i>Preoperative education has been widely used in a number of surgical cohorts and more recently has demonstrated clear benefits in reducing postoperative morbidity (Boden et al., 2018; Moore, Conway, Thomas, Cummings, & Atkinson, 2017). The purpose of providing preoperative education is to involve the patient in the preparation of their surgery and arm them with the information they need to enhance their peri and postoperative experience.</i>	• Attendance at pre-admission clinic or Surgery School prior to surgery • Provision of written or audio-visual resources with the intended educational material • Opportunity for patients to ask questions and participate in the preparation for surgery • Included topics: type of surgery, standard postoperative course, expected length of stay/discharge options, risk factors for postoperative complications, preoperative guidance for physical activity levels/ oral health/ nutrition/ breathing exercises, family support and expected roles as well as advice about general health.

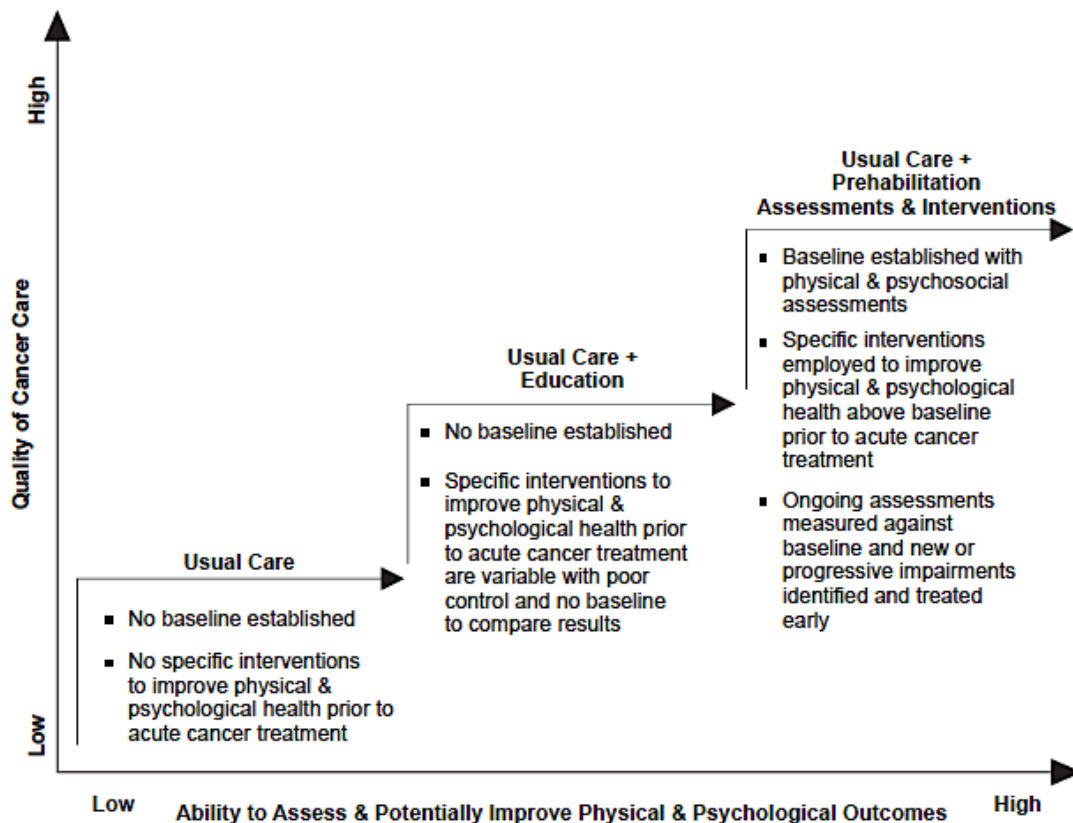


Figure 4.1: Cancer prehabilitation vs usual care

(J. K. Silver, 2015)

4.2.2 Target population

Who best benefits from prehabilitation is a question which remains to be answered. Studies have found varied benefits for prehabilitation across different cancer tumour streams/surgical specialties, either in terms of patient outcomes, functional capacity or postoperative morbidity. In fact the only population studied where prehabilitation has shown minimal benefit has been patients who have had knee or hip arthroplasty for osteoarthritis (Cabilan, Hines, & Munday, 2015). As prehabilitation has been shown to prepare the patient physically, psychologically and/or emotionally for their scheduled treatment (Santa Mina, Scheede-Bergdahl, Gillis, & Carli, 2015) it would seem plausible that almost all oncology patients presenting for surgery would benefit from one or more of the components of multimodal prehabilitation. However, perhaps targeting the factors that have been

shown to lead to the worst outcomes, e.g. identified modifiable risk factors and those with deficits in functional capacity, would be a more economical and efficient way to implement prehabilitation.

One such at-risk population is the older person. This group is more susceptible to the negative effects of surgical stress and may suffer prolonged impairment, never completely regaining their premorbid level of function (Carli et al., 2017). This is because of the reduced resilience and increased vulnerability that occurs with age due to the consequences of multiple comorbidities, polypharmacy and physical decline making the individual more prone to frailty (Gurlit & Gogol, 2019). Age combined with poor preoperative fitness and physical status serve to increase risk for serious postoperative complications and prolonged disability (Wilson, Davies, Yates, Redman, & Stone, 2010). Two recent studies, one in lung cancer and the other in upper gastrointestinal cancer, have specifically examined the effect that prehabilitation has on older patients (> 70 years) undergoing cancer surgery. The first study by Lai et al, included 60 older patients with lung cancer randomly allocated to either intervention (7-day prehabilitation program prior to lung resection surgery consisting of exercise endurance training using a NuStep cross-trainer and inspiratory muscle training, n=30) or control groups (no preoperative intervention, n=30). Participants in the intervention group performed the program daily prior to surgery, both groups were measured for exercise capacity (6MWD), pulmonary function (peak expiratory flow - PEF), symptoms and health-related quality of life (EORTC-QLQ C-30 questionnaire) as well as postoperative outcomes (length of stay and 30-day PPCs). The main results of the study indicated that the mean postoperative hospital length of stay was significantly reduced in the intervention group (6.9 days, SD +/- 4 days) compared to the control group (10.7 days, SD +/- 6.4 days) ($p = 0.010$), 30-day PPCs were noted in 4 (13.3%) of the intervention patients and 11 (36.7%) of the control patients with a statistically significant difference between groups ($p = 0.037$). The intervention group also significantly improved in performance between pre and postoperative timepoints in their 6MWD (between group difference 19.2m, $p = 0.029$) and PEF (between group difference 18.0L/min, $p < 0.001$). The author concluded that an intensive 7-

day prehabilitation program in older patients with lung cancer was feasible and demonstrated positive physical and psychological effects (Lai, Huang, et al., 2017). The second study examined the effect of prehabilitation on frail older cancer patients. In this study by Mazzola et al, 76 patients with upper gastrointestinal cancer were assessed for frailty prior to surgery using a modified frailty index. Forty-one patients underwent prehabilitation consisting of: nutritional counselling, smoking cessation, breathing exercises and moderate intensity walking, prior to surgery. Thirty-five patients with comparable disease type/stage and frailty measures were used as a retrospective control. Results showed that prehabilitation had the effect of significantly reducing both 30-day and 3-month mortality as well as overall postoperative complication rates ($p < 0.05$) when compared to the control. No significant differences were found in terms of length of stay, referral to post-discharge institution or hospital re-admission. The study concluded that prehabilitation for frail older surgical patients provided modest benefits and should be considered as a means of reducing postoperative morbidity and mortality in this population (Mazzola et al., 2017). Clearly both of these studies demonstrate that prehabilitation in older cancer patients is safe and feasible, however further robust studies in other cancer cohorts are required to build on this evidence. Interdisciplinary teamwork in the form of multimodal prehabilitation for these frail older patients will serve to enhance their cancer journey and optimise the outcomes of their treatment (Gurlit & Gogol, 2019).

Another patient population with significant gains to be made from prehabilitation includes patients identified as having low or reduced baseline exercise capacity. It is known that patients with cancer present with reduced levels of physical activity as a result of their disease and symptoms (C. Granger et al., 2014) and conversely that positive associations exist between increasing levels of physical activity and improved quality of life, cancer-specific mortality and all-cause mortality for survivors of cancer (Gunnell et al., 2017). An article by Minella et al emphasizes the point that individuals with poor baseline exercise capacity have the most to gain from participation in prehabilitation. In this cohort study of 106 cancer patients undergoing colorectal surgery, multimodal prehabilitation (aerobic and resistance

exercise, nutrition counselling and protein supplementation plus anti-anxiety techniques) was assessed to determine its effects on functional capacity in patients with varied levels of fitness. The sample was divided into groups based on 6-minute walk test distance (6MWD) as previous studies have shown that a 6MWD of < 409m is predictive of peak oxygen uptake (peak VO_2) < 15mL/kg/min^{-1} measured with CPET (the gold standard in exercise testing) and indicative of low functional capacity (Sinclair, Batterham, Davies, Cawthorn, & Danjoux, 2012). Group A included patients with a 6MWD > 400m (66%, n=70) and Group B included patients with a 6MWD < 400m (34%, n=36). As well as functional capacity (measured by change in 6MWD), other secondary outcome measures included self-reported physical activity and HRQoL. Results of the study showed that, after prehabilitation, patients in Group B with lower baseline fitness had greater improvements in functional walking capacity (+46.5m, SD 53.8) compared to those in Group A with higher baseline fitness (+22.6m, SD 41.8) ($p = 0.012$). Also, at 4 weeks post-surgery, those in Group B were more likely to have recovered to their baseline 6MWD than those in Group A with higher fitness (74% vs 50%, $p = 0.029$). No difference was found in any of the secondary outcomes. The study concluded that those with lower baseline fitness (6MWD < 400m) showed greater improvement throughout the perioperative period and were able to make more meaningful improvements in physical function compared with those with higher preoperative levels of fitness (Minnella et al., 2016). Although these results have not been replicated in other cancer cohorts, strong evidence does exist for inactivity being associated with increased morbidity and all-cause mortality (Richardson, Levett, Jack, & Grocott, 2017). This provides a strong case for prehabilitation programs targeting this population with reduced levels of physical activity and reduced exercise capacity. Figure 4.2 demonstrates factors to consider when attempting to increase an individual's functional capacity prior to treatment or surgery in a 'prehabilitation triangle'.

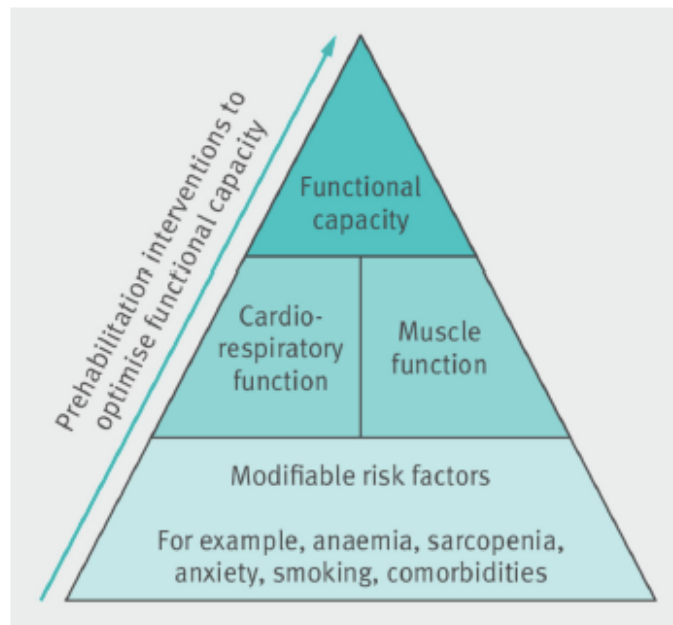


Fig 1 Prehabilitation triangle

Figure 4.2: Increasing functional capacity with prehabilitation

Taken from (Wynter-Blyth & Moorthy, 2017)

4.3 PREHABILITATION IN LUNG CANCER

Topical interest in prehabilitation has stimulated a large amount of research investigating the effect of prehabilitation in the lung cancer population. Table 4.2 provides details of the trials currently registered on clinicaltrials.gov and outlines the ongoing work within the field of prehabilitation in lung cancer. Early studies examined the safety of exercise within this patient population and concluded that preoperative exercise is safe (L. E. Jones, N.D; Waner,E; Joy,A.A, 2009; L. W. Jones et al., 2007; Schmitz K, 2005). Since 2011, 10 systematic reviews (inclusive of 10 randomized controlled trials) and 1 Cochrane Review have been published which examine different components of preoperative exercise intervention and their effects on various outcomes. Table 4.3 summarises the systematic reviews and Table 4.4. summarises the 10 RCTs completed to date. The RCT's within table 4.4 have been scored with a Physiotherapy Evidence Database: (PEDro) score, this was developed to help identify clinical trials that are likely to be internally valid and have sufficient statistical information to make their results interpretable. Each

RCT is scored on a 0 - 10 scale, the mean methodological quality score is 5.4 (Moseley, Herbert, Maher, Sherrington, & Elkins, 2011) and higher scores represent trials with better methodological quality. The research outlined in tables 4.3 and 4.4 provides the best evidence in support of prehabilitation within the lung cancer population (Cavalheri & Granger, 2017; Crandall, Maguire, Campbell, & Kearney, 2014; Driessen et al., 2017; C. L. Granger, McDonald, Berney, Chao, & Denehy, 2011; Mainini et al., 2016; Ni et al., 2017; Pouwels et al., 2015; Rodriguez-Larrad et al., 2014; Rosero et al., 2019; R. Sebio Garcia, Yanez Brage, Gimenez Moolhuyzen, Granger, & Denehy, 2016; Steffens, Beckenkamp, Hancock, Solomon, & Young, 2018). Many of these reviews involving patients with lung cancer examine the effects of exercise both in the preoperative and postoperative/post cancer treatment (survivorship) stages. This can make definitive conclusions about the effects of exercise intervention in lung cancer challenging. Due to the heterogeneity of the exercise interventions included in these studies, variable time points assessed and outcome measures used, meta-analysis was only performed in 3 of 10 systematic reviews. For the purpose of this review of the literature, only the preoperative/prehabilitation studies included in these reviews will be discussed and opportunities for future research will be explored.

Table 4.2: Registered studies on clinicaltrials.gov (accessed June 2020)

Title of study	Status	Location	Intervention
Multimodal prehabilitation in thoracic surgery	Recruiting	Spain	Multimodal prehabilitation vs Usual care
The impact of trimodal prehabilitation strategy on patients undergoing thoroscopic lobectomy	Completed	China	Behavioural trimodal prehabilitation
Multimodal prehabilitation to enhance functional recovery after lung surgery	Completed	Canada	Physical exercise + dietary supplementation + behavioural relaxation techniques
Physiotherapy prehabilitation in patients undergoing cardiac or thoracic surgery	Completed	United Kingdom	Walking program + incentive spirometer + deep breathing exercises
Comparing the impact of multimodal prehabilitation to aerobic training on patients undergoing thoroscopic lobectomy	Not yet recruiting	China	Multimodal prehabilitation vs aerobic training
Effect of two different preoperative training densities in patients with non-small cell lung cancer before lung resection surgery	Recruiting	France	Preoperative pulmonary rehabilitation

Table 4.3: Summary of Systematic Reviews and Reviews of Prehabilitation in Lung Cancer

Author	Included studies	Title	Intervention timing	Main pre-operative exercise results
Granger* 2011	16 studies 675 patients	Exercise intervention to improve exercise capacity and health related quality of life for patients with non-small cell lung cancer: a systematic review	Both pre and postoperative	Exercise intervention is safe before cancer treatment. Interventions were associated with improvements in exercise capacity, symptoms and some domains of HRQoL
Crandall* 2014	20 studies identified (inclusive of 8 RCTs), 575 patients	Exercise intervention for patients surgically treated for non-small cell lung cancer (NSCLC): a systematic review	Both pre and postoperative	Exercise intervention compared with usual care pre-surgery is associated with improved cardiorespiratory exercise capacity, increased muscle strength and reduced fatigue, postoperative complications and length of stay
Rodriguez-Larrad* 2014	8 studies identified, 599 patients.	Perioperative physiotherapy in patients undergoing lung cancer resection	Both pre and postoperative	Pre-surgical interventions based on moderate-intensity aerobic exercise were associated with improvements in functional capacity and reduced postoperative morbidity
Pouwels* 2015	10 studies (inclusive of 4 RCT's) 277 patients	Preoperative exercise therapy in lung surgery patients: a systematic review	Preoperative	Preoperative intervention based on moderate-to-intense exercise was associated with improvements in aerobic capacity, physical fitness and quality of life, as well as reductions in postoperative complications and hospital length of stay

Author	Included studies	Title	Intervention timing	Main pre-operative exercise results
Bade 2015	n/a	Increasing physical activity and exercise in lung cancer: reviewing safety, benefits and application		Exercise is safe and beneficial in all stages of lung cancer and in lung cancer survivors. Benefits shown in: HRQoL, improved symptoms, exercise tolerance, post-op complications. Ideal program or means of implementation is still unknown. Patients identify pre-treatment counselling and referral to health professionals as barriers.
Sebio-Garcia** 2016	21 studies on 17 patient samples (inclusive of 5 RCTs) 1189 patients	Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis	Preoperative	Preoperative exercise-based intervention increases exercise capacity and improves pulmonary function before surgery, and may have beneficial effects on hospital length of stay and postoperative pulmonary complications (more research needed as studies were too heterogenous)
Mainini* 2016	Update of the SR done by Crandall in 2014. 6 studies (6 RCTs) 414 patients	Perioperative physical exercise interventions for patients undergoing lung cancer surgery: what is the evidence?	Both preoperative and postoperative	Pre-op intervention should include aerobic, resistance and breathing exercises and be 2-4 weeks duration. Current evidence show inconsistent results and variable protocols therefore firm conclusions are difficult. More RCTs required.
Ni** 2017	15 studies (8 RCTs) 350 patients	Exercise training for patients pre and post-surgically treated for non-small cell lung cancer: a systematic review and meta-analysis	Both preoperative and postoperative	Preoperative exercise training shortens LOS, decreases PPCs and increases 6MWD.
Driessen* 2017	11 studies (4 RCTs)	Effects of prehabilitation and rehabilitation including a home-	Both preoperative	Improvements in physical fitness were shown in prehabilitation studies. Combining (home-based)

Author	Included studies	Title	Intervention timing	Main pre-operative exercise results
	451 patients	based component on physical fitness, adherence, treatment tolerance and recovery in patients with non-small cell lung cancer: a systematic review	and postoperative	resistance and endurance training, along with supervision and personalization, optimizes adherence, treatment tolerance and recovery
Cavalheri 2017	5 RCT's 167 patients	Preoperative exercise training for patients with non-small cell lung cancer (Review)	Preoperative	Preoperative exercise training reduced the risk of developing a PPC by 67%, reduced the number of days needing a chest tube (-3.3 days) and reduced hospital length of stay by 4.24 days. Preoperative exercise intervention also improves exercise capacity and FVC. Included studies had high risk of bias and small sample sizes.
Li 2017	n/a	Prehabilitation and rehabilitation for surgically treated lung cancer patients	Both preoperative and postoperative	Review of prehabilitation in lung cancer resection. Pre-op interventions aim to: optimize physical status and medical stability prior to surgery, reduce post-op morbidity and increase % of operable cases.
Kendall 2017	n/a	The role of physiotherapy in patients undergoing pulmonary surgery for lung cancer: a literature review	Included pre, peri and postoperative	Pre-op = aims of physiotherapy should be to reduce PPCs and LOS by using IMT, exercise, and education re: healthy lifestyle
Steffens* 2018	17 studies (11 RCT's) reporting on 13 different trials including 806 patients.	Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer	Preoperative	Preoperative exercise intervention significantly reduces postoperative complications by 48% and shortens hospital length of stay by 3 days in patients with lung cancer

Author	Included studies	Title	Intervention timing	Main pre-operative exercise results
Sanchez-Lorente 2018	n/a	Prehabilitation in thoracic surgery	Preoperative	Review of the literature for prehabilitation in lung cancer. Prehabilitation is safe, high intensity interval training (HIIT) of 2-6 weeks duration appears to be best method. Patients with impaired lung function may be the ones that benefit most from prehabilitation in lung cancer
Templeton 2019	n/a	Preoperative rehabilitation for thoracic surgery	Preoperative	Review of literature on preoperative rehabilitation pathways in thoracic surgery. Prehabilitation programs are an effective tool to reduce an individual's perioperative risk and therefore improve postoperative recovery and reducing postoperative morbidity. Prehabilitation must be a multidisciplinary approach and include: exercise, smoking cessation, correction of anaemia, improving nutrition and optimizing oral hygiene.
Rosero** 2019	10 studies (10 RCT) 676 patients	Systematic review and meta-analysis of randomized controlled trials on preoperative exercise interventions in patients with NSCLC	Preoperative	Preoperative exercise intervention induced improvement in walking endurance, peak exercise capacity, dyspnoea, risk of hospitalization and PPCs.

Key: * indicates systematic reviews without meta-analysis, ** indicates systematic reviews with meta-analysis, RCT – randomized controlled trial, NSCLC – non-small cell lung cancer, HRQoL – health related quality of life, HIIT – high intensity interval training, LOS – length of stay, PPC – postoperative pulmonary complications, ROM – range of motion, IMT – inspiratory muscle training, FVC – forced expiratory volume, 6MWD – six minute walk distance, n/a – not applicable (narrative review)

Table 4.4: Exercise trials (RCT) in lung cancer prehabilitation

Reference Year	Intervention	Duration Frequency	Participants	Outcomes	PEDRO Score
(Benzo et al., 2011)	Two studies: I. NR II. Two conditions: 1. (a) EET (LE/UE) (NuStep): 20min (b) Strength alternating UE/LE every other day (Thera-band):2 sets of 10–12 rep (c) (IMT) (Threshold IMT or the P-Flex valve) (EG): 15–20 min of daily use. 2. Usual care (CG)	I. 4 weeks II. 1 week 2 times a day	I. 9 patients were randomized II. 17 patients were randomized	I. Feasibility II. Hospitalization postoperative days PPCs	6/10
(Stefanelli et al., 2013)	Two conditions: 1. (a) IMT: Respiratory exercises on the bench, mattress pad and wall bar. (b) EET: High intensity training of UE (rowing ergometer) and LE (treadmill and the ergometric bicycle), 70% PWC (c) Pharmacotherapy (bronchodilators, inhaled corticosteroids) 2. Usual care (CG)	3 weeks 5x/week	N = 40	FEV1 (L) VO2peak (mL/kg/min) DLCO (ml/min/mmHg) Dyspnoea	4/10
(Morano M, 2014)	Two conditions: 1. (a) Stretching LE/UE (b) warm-up exercises (c) strengthening UE (50% PWC), PNF (barbells) (d) EET(treadmill) 80% PWC	4 weeks 5x/week	N = 30	6MWD (meters) HRQoL	7/10

Reference Year	Intervention	Duration Frequency	Participants	Outcomes	PEDRO Score
	(e) IMT (f) educational sessions 2. (a) CPT (routine protocol of the hospital comprising lung expansion techniques): -sustained maximum inspiration -fractional inspiration -breathing patterns -pursed lip breathing -use of a flow-based incentive spirometer (Respirom) (b) Educational sessions (CG)				
(Lai, Su, Yang, Zhou, & Che, 2016)	Two conditions: 1. I. Pharmacotherapy (Bricanyl, Pulmicort, Mucosolvan): 2 times/day; II. Physical rehabilitation: (a) IMT-ABT: (20–30 rep in 15–30min), -TBT (Voldyne 5000): 2–3 sets, 12–20 rep/2 h (b) -EET-LE (NuStep): 15–20 min/day, -Climbing ladder training (EG):15–30 min/day 2. Underwent standard preoperative (CG)	1 week Daily	N = 48	Hospitalization postoperative days PEF (L/min) 6MWD (meters) HRQoL Physical function Emotional function Dyspnoea Fatigue PPCs	4/10
(Huang et al., 2017)	Three conditions: 1. (a) IMT-ABT: two to three times daily for 15–20 min/s -TBT (Voldyne 5000): 20 min at least four times daily	1 week Twice/day	N = 60	Hospitalization postoperative days PPCs 6MWD (meters)	Nil found

Reference Year	Intervention	Duration Frequency	Participants	Outcomes	PEDRO Score
	(b) CRT (NuStep): twice daily for 20 min/s (c) psychological educational guidance (EG) 2. Single IMT (SG) 3. Routine preoperative preparation (CG)			PEF (L/min) FEV1 (L) FVC (L) Fatigue Dyspnoea DLCO (mL/min/mmHg) HRQoL Physical function Emotional function	
(Lai, Huang, et al., 2017)	Two conditions: 1. (a) IMT-ABT: twice per day 15–20 min/s: -TBT (Voldyne 5000): 3 sets /day 20 min/s. (b) EET (NuStep): 30 min/day 2. Usual care (CG)	1 week Daily	N = 60	Hospitalization postoperative days PEF (L/min) FVC (L) FEV1 (L) DLCO (ml/min/mmHg) 6MWD (meters) HRQoL Physical function Emotional function Dyspnoea PPCs	7/10
(Lai, Su, et al., 2017)	Two conditions: 1. (a) IMT-TBT (HUDSON RCI 2500): 3 sets/day, 20 rep/s: -ABT:	1 week Daily	N = 101	Hospitalization postoperative days PEF (L/min)	7/10

Reference Year	Intervention	Duration Frequency	Participants	Outcomes	PEDRO Score
	twice per day 15–30 min/s. (b) EET (NuStep): 30 min/day 2. Usual care (CG)			6MWD (meters) HRQoL Physical function Emotional function Dyspnoea Fatigue PPCs	
(R. Y.-B. Sebio Garcia, M.I; Gimenez Moolhuyzen,E, 2017)	Two conditions: 1. (a) EET moderate (cycle ergometer-Monark): -30 min interval training -5 min warm-up (30% PWC)-1 min (80% PWC) -4 min (active rest 50% PWC).-4 min cool down (30% PWC) (b) CRT: - elastic bands (Thera-Band®) body-weight exercises: six different exercises:15 re, 3 sets, 45 sec micropause (increased to 4 sets if tolerated) (c) IMT (Coach 2 Incentive Spirometer®). -TBT: 2 s/day 30 sustained inspirations (80% MVC) end inspiratory hold (2–3 s). 6 cycles _ 5 rep, 1 min pause/cycle. 2. Usual care (CG)	3-4 weeks 2-3x/week	N = 40	Hospitalization postoperative days PPCs 6MWD (meters) Physical Component Physical functioning Emotional function	6/10
(Licker et al., 2016)	Two conditions: 1. (a) Warm-up: 5 min (50% PWC): 2 sets _ 10 min [(interv 15 s (80–100% PWC), micropause 15sec, macropause 4 min/s: Cool down: 5 min (30% PWC) (b) EET (cycle ergometer)	3-4 weeks 2-3x/week	N = 164	VO2peak (mL/kg/min) 6MWD (meters) PPCs Hospitalization	8/10

Reference Year	Intervention	Duration Frequency	Participants	Outcomes	PEDRO Score
	(c) strengthening UE/LE: leg press, leg extension, back extension, seat row, biceps curls or chest and shoulder press 2. Usual care (CG)			postoperative (days)	
(Karenovics et al., 2017)	Two conditions: 1. (a) Warm-up: 5 min (50% PWC): 2 sets of 10 min (intervals 15 s sprint and 15 s pause, macropause 4 min/s): Cool down: 5 min (30% PWC) (b) EET (cycle ergometer) 2. Usual care (CG)	2-4 weeks 3x/week	N = 164	VO2peak (mL/kg/min) PPCs	8/10

Table adapted from Rosero et al 2019 (pages 5-8)

Key: Preoperative pulmonary rehabilitation (PPR), lower extremity (LE), upper extremity (UE), experimental group (EG), control group (CG), single group (SG), exercise endurance training (EET), inspiratory muscle training (IMT), postoperative pulmonary complications (PPCs), adverse events (AE), standard deviation (SD); not reported (NR); abdominal breathing training (ABT), thoracic breathing training (TBT), 6-min walking distance (6MWD), peak expiratory flow (PEF), health-related quality of life (HRQoL), chest physical therapy (CPT), peak work capacity (PWC), unsupported upper limb exercise test (UULEX), whole-body vibration training (WBVT), conventional resistance training (CRT), maximal vital capacity (MVC), video-assisted thoracoscopy (VATS), non-small-cell lung cancer (NSCLC), forced vital capacity (FVC), peak of oxygen consumption (VO2peak), forced expiratory volume in one second (FEV1), diffusion capacity of the lung to carbon monoxide (DLCO), chronic obstructive pulmonary disease (COPD), high intensity interval training (HIIT), proprioceptive neuromuscular facilitation (PNF).

PEDRO score – Physiotherapy Evidence Database: the PEDro scale was developed to help the users of the PEDro database to rapidly identify clinical trials that are likely to be internally valid and have sufficient statistical information to make their results interpretable (PEDro, 1999)

4.3.1 Aims of prehabilitation in lung cancer

Prehabilitation for patients with lung cancer can be thought of as aiming to fulfil one of two clinical scenarios: to increase functional capacity in patients with borderline fitness for surgery so they may be re-evaluated as fit for surgery or to maximize an operable patient prior to surgery and reduce the risk of postoperative morbidity and mortality.

→ Improving fitness for surgery

Capitalising on the waiting period between cancer diagnosis and surgery, prehabilitation provides a means of optimising multiple facets of an individual's 'current state' in order to better prepare them for the stress of treatment/surgery as well as attempting to reduce postoperative morbidity. This is particularly relevant as it has been recognised that surgery is associated with a 40% reduction in functional capacity (Carli & Scheede-Bergdahl, 2015). Providing interventions in the postoperative period to address the deficits following surgery may not be the most opportune time. Instead, beginning interventions in the preoperative period by actively engaging the patient in the preparation for their surgery has been shown to have both physical and psychological benefits (D. Z. H. Levett & Grimmett, 2019) as well as enhancing physiologic reserve and facilitating recovery (Carli & Scheede-Bergdahl, 2015).

The physiological basis by which prehabilitation delivers positive effects includes improvements in cardiovascular, respiratory, muscular, neural and endocrine systems. Regular bouts of exercise induce stress on the body, which in turn assists the body to adapt and become more efficient in its response to stress (exercise) and therefore more equipped to compensate. *"Trained individuals are able to tax a greater percentage of their functional range, or maximal physiological capacity, during periods of physical stress"* (Carli & Scheede-Bergdahl, 2015). It is known that physiological reserve (functional capacity) diminishes with age (Nigam, Knight, Bhattacharya, & Bayer, 2012) and this may be compounded by a sedentary lifestyle.

Exercise may attenuate the declines in physiological reserve that occur with ageing and buffer some of the negative sequelae of being sedentary such as increased cardio-metabolic risk biomarkers, type 2 diabetes and premature mortality (Dunstan, Howard, Healy, & Owen, 2012). In addition to these factors, surgery itself has negative effects on functional capacity due to surgical trauma and inflammation, along with the effects of cancer disease progression. Prehabilitation which combines exercise training that enhances an individual's physiological capacity, aims to reduce the risks associated with cancer treatment, in particular the stress of surgery. Figure 4.3 demonstrates the effects of prehabilitation prior to surgery and compares the functional decline in the period after surgery that occurs with prehabilitation versus no-prehabilitation.

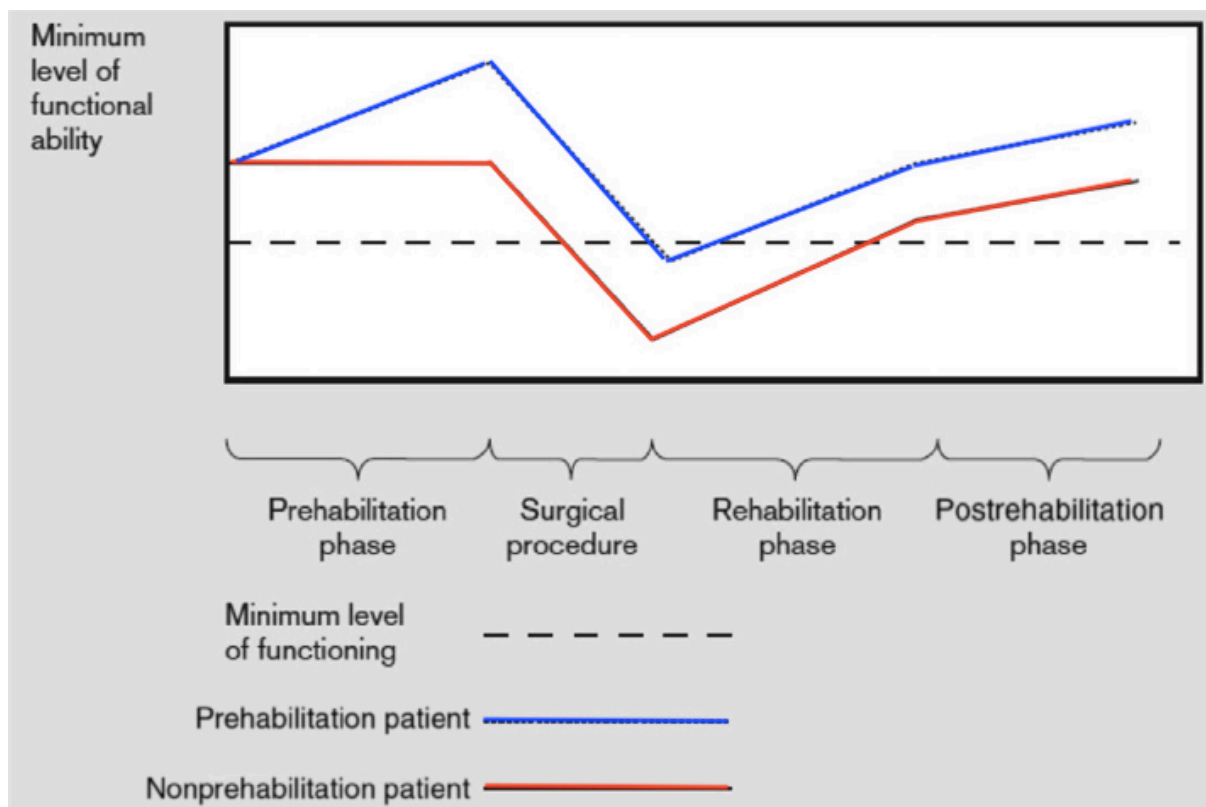


Figure 4.3: Trajectory of functional capacity throughout the surgical process
(Adapted from Carli et al 2015)

By enhancing functional capacity, prehabilitation aims to achieve multiple benefits including: lower postoperative morbidity and mortality, more rapid recovery from surgery, improved physical function, reduced emotional distress and improved quality of life (Myers, 2016). For those with borderline fitness for surgery, prehabilitation may be an opportunity for objective risk assessment and perhaps, with optimisation of physiological capacity, a wider range of treatment options.

→ Enhancing surgical outcomes

Much of the work that has been completed thus far in lung cancer prehabilitation has aimed to address the high levels of postoperative morbidity experienced by this vulnerable population. This is demonstrated by the primary outcome for many of the preoperative exercise intervention studies incorporating measures of postoperative morbidity such as length of stay (LOS) and rate of postoperative pulmonary complications (PPC's) as indicators of prehabilitation effectiveness. A recent systematic review by Steffens et al examining the effects of preoperative exercise on rate of complications, length of stay and HRQoL in patients with lung cancer concluded that there was moderate quality evidence that prehabilitation significantly reduced postoperative complication rates (RR 0.52, 95% C.I 0.36 to 0.74) and length of hospital stay (Mean Difference -2.86 days, 95% C.I -5.40 to -0.33) for patients undergoing lung resection compared with the control (Steffens et al 2018). Despite emerging evidence demonstrating the positive impact that prehabilitation may have on postoperative outcomes as outlined above, translation of prehabilitation into routine care has been slow. Emergence of clinical pathways and enhanced recovery after surgery (ERAS) initiatives to streamline postoperative care in many surgical specialties has helped to place greater focus on postoperative outcomes and has resulted in reduced postoperative morbidity. Despite these advances, there is a general lack of preoperative intervention within these clinical pathways. Implementing a new program (such as prehabilitation) into an existing model may be a way that prehabilitation may be better utilized. An example of how prehabilitation has been incorporated into this perioperative pathway with great success is detailed in a quality improvement programme published by Moore et al

in 2017. In this paper, the impact of introducing prehabilitation (defined as Enhanced Recovery After Surgery (ERAS) +) into a pre-existing enhanced recovery service for patients undergoing elective major surgery was assessed, with the specific aim of reducing postoperative pulmonary complications. The details of the ERAS (pre-existing program) and ERAS+ (addition of prehabilitation components to ERAS) are outlined in figure 4.4. Results from this paper demonstrated that addition of prehabilitation to an existing ERAS program reduced the incidence of postoperative pulmonary complications after 1-year of implementation to 8.7% (from 19.3%) and that median hospital length of stay also reduced from 12 (IQR 9-15) to 9 (IQR 5.5 – 10.5) days (Moore et al., 2017).

	Pre-operative	Intra-operative	Postoperative
ERAS (baseline)	Advice to cease smoking and reduce alcohol intake Pre-operative carbohydrate-rich drinks (2 h and 8 h) Day of surgery admission Cardiopulmonary exercise testing (CPET)	Intra-operative fluid management techniques, including use of oesophageal Doppler, pulse contour analysis and/or echocardiography Normothermia Minimally invasive surgery, minimise drains	Multimodal analgesia: local anaesthetic infusion via epidural and tissue plane blocks. Minimisation of i.v. opioid use. Physiotherapy session for chest and mobilisation Early enteral nutrition (oral or jejunal) with cessation of i.v. fluids Early removal of surgical drains
ERAS+ (additional elements added to baseline ERAS)	Surgery School invitation ICOUGH-UK YouTube channel Deep breathing exercises with incentive spirometers Increase usual physical activity by at least 50% Oral health advice Nutritional advice	No change	ICOUGH prescription Breathing and coughing exercises with incentive spirometry every 4-8 h Mobilisation twice daily Twice-daily toothbrush and chlorhexidine mouthwash Prepare for recovery at home

ERAS, enhanced recovery after surgery; i.v., intravenous.

Figure 4.4: ERAS compared to ERAS+ (inclusion of prehabilitation)

(Moore et al., 2017)

4.3.2 Evidence for prehabilitation in lung cancer

4.3.2.1 → Evidence from systematic reviews

Within the last 3 years, the strongest evidence for prehabilitation in lung cancer has been produced from a Cochrane review and 2 subsequent systematic reviews (Table 4.3). The Cochrane review, conducted by Cavalheri & Granger in 2017, examined the effect of preoperative exercise training on the following postoperative outcomes: risk of developing a postoperative pulmonary complication, postoperative duration of intercostal catheter, length of hospital stay, post intervention exercise capacity (6MWD) and post intervention forced vital capacity (FVC). This systematic review identified 5 RCTs involving 167 patients. The overall methodological quality of the studies was low with a high risk of bias within the studies and small sample sizes. A meta-analysis including 4 studies concluded that preoperative exercise intervention: reduced the risk of developing a postoperative pulmonary complications by 67% (risk ratio (RR) 0.33, 95% CI 0.17 to 0.61, $p=0.00042$), and reduced hospital length of stay (mean difference -4.24 days, 95% CI -5.43 to -3.06 days, $p=0.00001$). Meta-analysis of at least 2 studies also provided the following results favouring preoperative exercise interventions: a reduction in the number of days requiring an intercostal catheter (mean difference (MD) -3.33 days, 95% CI -5.35 to -1.30 days, $p=0.0013$), an increase in 6MWD (MD 18.23m, 95% CI 8.50 to 27.96m, $p=0.00024$) and an improvement in FVC (MD 2.97% predicted, 95% CI 1.78 to 4.16% predicted, $p=0.00001$) (Cavalheri & Granger, 2017). This review also acknowledged the need for additional large RCTs to further quantify the efficacy of preoperative exercise training.

Two further systematic reviews have been published since this time (Table 4.3). Steffens et al conducted a systematic review and meta-analysis in 2018 examining the effects of preoperative exercise on postoperative complications and length of stay in patients with cancer undergoing surgery. In this review, 17 studies were included (11 RCTs, 5 RCTs specifically on lung cancer) involving 806 oncology patients (432 with lung cancer). The results from meta-analysis of the lung cancer cohort demonstrates a significant effect favouring preoperative pulmonary

rehabilitation (prehabilitation) over control, with a reduction in postoperative complication rates (RR 0.52, 95% C.I 0.36 to 0.74) and length of hospital stay (MD - 2.86 days, 95% C.I -5.40 to -0.33) (Steffens et al., 2018). The most recent systematic review and meta-analysis published in 2019 by Rosero et al, assessed the effects of different modalities or combinations of preoperative exercise interventions in patients with NSCLC. This review included 10 studies (all RCTs) with a total of 676 patients. Effects of the intervention were intended to be assessed according to the type of intervention: combined aerobic exercise training + inspiratory muscle training (IMT) vs usual care (5 RCTs), combined aerobic exercise training + strength training + IMT vs usual care (3 RCTs), combined aerobic exercise training + strength training vs usual care (1 RCT) and aerobic exercise training vs usual care (1 RCT). However, due to the heterogeneity of prescribed interventions, definitive conclusions regarding the optimal type of training/ program were unable to be drawn. The results of the review did demonstrate that preoperative exercise intervention improves walking endurance (6MWD) (Standardized Mean Difference (SMD) = 0.27, 95% CI 0.11 to 0.44), peak exercise capacity (VO_2 peak) (SMD = 0.78, 95% CI 0.35 to 1.21), dyspnoea (SMD = -0.30, 95% CI - 0.51 to - 0.10), risk of hospitalization (SMD = - 0.58, 95% CI -0.97 to - 0.20) and postoperative pulmonary complications (RR = 0.50, 95% CI 0.39 to 0.66). No statistically significant results were found for mental wellness or quality of life. This is in concordance with the previous systematic reviews. The optimal training parameters recommended as part of a prehabilitation program included a combination of aerobic, resistance and inspiratory muscle training for 1-4 weeks preoperatively, performed 1-3 sessions per week ranging between 20-60 minutes duration, at a moderate intensity (Rosero et al., 2019).

In addition to this evidence for prehabilitation in lung cancer, a recently published landmark trial by Boden et al 2018 in abdominal surgery provides further insight into the value of preoperative intervention. In this prospective, randomized controlled trial of 441 patients undergoing major elective open upper abdominal surgery, delivery of a single physiotherapy session prior to surgery was assessed to determine the effect of this single intervention on the risk of developing a postoperative pulmonary complication. Participants were randomly assigned to either receive an information booklet (control) or preoperative physiotherapy session (intervention) and then followed for 12 months. The intervention group received one 30-minute education session focusing on PPCs and their prevention with early mobilisation and the initiation of breathing exercises immediately after surgery. Standard postoperative physiotherapy was delivered to both groups after surgery (consisting of early mobilisation). The overall incidence of PPCs within this sample was 20% however, there were significantly fewer PPCs in the intervention group (27/218, 12%) compared to the control group (58/214, 27%). Results indicate that the incidence of PPCs was halved in the intervention group (adjusted hazard ratio 0.48, 95% CI 0.30 to 0.75, $p=0.001$) compared to the control group and that there was an absolute risk reduction of 15% (95% CI 7% to 22%) (Boden et al., 2018). No statistically significant differences were found in any of the secondary outcomes (pneumonia, health-related quality of life (HRQoL), physical function, hospital re-admissions or 12-month all-cause mortality). The study concluded that addition of a 30-minute preoperative physiotherapy education session to the existing infrastructure of a multidisciplinary preadmission clinic was successful in halving the incidence of PPCs in the abdominal surgery population (Boden et al., 2018). This evidence further strengthens the argument for prehabilitation as, in addition to the traditional role of physical activity and exercise capacity optimisation prior to surgery, the above study demonstrates the important role physiotherapists undertake in the education and risk stratification of patients prior to surgery which can have significant impact on reducing postoperative morbidity.

4.3.2.2 → *Types of interventions tested in the literature to date*

Within the literature to date, the types of preoperative exercise interventions tested vary greatly in regard to: type of exercise, location and timing of exercise, intensity, duration, frequency, adherence as well as time available preoperatively to perform the exercise intervention. Table 4.4 (modified from Rosero et al 2019) details the variable prehabilitation exercise program designs within the RCT's outlined in this systematic review. The majority of these exercise intervention studies have targeted patients with NSCLC, specifically patients with resectable/operable disease. These surgical patients often have varying stages of disease which may have implications on intervention effect and success due to the differences in disease progression. Small sample sizes within these RCT's, which include limited participant numbers in the intervention group, contribute to the problem of these studies being under-powered. Sample sizes range from 9 – 53 participants: difficulty with recruitment of this patient population along with high symptom burden may be the limiting factor preventing larger sample sizes within these studies.

Most commonly, the exercise interventions reported in the literature share the following characteristics: 2-6 week program, consisting of aerobic +/- resistance training, at a frequency of 3-7 times per week for 30-60 minutes and working at an intensity of 50-80% maximum work rate. The studies differ in terms of type of aerobic exercise (bike versus treadmill or walking), inclusion of breathing or chest physiotherapy interventions and inclusion of other components of the intervention program, i.e. education (patients' role in recovery, dietary advice, pulmonary pathophysiology, breathing techniques and relaxation/stress management), smoking cessation and telephone calls to encourage adherence and monitor progress. These additional variables make it difficult to determine with absolute certainty that the results were primarily due to the exercise intervention. Because of the heterogeneity in exercise design and delivery within the individual prehabilitation studies, it is difficult to determine the best method of exercise prescription for this population.

Another factor which must be considered is the nature of supervision within the exercise intervention. Studies within the lung cancer population vary in terms of program design, consisting of both center or hospital-based and home based programs in either supervised or unsupervised capacities. In an RCT by Bocki et al the short and long-term effects of supervised versus unsupervised exercise training on HRQoL and functional outcomes following lung cancer surgery was assessed. In this trial of 78 participants, the intervention group (n=41) participated in supervised out-patient exercise training sessions for 1 hour/ once per week (10 week program duration) consisting of aerobic/ resistance training and dyspnoea management while the control group (n = 37) received one individual instruction in exercise training. The outcomes of interest included: HRQoL (assessed via SF36), six-minute walk test (6MWT) and lung function (spirometry) measured 3 weeks, 4 months and 12 months after surgery. The results of this trial indicated that the supervised intervention failed to demonstrate any significant effects in terms of 6MWT distance or lung volumes at any time-point and that the gains in HRQoL (pain domain and role physical functioning domain of the SF36) in the intervention group at 4 months were reversed at the 12 moth follow-up timepoint (Brocki et al., 2014). This study failed to demonstrate any significant benefit of supervised exercise for patients with lung cancer undergoing lung surgery compared to unsupervised exercise.

Further research is needed to confirm the optimal exercise intervention (timing, mode, delivery, supervision, setting) in lung cancer, as comparisons of programs have infrequently been investigated.

4.3.2.3 → Types of outcomes

Various outcome measures have been validated and utilised in the prehabilitation/ preoperative exercise intervention studies within the lung cancer population. The majority of these studies incorporate exercise capacity as the primary outcome as a means of evaluating the effectiveness of the intervention. The most commonly used outcome measures for this variable include the six-minute walk test (6MWT) or

incremental shuttle walk test (ISWT), which are both readily accessible and easy to administer and cardiopulmonary exercise testing (CPET) which is expensive and less readily available. The gold standard test for exercise capacity is CPET, however the ISWT has been validated against CPET with strong correlation (C. L. Granger et al., 2015). Other primary outcome measures used within the prehabilitation literature include measures of postoperative morbidity (i.e. hospital LOS and incidence of Postoperative Pulmonary Complication's).

Health-related quality of life (HRQoL) is another measure frequently used in the lung cancer population as it has been recognised that psychosocial aspects of health can influence responses to treatment and intervention. Commonly used tools include: the Functional Assessment of Cancer Therapy-Lung Scale (FACT-L), the European Organisation for the Research and Treatment of Cancer QLQ-C30 and lung scale (EORTC-QLQ-C30 L-13), the Short-Form 36 (SF-36) and the Hospital Anxiety and Depression Scale (HADS).

Lastly, secondary outcome measures often utilised in prehabilitation studies include: muscle strength, fatigue, feasibility, adherence to program, incidence of adverse events, pulmonary function, blood gas results and inflammatory markers. Outcomes measures that are infrequently used include: daily physical activity levels and mortality.

Current literature for the benefits of exercise in individuals with NSCLC before undergoing their definitive cancer treatment is still evolving. Despite this growth, the question remains – ‘What is the most effective exercise intervention to optimise these patients *preoperatively* and reduce postoperative morbidity?’ The most recent evidence published on prehabilitation in lung cancer (presented in tables 4.2 and 4.3) clearly demonstrates the beneficial effects that preoperative exercise can produce, however many of these included studies are small and underpowered thus further research is urgently required. With regards to the lung cancer prehabilitation research currently underway, a number of well-designed international multi-centre RCTs are currently being conducted which will provide further evidence on the best prescription and timing of preoperative intervention

for this cancer cohort. Currently in Australia there have been no studies specifically addressing prehabilitation in individuals with NSCLC. The proposed research project discussed in this thesis will address this gap and assist in determining the feasibility, safety and efficacy of a preoperative exercise intervention incorporating aerobic and resistance exercise for this vulnerable cancer population. It will also provide evidence that will contribute to advances in the current standards of care within Australia for patients with lung cancer and pilot data to support a larger RCT.

4.4 SUMMARY

The evidence to date for prehabilitation amongst the general oncology population suggests that exercise based prehabilitation improves functional capacity/physical fitness and has been shown to reduce postoperative complications in the lung cancer population (Ismail et al., 2018). Within the lung cancer population, exercise based prehabilitation may reduce the risk of developing a postoperative pulmonary complication, the duration of an intercostal catheter and the length of postoperative hospital length of stay (Cavalheri & Granger, 2017). Improvements in exercise capacity and lung function (Forced vital capacity FVC) have also been shown (Cavalheri & Granger, 2017; R. Sebio Garcia et al., 2016). Greater consensus amongst researchers and clinicians about what is considered clinically important and relevant within prehabilitation will also help create standards for future work, which will then allow more clarity in determining the ideal prehabilitation program for cancer patients. The next chapter details the first study of this thesis, a pilot randomized controlled trial titled 'Prehabilitation for individuals having lung cancer surgery' conducted to examine the feasibility of prehabilitation for lung cancer in the Australian setting.

CHAPTER 5 STUDY 1

PREHABILITATION FOR INDIVIDUALS HAVING LUNG CANCER SURGERY: A PILOT RANDOMIZED CONTROLLED TRIAL

5.1 INTRODUCTION

Lung cancer is associated with a range of complex symptoms, including fatigue and breathlessness, which frequently lead to a vicious cycle of inactivity and functional decline. Compounding this is the fact that a large proportion of patients have multiple co-morbidities, including chronic obstructive pulmonary disease (COPD). As discussed earlier in this thesis, there have been several studies demonstrating promising outcomes of prehabilitation for patients awaiting surgery for lung cancer, however none of these studies have been conducted in the Australian healthcare setting. Additionally, despite the emerging international evidence, prehabilitation in lung cancer has not become standard practice in Australia or globally. Therefore, investigation into the feasibility of prehabilitation in lung cancer in the Australian setting is warranted. This chapter will focus on a pilot randomized controlled trial (RCT) conducted to specifically address this issue.

The overall aims of this trial were to determine if a prehabilitation program for individuals undergoing lung cancer surgery was feasible and safe within the Australian setting. The CONSORT guidelines for pilot and feasibility trials were adhered to in the conduct and reporting of this trial (Eldridge, 2010).

5.2 AIMS AND HYPOTHESES

The primary aims of this trial were to investigate the feasibility and safety of a pre-surgical exercise intervention (prehabilitation) for individuals with stage I-IIIa NSCLC. The primary hypotheses were that prehabilitation would be deemed to be feasible and safe in this population (determined as >50% of eligible participants consenting to participate: >70% of participants randomized to the intervention

group completing the prehabilitation program: and no serious adverse events). The secondary aims were to explore the benefit of prehabilitation on exercise capacity, physical activity levels, muscle strength, HRQoL, anxiety and depression: and to explore the views and experiences of participants in both the prehabilitation and usual care group with regards to preoperative care and prehabilitation.

5.3 METHODS

5.3.1 Trial design

This was a single centre, assessor-blinded, prospective, pilot randomized controlled trial comparing preoperative exercise intervention (prehabilitation) to usual care (no preoperative intervention). The trial was conducted at a tertiary public and private hospital in Melbourne Australia. Ethical approval to conduct the trial was granted from St Vincent's Human Research & Ethics Committee on 4th May 2015 (ethics number HREC-A 022/15). The trial was registered retrospectively online - Australian New Zealand Clinical Trials Registry Number (ACTRN): ACTRN12619001550190.

5.3.2 Participants

Patients were eligible for inclusion if they were: adults aged ≥ 18 years, who had suspected stage I-IIIa NSCLC presenting for surgical consult, and primary treating surgeon approval for enrolment into the trial. Patients were excluded if they were already relatively fit (based on functional exercise capacity performance $> 70\%$ predicted in the 6MWD)(Jenkins et al., 2009): had an unstable psychiatric or cognitive disorder: had a major comorbidity preventing participation in exercise: were unable to give informed consent: or were from a non-English speaking background (and therefore not able to complete the questionnaires). Other factors that exclude use of surgery for an individual with NSCLC at this tertiary hospital include; poor respiratory function test results, advanced disease (stages III and IV) or co-existing pathology/comorbidity limiting the efficacy of surgery. In the initial 12 months of study recruitment participants were excluded if they resided outside metropolitan Melbourne, due to slow recruitment and a high proportion of patients

from rural locations this was later revised to include patients from outside metropolitan Melbourne.

Patients were screened for inclusion into the trial at the public and private hospital sites from July 2015 to December 2018. Patients suspected of a lung cancer diagnosis as per usual practice are referred to the St Vincent's Hospital lung outpatient clinic and/or presented in the weekly lung multidisciplinary meeting (MDM). The trial recruiter attended the outpatient clinic and weekly lung MDM to screen all potential patients and approach any eligible patients who were identified about participation in the trial. Patients were approached when the treating surgeon and trial recruiter obtained consensus about patient's eligibility into the trial and after the patient had already consented to surgery. Patients receiving a lung cancer diagnosis on the day of clinic were not approached on the same day of diagnosis: these patients were followed-up by telephone over the subsequent days to determine their interest in the trial. Following agreement to participate, all patients were required to provide written informed consent and after this time baseline testing of participants occurred.

5.3.3 Intervention

Intervention group – Prehabilitation

In addition to standard preoperative care (described in the next section), participants randomly allocated to the intervention group underwent an individualised training program before surgery. The exercise program was taught and delivered by a physiotherapist or physiotherapy allied health assistant with experience in oncology. The therapists providing the intervention underwent training by the principle researcher (AS) in accordance with the intervention protocol. The exercise program involved both supervised and non-supervised (home-based) sessions, to make up a total of 5 exercise sessions per week. The program ran for as many weeks as possible between recruitment and the patient's scheduled date of surgery. Data on the duration of the patient's programs (in weeks) were collected.

The prehabilitation program consisted of:

1. Hospital-based supervised gym sessions (3x week, 45 minutes): Supervised gym sessions involved aerobic exercise (stationary bike or treadmill) and resistance exercises (free weight or resistance machine) for major upper limb and lower limb muscle groups. Aerobic intensity varied with the capacity of each patient but aimed for a work rate of 60-80% of predicted maximum based on outcome of their baseline incremental shuttle walk test (ISWT). Resistance training intensity was based on the individuals 10 repetition maximum (ability to lift a specified weight for 10 repetitions). The program was progressed according to the patient's individual response but was monitored via the BORG scale (target 3-5)(Scherr et al., 2013) and increasing the prescribed repetitions within the allocated training time.
2. Home-based exercise (2x week, 30-45 minutes): Unsupervised home exercise consisted of aerobic exercise (home stationary bike or outdoor walking program) and resistance exercises (TheraBand). The option of bike hire was provided to participants as an alternative to walking for aerobic exercise. If desired, participants were provided with a stationary bike to use whilst exercising at home for the duration of the program. The home bike and / or walking program was individualized to each patient, based on their initial baseline testing, aiming to reach a work rate of 60-80% maximal workload. Exercises were monitored weekly to progress as appropriate. Home visits (exercise program set up and/or review only) were also provided as required, for those requiring more assistance (i.e. new to exercise or unfamiliar with training method). One to two home visits were offered, most participants only required one home visit. Weekly phone calls from the physiotherapist to the patient on a non-face-to-face training day were conducted to encourage home adherence, check compliance and monitor progress. The phone calls were not scripted however aimed to ascertain the level of compliance with the home exercise program and provide verbal motivation/support to the intervention participants. Participants were also given an exercise diary to complete with their home-exercise session details and monitor adherence (see appendices II and III).

3. Participants were provided with general education about lung cancer, the importance of staying active, eating well and symptom control. This information was given verbally at the initial meeting with the participant and was adapted to the individual's needs. Many participants received information from their treating oncologist/surgeon therefore only requested additional information about exercise. This education focused on the frequency, intensity duration and type of exercise that was appropriate for the individual. Written material on exercise was not provided.

All exercise programs were tailored to the individual participant as it was recognised that individuals with lung cancer have multiple co-morbidities, combined with the cluster of cancer symptoms, which may influence their ability to exercise. Exercise prescription was modified as appropriate to allow compliance with and achievement of the program for the individual. For example: participants were monitored for dyspnoea (a frequent symptom of their disease) via the BORG scale and rest periods were provided to account for these symptoms; alternative upper limb exercises were provided to those with pre-existing shoulder problems.

Control group – no prehabilitation

Participants allocated to the control group received standard/usual preoperative care. Standard care did not include preoperative exercise training, information/education or physiotherapy.

After surgery participants in both groups received standard postoperative care. Standard care in the hospital inpatient postoperative period included postoperative physiotherapy aimed at respiratory management and early mobilization according to a clinical pathway (C. L. Granger, 2016). Table 3.3 in chapter 3 outlines a standard postoperative thoracic surgery clinical pathway. Following discharge from hospital, standard care did not include referral to a postoperative exercise program. This is representative of current standard practice in Australia and in many other countries at the time the trial was conducted.

5.3.4 Outcomes

Primary outcomes

Data regarding feasibility and safety were collected prospectively throughout the trial on specifically designed data sheets (Appendix I: outcome measures booklet).

→ **Feasibility:** Data collected included:

- recruitment and consent rate, including reasons for decline
- participation, adherence to and completion of exercise
- compliance completing an exercise diary
- duration of prehabilitation program

→ **Safety:** Data collected:

- number and details of adverse events (minor and major adverse events) occurring during and one hour after the exercise program, or during outcome measure testing. Please refer to Appendix I for Safety and adverse events protocol and description of adverse event.

Secondary outcomes

Time points for the outcome measure testing (Table 5.1) were:

- T0 - baseline (prior to randomization)
- T1 - immediately prior to surgery following completion of the prehabilitation program/standard care (control group)
- T2 - 30-days post-surgery

A blinded outcome assessor completed all outcome measure testing.

Table 5.1: Summary of secondary outcome measures

Outcome measure		ISWT	Muscle strength	IPAQ	EORTC-QLQ	HADS	Interviews
Time point	T0 - Baseline	✓	✓	✓	✓	✓	
	T1 – Pre-op	✓	✓			✓	
	T2 – 30-days post-op	✓	✓	✓	✓	✓	✓

Abbreviations: IPAQ – International Physical Activity Questionnaire, EORTC-QLQ – European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire, HADS – Hospital Anxiety and Depression Scale, ISWT – Incremental Shuttle Walk Test

→ **Functional exercise capacity** measured with the incremental Shuttle Walk Test (ISWT). The ISWT is an externally paced exercise test that measures distance (in meters) completed during a shuttle walking task consisting of 12 progressively harder levels. This test is a valid and reliable test to assess functional exercise capacity in people with chronic respiratory diseases (Parreira et al., 2014) and has demonstrated construct validity in the lung cancer population (Granger, 2013). The ISWT has been validated against cardiopulmonary exercise testing (CPET) (Arnardottir, Emtner, Hedenstrom, Larsson, & Boman, 2006; Lima et al., 2019).

→ **Muscle strength** measured with a dynamometer. Participants had their quadriceps, rotator cuff and hand grip strength measured bilaterally using the Powertrack II commander 1500 dynamometer. This device provides a simple, quick and accurate measurement of muscle strength in the units of kilograms (kg). In the older person population, hand-held dynamometry has strong concurrent validity against the gold standard measure of muscle strength (isokinetic dynamometry) ($r = 0.91$) (Martin et al., 2006). Hand-held dynamometry also has good stability in the older person population (Bohannon, Bubela, Magasi, & Gershon, 2011). For all strength measures, quadricep, rotator cuff and hand grip strength, participants had 3 attempts at each muscle group, the highest scores were then selected for the strongest side (left or right) for each patient and used in analyses.

→ **Physical activity levels:** Self-reported physical activity was measured using the International Physical Activity Questionnaire (IPAQ), a valid and reliable tool to measure physical activity levels in oncology populations (Craig et al., 2003). The questionnaire asks participants to recall their level of physical activity (across 3 domains: walking, moderate and vigorous physical activity) over the past seven days. Results from the questionnaire may be presented as categories (low, moderate or high activity levels) or a continuous variable (MET minutes per week). MET minutes can be defined as the amount of energy expended carrying out physical activity (e.g. walking considered to be 3.3 METS)(Forde, 2018). The higher the total MET minutes per week (across all 3 domains of walking, moderate and vigorous activity), the higher the physical activity levels.

→ **Health-related Quality of Life (HRQoL)** was assessed with the European Organization for the Research and Treatment on Cancer Questionnaire (EORTC-QLQ-LC), a valid and reliable lung cancer specific quality of life measurement tool (Aaronson, 1993; Bergman, 1994). The questionnaire contains 30 questions in 15 subscales (range for each 0-100). These include 5 functional scales (physical, role, emotional, cognitive, social), 8 symptoms (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea), financial difficulties and a global health status/QoL scale. A high scale score represents a higher response level, for example higher scores indicate better outcomes on global quality of life/functional scales and worse outcomes on symptom scales and for financial problems (Fayers, 1995; Mercieca-Bebber et al., 2019).

→ **Anxiety and depression** measured with the Hospital Anxiety and Depression questionnaire (HADS) (Bjelland, 2002; Mitchell, 2010). The HADS is a tool for screening of depression, anxiety and distress (Bjelland, 2002, (Luckett, 2010; Zigmond, 1983) and is commonly used in the cancer population. The questionnaire has 14 items divided into two 7 item subscales, depression and anxiety. Each item is scored on a 4-point scale ranging from 0 (absence) to 3 (extreme presence), giving a total score out of 42 . Higher scores in each subscale indicate greater levels of anxiety and depression.

→ **Patient experience (interviews):** Semi-structured individual interviews were conducted 30-days post-surgery with participants in both groups via telephone. Questions explored the participants' views on: preparation for surgery, desire for information preoperatively, challenges and facilitators to exercise, available support networks during treatment and opinions on prehabilitation as well as post-operative recovery. A copy of the semi-structured interview guide is provided in Table 5.2.

Table 5.2: Semi-structured interview guide

Questions for Intervention group	Questions for Control group
1. How did you find the prehabilitation program from start to finish? <u>Prompts:</u> • How did you find out about the study? • Did the timing of the prehab program suit you (i.e. would it have been better earlier or later in your cancer journey?) • What was your experience of the St Vincent's staff in explaining the prehab program and guiding you through it? • How did you find the prehab program duration?	1 How did you prepare for your surgery? <u>Prompts:</u> • Did this include exercise? • Did you continue your normal activity levels? • Did you change anything else (diet, sleep, smoking)?
2. Do you feel you had the support of family to participate in the prehab program? <u>Prompts:</u> • How did the Surgeon / oncologists feel about you participating in exercise? • Did your family attend appointments with you and/or assist you with the exercise program?	2 How did you feel about not being allocated to the prehab exercise group? <u>Prompts:</u> • Why? • Do you normally participate in exercise? • Did you perform any of your own hobby/leisure activities/exercise whilst on the study? • Did you change your normal activity levels as a result of being in the control group?
3. Was the exercise program tailored to your specific needs/ability? <u>Prompts:</u> • What exercises did you like? • What exercises did you not like? • How did the exercise make you feel? • Do you think the exercise occurred often enough? • How did you find the intensity of the exercise?	3 Did you seek your own information about exercise or remaining active during your cancer treatment? <u>Prompts:</u> • When? • From where did you get information? • Did someone help you with this? • Did you seek information about exercise after your surgery?

Questions for Intervention group	Questions for Control group
4. What factors assisted you to participate in the exercise program? <u>Prompts:</u> • What things motivated you? • Were you able to do the exercises?	4 What factors assisted you to determine the ideal level of activity before and after your lung surgery? <u>Prompts:</u> • Advice from medical team? • Advice from family/friends? • Own knowledge/experience? • Advice sought from other allied health professionals?
5. Were there factors that made it challenging to adhere to the exercise program? <u>Prompts: if yes....</u> • Were there any social/family factors that made exercise challenging? (i.e. caring for family/grandchildren, work, other commitments) • Did you experience changes in your motivation or mood as a result of your cancer diagnosis and need for surgery? • How did you find the time commitment?	5 Were there factors that made it challenging for you in preparation for your lung surgery? Prompts: • Did you have multiple hospital appointments? • What symptoms did you experience (SOB, fatigue, cough)? • Did you experience low mood, anxiety, worry? • How far did you travel to get to tests & appointments? • What was the time period between diagnosis and surgery?
6. Did your thoughts about exercise during cancer treatment change as a result of participating in the study? <u>Prompts:</u> • Did the effects surprise you/change your opinion?	6 What type of prehab program do you think would be ideal for people prior to lung surgery? Prompts: • Do you prefer individual or group exercise? • Do you like gym based or home-based exercise? • Would you like more education/advice? • Who else would you like involved in a prehab program? • Did you have support from medical team and/or family to participate in prehab?

Questions for Intervention group	Questions for Control group
7. Are there any changes you would suggest making to the exercise program? <u>Prompts:</u> • What factors would make exercising before surgery achievable for people who have been recently diagnosed with lung cancer? • How did you find the regular follow-up phone calls? • Would you prefer another type of exercise (swimming/tennis etc.)? • Do you prefer exercising at home or supervised in a gym? Individually or in a group?	7 What information would you like to receive about exercise before undergoing surgery for lung cancer? <u>Prompts:</u> • More written information? • Audio or visual information? • Guidance on where to get general information about exercise and lung cancer? • Information on Support groups?
8. Have you continued exercising beyond the study? (has the behavior maintained after surgery) <u>Prompts:</u> • Have you continued the program exercises? • Have you started new exercise?	8 Can you tell me about your recovery after lung surgery? <u>Prompts:</u> • Was the postoperative recovery as you expected? • Where were you discharged to? • Have your exercise habits changed as a result of participation in the study?
9. Can you tell me about your recovery after lung surgery? <u>Prompts:</u> • Do you think exercise had an effect on recovery? • Was the postoperative recovery as you expected? • How prepared did you feel for your surgery? • Where were you discharged to?	
10.What other information/resources would you like to assist you during your lung cancer treatment? <u>Prompts:</u> • Do you prefer written information? • Do you prefer audio/visual methods of information? • Would you like access to general information on lung cancer or support groups?	

Demographic data were also collected including age, sex, height, weight, respiratory function, type of cancer, type of surgery, social history and occupation.

5.3.2 Sample size

The pragmatic sample size for this pilot trial was set at 40. This number was chosen as it was postulated that there would be 2 eligible lung cancer resection cases per week (total of 8 per month) therefore recruitment would take approximately 5-6 months. The trial was not powered to identify statistically significant changes in secondary outcomes; however, those measures were included to describe trends that may assist with development of a future phase II trial.

5.3.3 Randomization

Participants were randomized 1:1 to either the intervention or control groups. Randomization took place remotely and independently using an off-site computer-generated random number of table and sequentially numbered sealed opaque envelopes prepared by personnel not involved in the trial. Randomization occurred after consent and baseline testing. For each consented participant, immediately after baseline testing was complete, the next consecutive assignment envelope was opened by personnel not involved in the trial and the intervention therapist was notified of allocation. Outcome assessors were blinded to allocation, but it was not possible to blind participants to allocation given the nature of the intervention in the trial.

5.3.4 Statistical analyses

Quantitative data analyses were performed using SPSS version 23 for Windows using a variety of descriptive statistical methods. Data are presented as mean $\pm$ standard deviation (SD), median (inter-quartile range), or frequency (percent). Feasibility data, baseline data and demographic data were analysed and presented descriptively. For the secondary outcome measures (repeat measures of ISWT, muscle strength, IPAQ, EORTC-QLQ-C30, HADS), data were analysed and presented

descriptively for each time-point and for each group separately according to an intention to treat approach. Given the pilot nature of the trial and small (un-powered sample size) no statistical comparisons between groups or over time were conducted on the secondary outcomes.

Qualitative analyses were performed on the data gained from participant interviews. Information from recorded phone interviews were transcribed and then collated and summarized. Data were then categorized according to responses for each question. The main points of interest were then identified and included: program satisfaction, key barriers and facilitators to physical activity and factors impacting adherence over time. Two researchers (AS, LE) then conducted the thematic analysis of the data to determine key themes and sub-themes common to both intervention and control groups.

5.4 RESULTS

Between July 2015 and December 2018, 24 participants were recruited to the trial. Figure 5.1 outlines the flow of participants through the trial. Eleven participants were recruited into the intervention group and 13 participants were recruited into the control group. The demographics of participants are shown in Table 5.3.

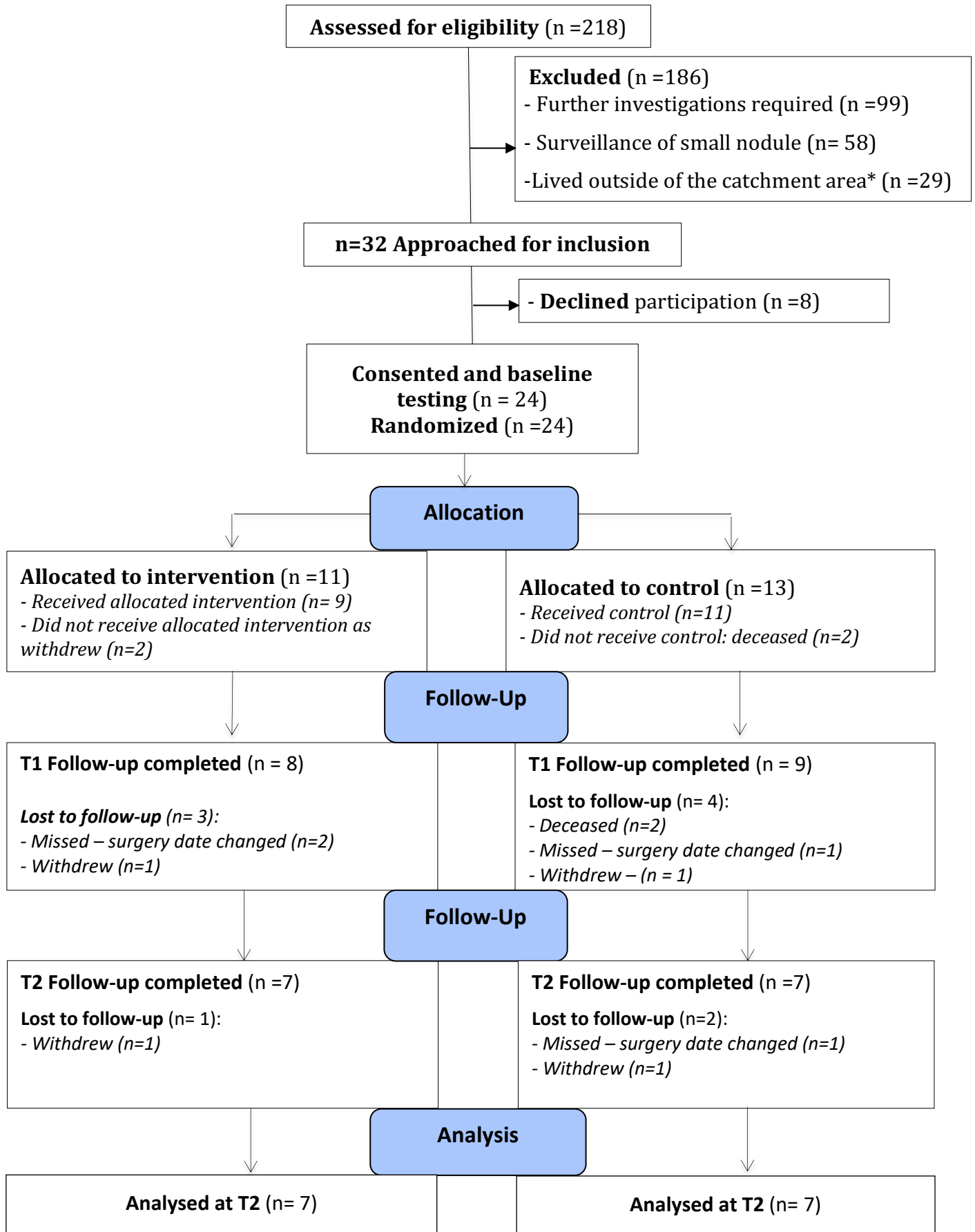


Figure 5.1: CONSORT diagram

Note: * Exclusion criterion used for first 12 months of study only due to slow recruitment

Table 5.3: Demographic data

Characteristic	Intervention (n=11)	Control (n=13)
Age (years)	66.5 (8.6)	68.6 (9.2)
Sex (male)	5 (45%)	5 (38)
Weight (kg)	78.9 (13.2)	71.9 (14.3)
Height (cm)	165.3 (9.3)	164.2 (11.5)
Histological type		
Squamous	4 (36%)	3 (23%)
Adenocarcinoma	5 (45%)	9 (69%)
Other	2 (18%)	1 (8%)
Cancer Stage		
Stage IA	5 (50%)	3 (27%)
Stage IB	1 (10%)	1 (9%)
Stage IIA	1 (10%)	1 (9%)
Stage IIB	1 (10%)	3 (27%)
Stage IIIA	2 (20%)	3 (27%)
Stage IIIB	0	0
Stage IV	0	0
Missing	1	2
FEV₁ (liters)	1.63 (1.34, 2.55)	2.01 (1.30, 2.46)
FVC (liters)	2.56 (2.11, 3.30)	2.79 (1.86, 4.16)
TLCO (%)	69.5 (15.6)	67.9 (14.3)
Years smoked	40.4 (16.5)	40.1 (19.7)
Pack years	33.8 (27.5)	26.5 (17.4)
Time Dx to Sx (days)	54.3 (25.2)	62.6 (27.0)
COPD diagnosis	6 (46%)	7 (54%)
Social situation		
Home alone	6 (54%)	6 (46%)
Home with family	5 (45%)	7 (54%)
Employment status		
Working FT	1 (9%)	2 (15%)
Working PT	1 (9%)	0
Sick leave	0	2 (15%)
Retired	9 (82%)	9 (69%)
Activity level		
Fully active	6 (54%)	5 (38%)
Walking/ light work	5 (45%)	7 (54%)
RIB < half the day	0	1 (8%)

Characteristic	Intervention (n=11)	Control (n=13)
Operative approach		
VATs	8 (80%)	10 (83%)
Open Thoracotomy	2 (20%)	2 (17%)
Missing	1	1
Type of resection		
Lobectomy	7 (78%)	9 (75%)
Pneumonectomy	0	1 (8%)
Segmentectomy	1 (11%)	1 (8%)
Wedge	1 (11%)	1 (8%)
Missing	2	1
Hospital length of stay post-op (days)	6 (5, 12)	8 (6, 9)

Footnote: Values are reported as mean (standard deviation), median (interquartile range) or number (percentage)

Abbreviations: FEV1 – forced expiratory volume in 1 second, FVC – forced vital capacity, TLCO – transfer factor for carbon monoxide, Dx to Sx – diagnosis to surgery, COPD Dx – chronic obstructive pulmonary disease diagnosis, FT – full time, PT – part-time, RIB – rest in bed, VATS – video assisted thorascopic surgery

5.4.1 Primary outcomes – Feasibility and Safety

Patients were screened over a period of three years from July 2015 and December 2018 (no screening or recruitment took place for 12 months during 2017 due to the primary investigator being on leave). This gives a two-year period of screening in which 218 patients were assessed for eligibility in the multi-disciplinary meetings and lung clinic and 186 were not eligible for inclusion and therefore not approached (Figure 5.1). All patients who met the inclusion criteria were approached (32 patients) and 24 of these patients consented (consent rate = 75%). The reasons for decline were: already exercising, lack of interest in research participation, too difficult to travel to multiple hospital appointments and current high fitness level/functional capacity. The trial was ceased prior to reaching the target sample size of 40 participants. This was due to the feasibility of conducting this trial as part of the Master of Philosophy research degree and the time available to complete the trial.

There was a high attrition rate in the trial. At T1 only n=17/24 (71%) of participants completed follow-up testing and at T2 only n=14/24 (58%) completed follow-up testing. The reasons for missing data are noted in Figure 5.1.

Of the intervention group (n=11), 82% of participants (n=9) commenced the exercise program and all of these participants completed the program. The other two participants withdrew after baseline testing and therefore did not begin their prescribed exercise program. Time available for prehabilitation varied greatly amongst participants (ranged 24 – 103 days) but did not differ between participants in the public or private setting. There were no adverse events.

Additional feasibility outcomes related to the intervention are summarized in Table 5.4.

Table 5.4: Feasibility and safety outcomes for the intervention group

Variable	Result
Duration of prehabilitation program (weeks)	Mean 3.3, Range 4-8 weeks
Exercise participation and adherence (n=11)	
- Number of pts who commenced program (undertook at least 1 supervised session)	- 82% (9 of 11 participants)
- Number of pts who completed program	- 82% (9 of 11 participants)
- % of participants completing supervised sessions	- 27% (3 of 11 participants)
- % of participants completing home-based sessions	- 55% (6 of 11 participants)
- >75% compliance with 2x week strength training	- 64% (7 of 11 participants)
- >75% compliance with 3x week aerobic exercise	- 45% (5 of 11 participants)
- Compliance completing an exercise diary	- 82% (9 of 11 participants)
Home exercise program type	
- Aerobic exercise (walking program) and resistance exercises	- 27% (3 of 11 participants)
- Aerobic exercise (bike program) and resistance exercises	- 18% (2 of 11 participants)
- Aerobic exercise (walking and bike program) and resistance exercises	- 36% (4 of 11 participants)

Variable	Result
Type of home-based exercise equipment	
- Use of hire bike for trial	- 27% (3 of 11 participants)
- Use of own stationary bike	- 18% (2 of 11 participants)
- Use of own treadmill	- 0%
- No use of aerobic exercise equipment	- 36% (4 of 11 participants)
Home exercise program	
- Required a home visit from therapist	- 2 participants
Adverse events	Nil

5.4.2 Secondary Outcomes

Performance on the patient outcome measures at baseline and follow-up time points are reported in Table 5.5.

Table 5.5: Secondary outcome measures

Outcome measure	Time-point	(n) at time point	Control (n=13) Median (IQR)	(n) at time point	Intervention (n=11) Median (IQR)
ISWT (meters)	T0 Baseline	13	180 (100 - 240)	11	190 (155 - 285)
	T1 Pre-op	9	215 (160 - 360)	8	195 (173 - 380)
	T2 30-days PO	7	265 (200 - 315)	7	150 (140 - 395)
Muscle strength (kg) Quadriceps Rotator cuff Hand grip	T0 Baseline	13	22 (17 - 27.9)	11	24 (18 - 31.5)
	T1 Pre-op	9	22.5 (10 - 30.8)	8	16 (14 - 20.5)
	T2 30-days PO	7	18 (10 - 23)	7	18 (12.5 - 30.5)
	T0 Baseline	13	18 (14.9 - 27.3)	11	18 (14 - 23)
	T1 Pre-op	9	22.5 (11 - 29.1)	8	15 (14 - 22.5)
	T2 30-days PO	7	15.2 (12 - 30.3)	7	18 (10 - 30)
	T0 Baseline	13	31.5 (23.2 - 47.8)	11	28.5 (23.6 - 34)
	T1 Pre-op	9	34 (17.5 - 56.5)	8	30 (24 - 40)
	T2 30-days PO	7	29.7 (18 - 61.5)	7	32 (22 - 40)
IPAQ (METS)	T0 Baseline	13	319 (33 -1188)	11	792 (190 - 3065)
	T2 30-days PO	7	693 (508 - 2691)	7	1290 (605 - 2490)
EORTC-QLQ-C30					
Global Health domain score (/ 100)	T0 Baseline	13	66.7 (66.7 - 83.3)	11	58.3 (50 - 66.7)
	T2 30-days PO	7	58.3 (45.8 -66.7)	7	66.7 (62.5 - 70.8)
Physical function domain score (/100)	T0 Baseline	13	86.7 (66.7 - 86.7)	11	86.7 (63.3 - 93.3)
	T2 30-days PO	7	66.7 (60 - 76.7)	7	73.3 (66.7 - 86.7)
Fatigue domain score (/100)	T0 Baseline	13	33.3 (11.1 - 55.6)	11	22.2 (16.7 - 61.1)
	T2 30-days PO	7	33.3 (11.1 - 66.7)	7	33.3 (22.2 - 50)
Anxiety and depression	T0 Baseline	13	8.0 (5.0 - 10.0)	11	10.0 (5.0 - 13.5)
	T2 30-days PO	7	7.0 (3.5 - 12.0)	7	7.0 (5.0 - 19.5)

Abbreviations: IPAQ – International Physical Activity Questionnaire, EORTC-QLQ-C30 – European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ISWT – Incremental Shuttle Walk Test, IQR, inter-quartile range, METS - metabolic equivalents, PO- post op

5.4.3 Completers vs non-completers

Comparison across groups of those who completed the trial versus those who did not complete was also conducted. Descriptive data of completers (n=14) and non-completers (n=10) is outlined in table 5.6 below.

From this analysis, the key characteristics which differentiated completers from non-completers included: histological type (with completers showing a trend towards adenocarcinoma 78.6% compared to non-completers 30%), cancer stage (with completers having a higher proportion of early stage disease 1A 42.9% compared to non-completers 20%), smoking status (with 14.3% of completers current smokers compared to 70% of non-completers), COPD diagnosis (completers 42.9% compared to non-completers 70%), employment status (64.3% of completers retired compared to 90% of non-completers) and baseline self-reported activity levels (baseline IPAQ score – completers with a mean of 1000 total metabolic equivalents (METS) compared to non-completers with a mean of 206.3 total METS).

Table 5.6: Completers vs non-completers (across both groups)

Characteristic	Completer (n=14)	Non-completer (n=10)
Age (years) <i>mean, S.D</i>	67.1 (11.3)	68.3 (3.7)
Sex (male) %	35.7	50
Weight (kg) <i>mean, S.D</i>	76.1 (12.3)	73.8 (16.5)
Height (cm) <i>mean, S.D</i>	165.4 (10.7)	163.7 (10.3)
Histological type %		
Squamous	7.1	60
Adenocarcinoma	78.6	30
Other	14.3	10
Cancer Stage %		
Stage IA	42.9	20
Stage IB	7.1	10
Stage IIA	14.3	10
Stage IIB	21.4	10
Stage IIIA		50

Characteristic	Completer (n=14)	Non-completer (n=10)
Stage IIIB		
Stage IV		
Missing		
FEV₁ (liters) median, IQR	1.9 (1.3 – 2.6)	1.9 (1.2 – 2.3)
FVC (liters) median, IQR	2.9 (1.9 – 4.5)	2.7 (2.5 – 3.1)
TLCO (%) mean, S.D	70.6 (14.8)	65.4 (14.4)
Years smoked mean, S.D	36.9 (18.2)	45.1 (17.4)
Current smoker %		
Yes	14.3	70
Time Dx to Sx (days) mean, S.D	57.2 (27.1)	61.2 (25.5)
COPD diagnosis %	42.9	70
Social situation %		
Home alone	50	50
Home with family	50	50
Employment status %		
Working FT	14.3	10
Working PT	7.1	
Sick leave	14.3	
Retired	64.3	90
Activity level %		
Fully active	42.9	50
Walking/ light work	50	50
RIB > half the day	7.1	
Walking limitation %		
Yes	50	50
Operative approach %		
VATs	85.7	60
Open Thoracotomy	7.1	30
Missing	7.1	10
Type of resection %		
Lobectomy	64.3	70
Pneumonectomy	7.1	
Segmentectomy	7.1	10
Wedge	14.3	
Missing	7.1	20
Hospital length of stay post-op (days) median, IQR	6 (5 – 8.5)	8.5 (5.8 – 19.8)

Characteristic	Completer (n=14)	Non-completer (n=10)
Baseline ISWT (m) <i>median, IQR</i>	185 (112.5 – 377)	185 (102.5 – 197.5)
Baseline strength (N) <i>median, IQR</i>	21.2 (15.2 – 25.9)	23 (21.4 – 27.4)
Quadriceps	17 (13 – 24)	18 (15.8 – 25.3)
Rotator cuff	22.3 (19 – 48.1)	30.5 (28.2 – 38.9)
Hand grip		
Baseline HADS score <i>median, IQR</i>	9.5 (4.5 – 14)	8 (2.5 – 13.5)
Baseline QoL score <i>median, IQR</i>		
global health function	66.7 (58.3 – 75)	62.5 (50 – 77.1)
physical function	83.3 (58.3 – 93.3)	86.7 (65 – 93.3)
fatigue	27.8 (19.4 – 66.7)	16.7 (11.1 – 55.6)
Baseline IPAQ score (METS) <i>median, IQR</i>	1000.5 (272.3 – 4312.5)	206.3 (0 – 763)

KEY: Kg - kilograms, m – meters, cm - centimeters, N - newtons FEV1, FVC, TLCO, Time Dx to Sx – time diagnosis to surgery, COPD, FT – full time, PT – part time, RIB – rest in bed, VATs – video assisted thoracotomy, ISWT – incremental shuttle walk test, HADS – hospital anxiety and depression scale, QoL – quality of life, METS – metabolic equivalents

Twelve of the 24 participants completed semi-structured qualitative interviews at T2 (30 days post-surgery) (n=5 intervention, n=7 control). Nine participants were not contactable at 30 days after surgery or did not respond to requests for an interview and 3 participants had died prior to this time point. Interviews ranged in duration from 10 – 45 minutes.

Overall, participants were satisfied with the prehabilitation program with some participants randomized to the control group expressing dissatisfaction with their group allocation due to recognition of, or prior experience with, the benefits of exercise (but not specific to their lung cancer diagnosis). The themes that arose from the interviews across both groups are reported below, as well as supportive quotations from participants.

1. Reduced functional/exercise capacity due to symptoms and comorbidities

Participants reported that their symptoms and premorbid comorbidities limited their functional capacity prior to surgery. Fatigue and shortness of breath were identified as the two greatest barriers to exercise. Pain and motivation were also identified as limiting factors.

- *“I can’t go shopping, I have to use a wheelchair, because my shortness of breath really restricts me. It makes me sad because I can’t go anywhere unless I am being picked up. I used to love walking down the street and visit people, but I can’t anymore. I’d love to take my dog for a walk but I can’t because by the time I get down the steps I have to sit down and take a rest.”* (pt5, control)
- *“I felt like I was an old man, you know, almost crippling to be honest, it really felt crippling, I felt really restricted”* (pt16, control)
- *“The tightness of breath was the big issue (OK, tell me more about that), well with just the slightest amount of walking I used to be able to struggle, or going up stairs and anything like that”* (pt19, control)

2. Psychological impact of cancer diagnosis and stigma of lung cancer

The shame associated with a lung cancer diagnosis had a significant impact on the psychological wellbeing of participants preoperatively. Several participants expressed a degree of self-blame and responsibility for the diagnosis due their past or current smoking status.

- *“Lung cancer is a very loaded kind of disease, I mean I had been a smoker, so you know I brought it on myself”* (pt7, control)
- *“It’s like a ghost train rollercoaster the whole diagnosis and the waiting list and the certain amount of personal disempowerment”* (pt 20, intervention)

3. Motivation (external vs internal) and need for social support

Many participants reported that their motivation to participate in exercise or increase physical activity post cancer diagnosis was initiated by external factors. Shock, fear, along with being told by the treating medical/allied health team that exercise is an essential component of the treatment regime for lung cancer, formed the basis of why participants chose to change their exercise habits with only a few reporting they were motivated by an intrinsic need to improve their situation. All participants expressed a need for social or family support during their cancer journey and particularly in the lead up to surgery where there is a great deal of uncertainty.

- *“It’s a pretty lonely time and you know I think dealing with any kind of cancer stuff you tend to have to protect everyone around you, so you wear a lot, there is a big burden..... the option to follow up post-surgery, I think it’s a really missing part of the whole system”* (pt 7, control)

4. Benefits of prehabilitation/enablers: improvement in exercise capacity, mental health, positive distraction, structure/control/purpose

Many participants identified the general benefits of exercise and were keen to find out more about the benefits of exercise after a cancer diagnosis and before surgery. Enablers to exercise included: family support, easy access/transport, guidance from trained allied health professionals, time (many participants were retired) along with

a visible improvement in their symptoms or exercise capacity. Some participants expressed a responsibility to 'give back' and participate in exercise as a way of being proactive rather than take a more passive approach in the lead-up to surgery.

- *"It made me feel useful, I was being productive instead of being all negative about it"* (pt19, control)
- *"Well because my breathing capacity had increased so much more, it was quite a change which was very encouraging and that made me keep going, because I knew there was an improvement"* (pt16, control)
- *"It did make me feel like I was productive, like I was contributing"* (pt21, intervention)
- *"Being able to have some control over, oh well perceived control over the trajectory of the whole circumstance, you know, it certainly made a difference to me."* (pt 20, intervention)

5. Desire for support/guidance and follow-up

The importance of an adequate support network was highlighted by several participants. Those with limited supports expressed a sense of isolation during the cancer diagnosis and pre-treatment period, many suggesting that support groups would have been a welcomed option during this time. Participants also expressed a desire for ongoing follow-up and support from allied health professionals beyond the postoperative period, especially where they experience ongoing symptoms and were uncertain of the correct physical activity levels and timeframes to resume normal activities.

- *"I would be returned home and no I was fairly much on my own to do my own thing, that's the thing I learnt that if I don't be responsible to myself then no one else is going to do it"* (pt9, intervention)
- *"Well just being able to share how you are feeling and that with someone else as well, it's a pretty lonely track, doing everything on your own"* (pt21, intervention)

5.5 DISCUSSION

This was the first trial within the Australian setting to assess the feasibility of prehabilitation for patients awaiting surgery for lung cancer. Our hypotheses were not fully supported. Prehabilitation in this cohort was found to be safe (no adverse events), partly acceptable to patients (consent rate, completion rate for exercise, and good qualitative feedback), and center-based & home-based exercise components were feasible for some patients to undertake before surgery. Promisingly, we also found that patients perceived prehabilitation to be a useful tool to enhance both the physical and mental aspects of their fitness before surgery. However, we had large attrition at both time points of follow-up (pre and post-surgery) which suggests that a future scaled-up version of this pilot trial (as an adequately powered RCT) is not appropriate in its current form.

Contrary to other evidence (that there may not be enough time for patients with lung cancer to undertake prehabilitation before surgery (Cavalheri & Granger, 2017), we found that there was sufficient time available for participants in our trial to exercise before surgery. In fact, the time available to participate in prehabilitation in our trial ranged from 3 – 14 weeks. Recent literature suggests a minimum of 4 weeks prehabilitation duration as an adequate timeframe to demonstrate meaningful improvements in cardiorespiratory fitness and strength outcomes (Tew et al., 2018), and whilst we were not powered to measure improvement in clinical outcomes in our participants, certainly the qualitative feedback from participants supports their belief that they benefited from the program. Prehabilitation programs of around 4 weeks, are however, very different to the traditional pulmonary rehabilitation models (for patients with chronic respiratory diseases) which usually range from 6-12 weeks duration (McCarthy et al., 2015). It is difficult to conclude if longer training periods before surgery for lung cancer may lead to greater gains in patient outcomes, the evidence to date examines prehabilitation programs of up to 4-6 weeks duration only. Significantly delaying surgery for prehabilitation is not recommended however there is no strong evidence that delays, even up to 90 days, adversely affect the outcome of patients having NSCLC resections (Quarterman, McMillan, Ratcliffe, & Block, 2003) (Bozcuk, 2001; Shin et

al., 2013). Given the disease burden and low level of pre-morbid physical activity that patients with lung cancer present with, exercise training over a longer duration may enable this population to make more significant gains preoperatively, which may translate to less postoperative morbidity, particularly in high-risk patients.

Recent international studies examining different models of exercise training in prehabilitation in lung cancer have tested much shorter programs (7 days preoperatively) combined with high intensity exercise (High Intensity Interval Training – HIIT), and these also show promising results. A randomized controlled trial by Licker et al in 2016 examining the effect of HIIT training on patients awaiting lung cancer surgery found that the HIIT intervention group significantly improved in aerobic capacity (peak oxygen consumption and 6MWT) by completing high-intensity (up to 80-100% peak WR) cycle ergometer training 2-3 times per week prior to surgery. Patients exercised in short duration sessions of 30 minutes consisting of 15-second sprints interspersed with 15-second pauses to a target of near maximal heart rate (Licker et al., 2016). Further to this, another RCT examining the effects of an intense 7-day preoperative pulmonary rehabilitation program for patients with lung cancer by Lai et al in 2017 demonstrated improvements in 30-day PPC rates, peak expiratory flow and the 6MWT distance with preoperative intervention. These patients participated in 7 days of exercise endurance training (Nu Step exercise cross trainer, resistance adjusted according to patient effort) and inspiratory muscle training for 30 minutes daily as inpatients prior to surgery. At conclusion of the 7 days, the intervention group significantly improved 6MWD (between-group difference 19.2m, $p=0.029$) and peak expiratory flow (between-group difference 18.0L/min, $p < 0.001$) with effects carrying over to 30-days post-surgery showing a significant difference in postoperative pulmonary complication rate between the intervention group (13.3%) and control group (36.7%), $p = 0.037$ (Lai, Huang, et al., 2017). This trial suggests that short-duration intense prehabilitation in lung cancer may be an effective feasible alternative however the trial was conducted in Asia where the patients were inpatients rather than outpatients prior to surgery and this may not be a model that can be extrapolated to Australia or other international settings. The feasibility of utilizing HIIT with the

participants in our trial would be questionable given that they were all older and displayed a large range of comorbidities & symptoms related to their disease which impacted on their ability to exercise even at moderate-intensity levels (which was our protocol). The qualitative interviews we conducted revealed a high psychological impact that a lung cancer diagnosis brings to these patients, which is often under-evaluated by clinicians, but also has an enormous impact on motivation and the ability to participate in preoperative exercise. Further research is required to compare the effects and feasibility of moderate versus high-intensity exercise training in prehabilitation programs for lung cancer.

We had a high attrition rate throughout the trial, with dropouts in both the intervention and control group. Some of the attrition was due to deaths ($n=2$), but interestingly two other patients withdrew from the intervention group before even commencing the exercise program. We also lost participants at follow-up after surgery. Modifications to the trial design are required before a future scaled-up version of this pilot trial (as an adequately powered RCT) could be conducted. Instead, we recommend exploring why participants are withdrawing/dropping out so that we may be able to address these barriers for future research and clinical practice. Additionally, research is required to explore the ideal target population who would benefit from prehabilitation. It may be that future trials should focus on the high-risk surgical patients who may not have surgery unless they are fitter. You would expect this would be a highly invested cohort who have much to gain from participation.

Despite emerging research on exercise prehabilitation in lung cancer, the ideal program for patients with lung cancer is yet to be determined. What is known from the studies that have been done thus far is that a 'one program fits all' approach does not work, programs must be individualized and tailored to the patient's ability and supervised by a trained health professional (Tew et al., 2018). Another consideration is the patients' preference for exercise. Many of the participants in the study expressed a preference for walking as a form of aerobic exercise as it was easy to incorporate into their current lifestyle/activity regime and did not require

additional equipment. Participants who owned a bike prior to participation in the study were more willing to engage in cycling as a form of aerobic activity, with few participants (n=3) taking up the offer of bike hire to supplement their home exercise program. The trend of lack of improvement in the ISWT results for the intervention group from baseline to 30-days post-surgery may be reflected in their preference for the lower intensity walking activity and the fact that this was mostly completed unsupervised at home where walking to gain a training effect could not be monitored. The majority of patients also expressed a keen interest in engaging in strength exercise when instructed from an exercise professional, as reduced strength was self-identified by many as a current deficit in their physical health status. Unlike results from previous studies suggesting that many lung cancer patients (42%) report that they would not like to receive exercise counselling (Leach, Devonish, Bebb, Krenz, & Culos-Reed, 2015), participants in our study indicated a keen interest in more information, advice and opportunity to engage in exercise after their lung cancer diagnosis. This is consistent with a survey conducted by Philip et al in 2014 that examined the physical activity preferences for early-stage lung cancer survivors. This survey of 175 non-small cell lung cancer patients (treated with pulmonary resection) found that the majority of respondents (62%) reported a desire to receive advice regarding physical activity, mostly before surgery (68%), in face-to-face interaction (95%) with a physician (80%) (Philip et al., 2014). This last point was particularly obvious in our exercise prehabilitation study as the patients were found to be more compliant and willing to engage in an exercise program if suggested by the treating surgeon.

The adherence to the home-based exercise component in our trial was only 55%. Some participants in the interviews reported low levels of motivation during unsupervised home sessions compared with supervised exercise. Indeed, we did not measure the intensity of exercise of the home-based sessions and simply relied on participant recall for their exercise adherence (to complete an exercise diary). It could be that participants while exercising at home had an inadequate training stimulus during unsupervised exercise. With advances in technology now, further studies could look into the use of technology to monitor exercise adherence as well

as the use of technology to motivate patients. Including behavior change strategies and individual goal setting with patients may have also improved exercise adherence. Providing more motivation to exercise and using behavior change techniques in this largely sedentary population may have reduced attrition from the program. Further to this, certain characteristics were noted amongst those who completed the trial compared to those that did not. Completers trended towards the less aggressive histopathological type of adenocarcinoma and earlier cancer stage, were non or ex-smokers who did not have a COPD diagnosis and had higher levels of self-reported physical activity. Although the pilot nature of the trial makes results difficult to extrapolate, further work looking at those who respond best to prehabilitation (or are able to complete the program) needs to occur in order to address the challenge of adherence and attrition.

Online platforms and apps for exercise prescription and/or participation are already available for the general population, further research should look to test the incorporation of such technology as a means to deliver prehabilitation programs to those otherwise unable to access center-based programs. Previous research exploring the use of telemedicine technology in oncology has described the benefits of these new methods as “empowering patients to make strides in health care from their own homes” (Wolfgang, 2019). The benefits of telehealth include: better documentation, improved patient compliance, improved continuous care for patients and enhanced communication between provider and patient (Wolfgang, 2019). Enhancing patient-health professional relationships provides a more enabling path for effective prehabilitation programs and may provide the motivation patients need to succeed. It can be seen that telehealth and/or newer technologies could be used in the lung cancer sphere to address some of the challenges currently present, i.e. access to services, support, ongoing follow-up, education and advice, which were themes that were identified by patients in the qualitative interviews.

Another obvious characteristic of the participants of our trial, which imposed restrictions on the ability to exercise, was the degree of respiratory impairment and symptoms imposed by their lung cancer. The complex symptom burden, in particular dyspnoea, fatigue and cough, combined with the mental toll of a lung cancer diagnosis mentioned by participants in the qualitative interviews, made training at the required intensity challenging. Further to this, many participants reported their shortness of breath to be very debilitating, especially with any form of exertion. These respiratory limitations, combined with the largely home-based unsupervised nature of the exercise program, may explain the lower adherence with aerobic exercise (45%) compared with strength exercises (64%). Results from the secondary outcome incremental shuttle walk test (although not powered to detect change over time) did not appear to show signs towards improvement in the intervention group and may also reflect this limited ability to exercise aerobically.

The self-reported physical activity results from our study seem at odds with the objective incremental shuttle walk test data (see Table 5.5). This data demonstrates the intervention group to have higher levels of physical activity and also a larger improvement in this measure compared with control participants. Perhaps the instruction to walk or cycle at home was carried out by the intervention participants thereby increasing the IPAQ scores although this did not lead to changes in the distance walked on the Shuttle walk test. Alternatively, this may reflect the differences between results from subjective and objective outcome activity measures.

Other studies have examined whether the addition of respiratory intervention (+/- aerobic exercise) has beneficial outcomes for individuals with lung cancer undergoing surgery. In a systematic review and meta-analysis, Mans et al evaluated the evidence to determine whether inspiratory muscle training is effective in preventing PPC and reducing hospital length of stay in patients undergoing cardiothoracic or upper abdominal surgery. The review consisted of 8 studies inclusive of 295 participants and found that inspiratory muscle training led to significantly higher maximal inspiratory pressure (mean difference 15cmH2O, 95%

C.I 9-21) and significantly reduced PPC's (RR 0.48, 95% C.I 0.26-0.89). They concluded that preoperative inspiratory muscle training significantly improves respiratory function in the early postoperative period and halves the risk of pulmonary complications (Mans, Reeve, & Elkins, 2015). Perhaps the addition of specific respiratory interventions, such as inspiratory muscle training to address respiratory impairments, in addition to the exercise component of prehabilitation would enhance its efficacy and improve outcomes in this vulnerable population. Further studies in lung cancer patients examining exercise prehabilitation in combination with respiratory and/or psychological interventions may help gain further insight into how to combat these barriers.

Our trial demonstrated that prehabilitation in lung cancer, perhaps feasible in certain patient groups, requires further evidence to determine the optimal timing, mode and target patient type before it could become part of standard clinical care for patients with lung cancer. In addition, further studies examining the cost-effectiveness of prehabilitation and the effect on health service utilization/resource allocation are also warranted. Studies comparing the effects of prehabilitation in lung cancer between different patient subtypes (high vs medium risk, histological type or patients with specific comorbidities) may help to highlight the patient subtypes that are best suited for prehabilitation in lung cancer and have the most to gain from such interventions. Another important factor to consider prior to implementation is the views of thoracic surgeons and how surgeons may refer their patients for prehabilitation prior to surgery. The next chapter in this thesis is a study which specifically surveys surgeons to address this evidence gap and gain insight into potential referral practices: which is especially important given the poor feasibility and recruitment rate that we observed in our trial.

There were several limitations to our trial. Firstly, the sample size was small, and we were not powered to detect changes in patient outcomes. The pragmatic sample size of 40 was not reached and recruitment for the trial proved difficult due to low patient numbers for surgery at the study center combined with low numbers of eligible patients. Secondly, whilst the consent rate was good with 24 of 32 participants approached agreeing to participate in the study (75%), participant

drop-out was a problem throughout the trial at all follow-up time points. Consent and drop-out rates vary greatly within the prehabilitation literature with consent rates ranging from: 12.5% (R. Y.-B. Sebio Garcia, M.I; Gimenez Moolhuyzen,E, 2017) to 80.9% (Liu et al., 2019) and drop-out rates ranging from: 5.5% (Huang et al., 2017) to 52.2% (R. Y.-B. Sebio Garcia, M.I; Gimenez Moolhuyzen,E, 2017). Previous trials have reported difficulty recruiting lung cancer patients due to their poor performance status and fluctuating health status (Benzo et al., 2011; Schofield et al., 2008). In the current study, patients were recruited at a health service (consisting of public and private hospitals) which has a dedicated thoracic unit and MDM/clinic. Recruitment at other more high-volume surgical centers may provide greater patient numbers and provide a more robust sample size for future research. Approximately 40% of patients presenting to this lung MDM were from rural centers making participation in a supervised exercise intervention and the need for regular face-to-face follow-up unachievable. Exploring other means of intervention delivery, such as telehealth, may be means by which this obstacle can be overcome in future work. Other limitations to the trial were that we relied on self-reporting for exercise adherence via an exercise diary and therefore there is the potential for overestimation of exercise participation. The BORG scale was used to monitor exercise intensity, this scale has been used extensively in both the COPD and lung cancer populations, however more objective measures such as heart rate monitors or activity trackers/pedometers may provide more objective measures of exercise intensity and compliance with exercise prescription.

5.6 SUMMARY

This was the first trial on prehabilitation in lung cancer to be conducted within the Australian setting. Our results demonstrate that prehabilitation in lung cancer is safe, partly acceptable to patients, and that the exercise program was feasible for some participants to undertake before surgery. However, our results also show that participant attrition throughout the trial, both before and after surgery, was high. This suggests that a future scaled-up version of this pilot trial (as an adequately powered RCT) is not appropriate in its current form. Instead further research is required to explore why participants are withdrawing/dropping out to be able to effectively address this before conducting an RCT. Additionally research is required to explore the ideal target population who would benefit from prehabilitation. It may be that future trials should focus on the high-risk surgical patients who may not have surgery unless they are fitter. The next chapter within this thesis outlines a study conducted to examine the attitudes and perceptions of cardiothoracic surgeons to prehabilitation in lung cancer. As referrers into prehabilitation programs, their attitudes and perceptions are extremely important to understand.

CHAPTER 6 STUDY 2

ATTITUDES AND PERCEPTIONS TO PREHABILITATION: AN ONLINE SURVEY

6.1 INTRODUCTION

This chapter outlines the 2nd study of this thesis, an online survey which was conducted involving cardiothoracic surgeons within Australia and New Zealand, examining the attitudes and perceptions of surgeons to prehabilitation in lung cancer. The study within this chapter has recently been published in *Integrative Cancer Therapies* (refer to Appendix V).

As surgeons are often the ‘gate-keepers’ to referring patients for prehabilitation, it is important to gain insight into their perspectives on prehabilitation along with their thoughts on prehabilitation within the thoracic care pathway.

It is known that individuals with lung cancer experience a high symptom burden and present with reduced levels of physical activity (C. Granger et al., 2014). This poses a significant risk for patients with operable lung cancer as it is recognized that poor cardiorespiratory fitness prior to lung surgery is predictive of poor postoperative outcomes (Myers, 2016; Santa Mina et al., 2014). Evidence suggests that preoperative exercise prior to surgery improves pulmonary function and exercise capacity (Faithfull et al., 2019; Piraux et al., 2018; Santa Mina et al., 2014). This presents a strong case for prehabilitation, as improved fitness prior to lung cancer surgery has been shown to halve the rate of postoperative complications and reduce hospital length of stay (Cavalheri & Granger, 2017; R. Sebio Garcia et al., 2016; Steffens et al., 2018). Despite this evidence, and current randomized controlled trials designed to determine the ideal mode, optimal timing and patient selection for prehabilitation in lung cancer (6 international studies registered on

ClinicalTrials.gov, table 4.1), translation into practice in the Australian setting remains stagnant.

Barriers to the implementation of robust prehabilitation programs within lung cancer include the traditional hurdles of funding and clinician and healthcare system-related factors (C. L. Granger et al., 2017; C. L. Granger, Denehy, et al., 2016). Another factor to consider is the referral basis for prehabilitation, with thoracic surgeons acting as the main 'gate-keepers' to this service. Since the inception of prehabilitation, little research has been dedicated to uncovering the perceptions or attitudes to prehabilitation amongst these gatekeepers. Only one cross-sectional survey to date has examined the perceptions of both anesthetists and colorectal surgeons to prehabilitation in the colorectal cancer patient population (M. H. Li et al., 2019). The results of this research demonstrate a clear recognition by anesthetists and surgeons of the association between functional capacity and postoperative outcomes, along with the need for more robust evidence in order for prehabilitation to become routine practice. Li and colleagues concluded that there is a 'window of opportunity' for prehabilitation within the colorectal cancer cohort of 2-4 weeks after cancer diagnosis and recommended that further multi-center or implementation studies are required.

The study outlined in this chapter attempts to add to the evidence base by specifically examining the attitudes and perceptions regarding prehabilitation of surgeons working within the field of lung cancer surgery. Prehabilitation in this sense again refers to exercise prehabilitation only, rather than multimodal prehabilitation, as this was the intervention of interest within this research work.

6.2 STUDY DESIGN AND METHODS

6.2.1 Study aims

This study aimed to determine the acceptability and perceived benefit of prehabilitation in lung cancer patients amongst thoracic surgeons throughout Australia and New Zealand. It was postulated that responses from the survey could

be used to gain further insight into the referral pathways and reasons why surgeons may or may not choose to refer patients with lung cancer for prehabilitation prior to surgery. The survey also aimed to gather data on the perceived interest in prehabilitation amongst these gatekeepers to establish if, along with the evidence currently being generated, implementation of prehabilitation into standard care was a common goal within the thoracic surgical oncology field.

The specific aims of the survey were:

- To explore the acceptability of prehabilitation before lung cancer resection amongst thoracic surgeons in Australia and New Zealand
- To explore the perceived benefit of prehabilitation amongst thoracic surgeons in Australia and New Zealand
- To understand the thoracic surgeons' view on the optimal timing of preoperative interventions

6.2.1.1 Hypotheses

- The survey response rate from thoracic surgeons would be between 20-30%
- Thoracic surgeons within Australia and New Zealand would have mixed responses in their attitudes and perceptions to prehabilitation and this would depend on a number of factors such as: place of training, years of experience, work in a dedicated thoracic unit vs mixed cardiothoracic unit and access to and knowledge/interest of prehabilitation.

6.2.2 Study design

Ethics approval to conduct the study was granted 24th June 2016 by The University of Melbourne Research and Ethics Committee, ethics number 1646932.1.

The design of this study was an online survey (refer to Appendix IV for survey questions), utilising the survey program 'Survey Monkey'

(www.surveymonkey.com; Palo Alto, CA). A 24-item survey was specifically designed for this investigation and was piloted on two thoracic surgeons prior to distribution amongst the larger target population. Questions were of a mixed format (multiple-choice, open-ended, dichotomous and rating scales).

The online survey was distributed to thoracic surgeons throughout Australia and New Zealand (n=198). A contact list of cardiothoracic surgeons was created from the Royal Australasian College of Surgeons (as thoracic surgery is not a stand-alone specialty in Australia) and an initial email was sent out inviting the cardiothoracic surgeon to participate in the survey. All eligible cardiothoracic surgery consultants in Australia and New Zealand who perform lung resection surgery for patients with lung cancer were invited to participate in the survey. Cardiothoracic surgeons conducting purely cardiac surgery were excluded from the survey. In order to capture a wider proportion of surgeons, two further email invitations were distributed via college newsletters and digital press. Paper versions of the survey were also available as requested and were also distributed at the 2016 Australian and New Zealand Society of Cardiothoracic Surgery (ANZSCTS) Annual Scientific Meeting to maximise the response rate.

The survey invitation was sent with a cover letter briefly outlining the purpose of the survey along with instructions and intended use of the survey results. Consent was implied by participation in the survey. The survey began with an introduction explaining the concept of prehabilitation along with the purpose of the questionnaire (refer to Appendix IV). The survey then captured information on the thoracic surgeons surveyed: principle place and state of practice, caseload split cardiac vs. thoracic, years of experience. This was followed by questions addressing: perceived benefits of preoperative exercise, current barriers to exercise within the lung cancer population and current referral practices within the survey participants unit of practice. The survey took approximately 10 minutes to complete.

Demographic data along with answers to the survey were collated on the online portal Survey Monkey.

6.2.3 Analysis

Analysis of the data was performed using SPSS for Windows (Version 25) using a variety of descriptive statistical methods. Demographic details of thoracic surgeons were reported using mean (SD) for parametric data and proportions for categorical data where appropriate.

6.3 RESULTS

Respondents to the survey included cardiothoracic surgeons working in tertiary public and private hospitals throughout Australia and New Zealand. The response rate to the survey was 14% (n=28), with the highest response rate from surgeons in the state of Victoria (n=16). Only 23% of the entire sample reported practicing thoracic surgery exclusively (most surgeons perform a mix of cardiac and thoracic cases).

6.3.1 Baseline demographic details

Baseline demographics are detailed in Table 6.1. The mean age of surgeons who responded to the survey was 46 years (SD 12.3). The mean years of experience amongst the sample was 12.5 years (SD 8.6). Most of the surgeons completed an average of 3.4 thoracic cases per week (range 1-8) with the average waiting period reported by 38.5% of the sample as 20 days. The mean number of hospitals the respondents operated at was over 2 (range 1-4), the mix of hospitals being public (42.3%), private (3.9%) and a combination of public and private (53.9%). The majority of hospitals that survey respondents worked in did not have a dedicated thoracic surgery unit (60%).

Table 6.1: Demographics

Characteristic	Mean (SD)
Age (years)	46 (12.3)
Experience (years)	12.5 (8.6)
Volume of Thoracic Sx (cases/week)	3.4 (1.9)
Number of hospitals operating	2.6 (0.9)
Characteristic	N (%)
State of practice	
Victoria (VIC)	16 (61.5%)
New South Wales (NSW)	2 (7.7%)
South Australia (S.A)	0 (0%)
Western Australia (W.A)	2 (7.7%)
Queensland (Qld)	2 (7.7%)
Northern Territory (N.T)	0 (0%)
Tasmania (TAS)	1 (3.8%)
New Zealand (NZ)	3 (11.5%)
Clinical Caseload	
Cardiac + Thoracic	20 (76.9%)
Thoracic only	6 (23.1%)
Public vs private	
Public	11 (42.3%)
Private	1 (3.9%)
Combination	14 (53.9%)
Dedicated thoracic unit	
Yes	10 (40%)
No	15 (60%)
Average Waiting period (days)	
10	5 (19.2%)
20	10 (38.5%)
30	6 (23.0%)
40	3 (11.5%)
50	1 (3.9%)
% of patients that are surgical oncology	
0-25%	6 (23%)
25-50%	7 (26.9%)
50-75%	9 (34.6%)
75-100%	4 (15.4%)

Characteristic	Mean (SD)
% of VATS vs Thoracotomy cases	
VATS 0-25%	3 (11.5%)
VATS 25-50%	7 (26.9%)
VATS 50-75%	6 (23%)
VATS 75-100%	10 (38.5%)
Thoracotomy 0-25%	5 (19.2%)
Thoracotomy 25-50%	8 (30.8%)
Thoracotomy 50-75%	3 (11.5%)
Thoracotomy 75-100%	1 (3.9%)

Abbreviations: VATS – Video Assisted Thoracotomy

Most of the surgeons reported that between 50-75% of their patient population for thoracic surgery were surgical oncology (n=9, 34.6% of respondents) with the majority practicing minimally invasive VATS surgery in 75-100% of their cases (n=10, 38.5%) and only 3.9% of the sample performing a large proportion of their thoracic surgery cases (75-100%) via open thoracotomy.

6.3.2 Preoperative practice

Standard preoperative work-up of thoracic surgery patients was reported and followed the recommendations as set out by the British Thoracic Society and American College of Chest Physicians and included one or more of the following: chest x-ray, CT scan or PET scan, MRI, bronchoscopy, cardiopulmonary exercise testing, 6-minute walk test, stair climb test, preoperative clinic appointment, discussion at the lung multidisciplinary meeting and/or cardiac screening. As well as this medical work-up, the majority of respondents reported that there is a perceived need to refer patients prior to lung resection to preoperative physiotherapy or prehabilitation, particularly high-risk patients or those with borderline fitness for surgery. In fact, 91.3% of surgeons were willing to delay surgery (as indicated by cancer stage/type) to optimize patients via prehabilitation. Only 4.3% of respondents answered 'no' for willingness to delay surgery for prehabilitation.

In terms of referral to preoperative physiotherapy, only 32% of the sample (n=8) reported that they do refer their thoracic surgery patients preoperatively, another 16% (n=4) reported that they sometimes refer to physiotherapy preoperatively depending on need. Only 16.7% of surgeons reported that preoperative exercise intervention delivered by allied health professionals is readily available, 50% of the respondents reported that this service was either available but difficult to refer to or not available at all (refer to figure 6.1).

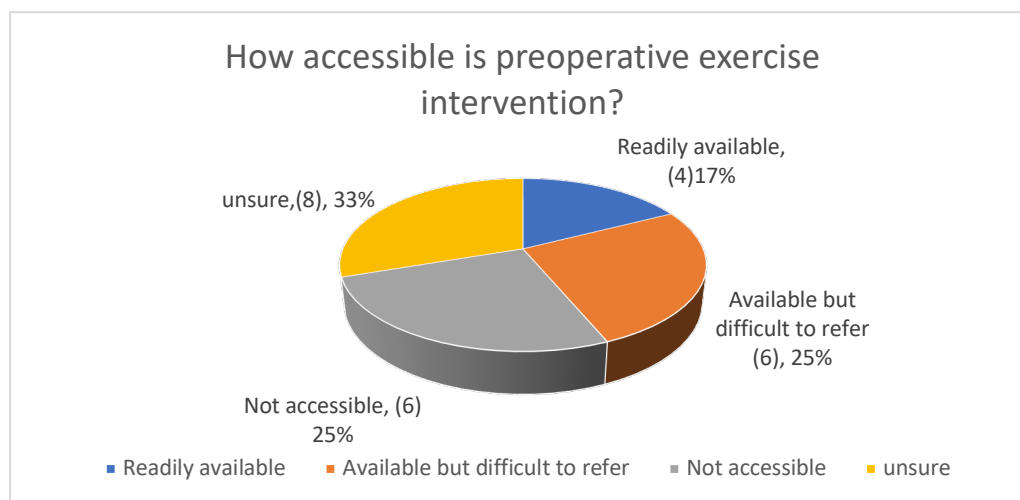


Figure 6.1: Accessibility to preoperative exercise intervention

The top three reasons why surgeons referred patients preoperatively included: high-risk for complications, standard of practice within the unit and in cases where patients were displaying borderline fitness for surgery. Table 6.2 outlines the main reasons for and against referral reported by the surgeons.

Table 6.2: Reasons for referral or non-referral to preoperative physiotherapy

Reasons for referral to preoperative physiotherapy <i>Response (n), %</i>		Reasons for not referring to preoperative physiotherapy <i>Response (n), %</i>	
High-risk patients	4 (36.4%)	Staffing limitations	2 (16.7%)
Standard practice in the unit	5 (45.5%)	Urgent need for surgery/ short waiting period	6 (50%)
Borderline fitness for surgery	5 (45.5%)	Minimal perceived need	4 (33.3%)
Surgeon/ anesthetist preference	0	Lack of evidence	1 (8.3%)
Patient request	0	Transport or access issues	2 (16.7%)
		Minimal resources available	1 (8.3%)
		Unsure who to refer to	3 (25%)

The main perceived benefits of prehabilitation (% of respondents that reported the benefit) included: reduced postoperative complications (85.7%), reduced postoperative length of stay (76.2%), improved exercise capacity (66.7%), improved quality of life (57.1%), improved symptom management (52.4%) and improved pulmonary function (47.6%) (refer to figure 6.2). A large number of surgeons reported that prehabilitation programs were either not accessible or available but difficult to refer to. The main barriers to prehabilitation recorded were: access to allied health professionals, patient comorbidities, transport or access issues, costs/financial constraints and time (refer to figure 6.3). Despite these difficulties, the perceived benefits of prehabilitation were clear and 91.7% of respondents believed that further research into prehabilitation in lung cancer was warranted.

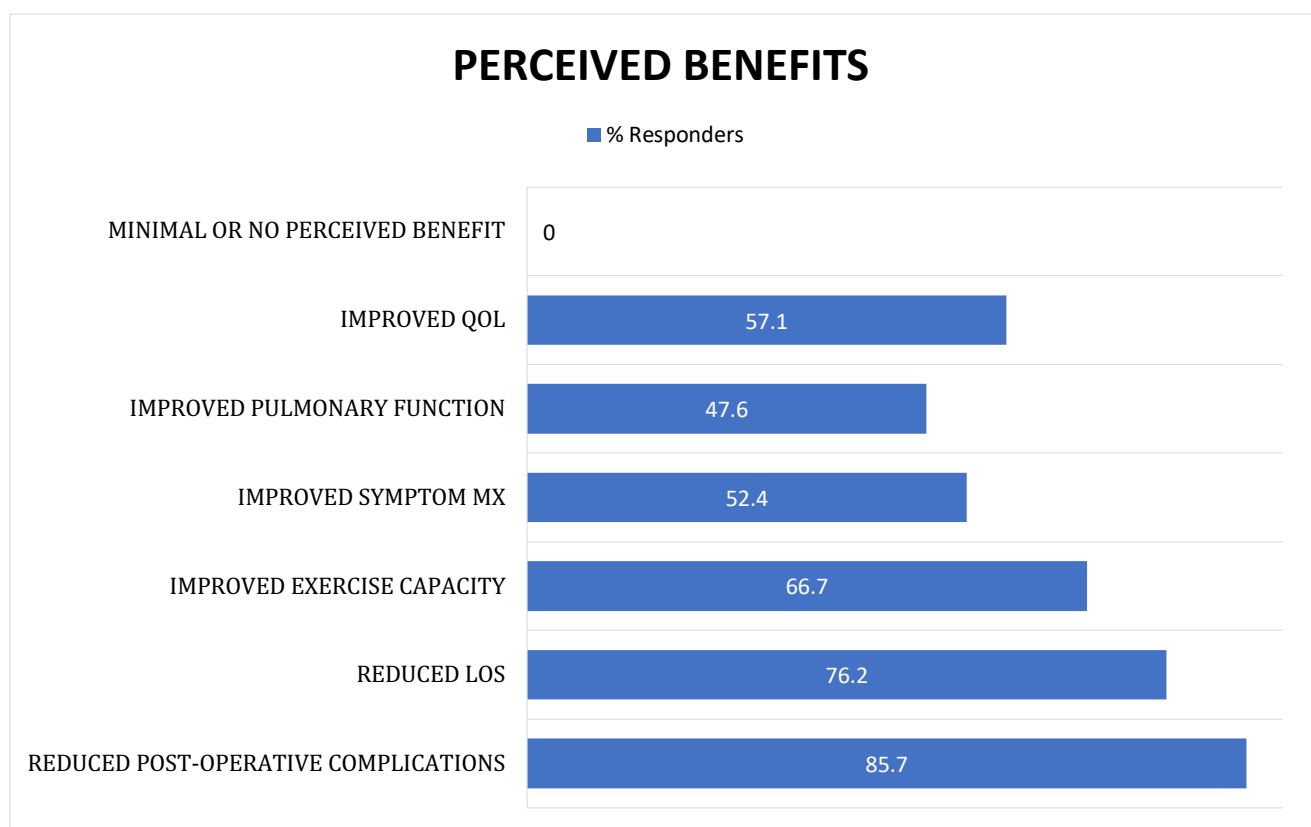


Figure 6.2: Perceived benefits of prehabilitation

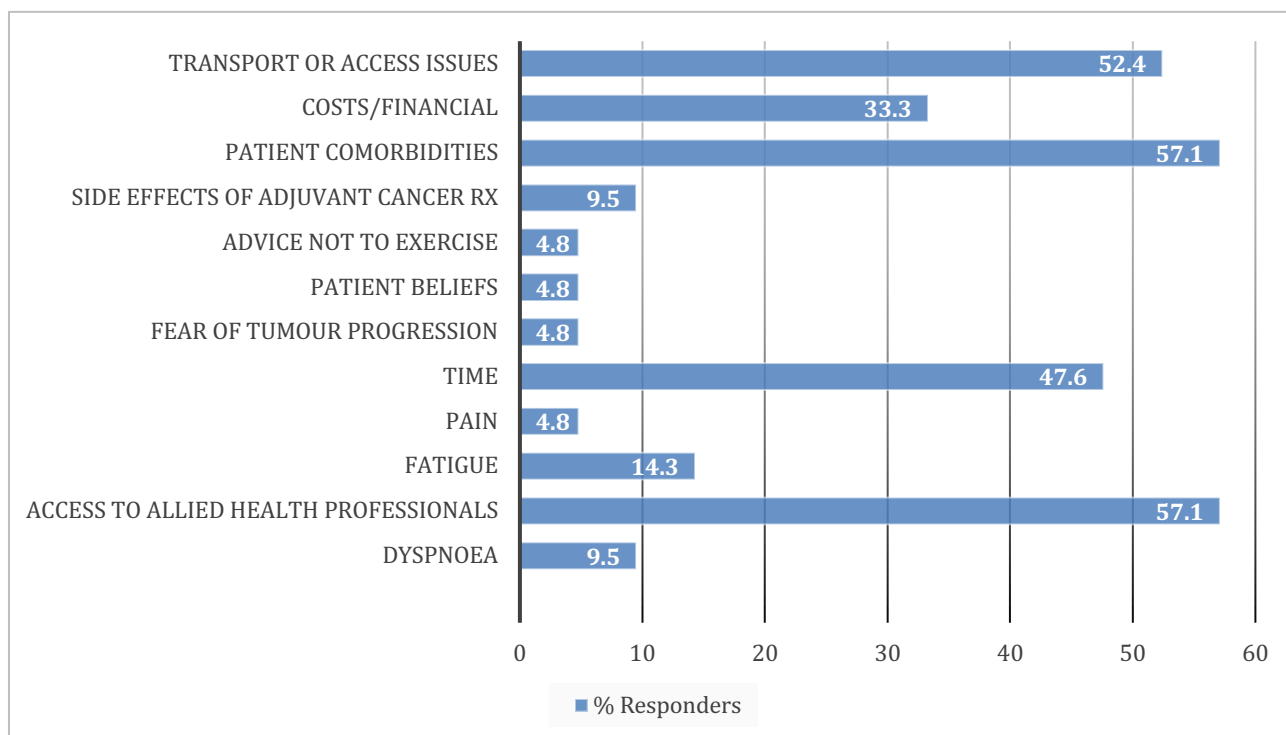


Figure 6.3: Perceived barriers to preoperative exercise in patients with lung cancer

The main factors influencing surgeons' preoperative practice on a scale of high influence to no influence included: *high influence* – literature/evidence (36%), *moderate influence* – personal experience (52%), surgical unit structure/practice (52%), and availability of resources (41.7%), *neutral influence* – staffing (50%) and patient type (public vs private) (20.8%), *little influence* – waiting lists (29.2%) and *no influence* – financial constraints (50%).

6.3.3 Postoperative practice

The average postoperative length of stay was 6-7 days (54.5% of respondents) with all surgeons reporting that respiratory physiotherapy was delivered as part of the standard postoperative care along with a thoracic surgery pathway. Only 18% of those surveyed reported that they refer patients post lung resection for pulmonary rehabilitation as part of their ongoing care. All surgeons reported that their units provide postoperative respiratory physiotherapy as part of the inpatient care (100%) with the majority being delivered via a specific thoracic surgery clinical

pathway (63.6%). Postoperative follow-up after hospital discharge in an outpatient clinic was also reported as standard practice by most surgeons (95.5%).

6.4 DISCUSSION

This was the first study in the Australian setting examining the attitudes and perceptions of thoracic surgeons to prehabilitation in lung cancer. The results of this study demonstrate a keen interest in prehabilitation amongst thoracic surgeons, with many willing to delay surgery for the optimization of their patients, however further robust evidence for prehabilitation in lung cancer is required. This is consistent with those of a recent survey performed on colorectal surgeons and anaesthetists which concluded that surgeons recognise the clear association between functional capacity and postoperative outcomes, robust evidence for prehabilitation is currently lacking and that surgeons would be willing to delay surgery (up to 2 weeks) in order to optimize their patients (M. H. Li et al., 2019).

The response rate for this study was low (14.1%) with only 28 of 198 cardiothoracic surgeons responding to the request for participation. This compares with the survey conducted by Li et al who surveyed both colorectal surgeons and anaesthetists regarding prehabilitation gaining an overall response rate of 18.7%. Within Li's study the target population was larger (approximately 1207 medical professionals), however responses from both anaesthetists and surgeons was low (15.5% and 34.3% respectively), reflecting what we know about surveys as a research method and the difficulty obtaining adequate response rates from the medical profession who have limited time available. Despite the low response rate in our study, a large proportion of the respondents were from the state of Victoria. (61.5%). This is an interesting point as many of the cardiothoracic surgeons within Australia practising purely thoracic surgery are based in Melbourne. This makes the responses directly representative of the current work practices of those working closely with patients with lung cancer and highlights the perceived need for further evidence in prehabilitation for lung cancer.

Despite the results of the survey demonstrating that the majority of cardiothoracic surgeons practice minimally invasive techniques (VATS), postoperative morbidity remains a concern for many surgeons in the postoperative phase. The incidence of postoperative pulmonary complications such as pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), pulmonary oedema and respiratory failure ranges from 4.8 – 54.6% (Jing, 2018) and is higher in patients with identifiable risk factors such as advanced age, smoking history, comorbid respiratory disease such as chronic obstructive pulmonary disease (COPD), reduced percentage predicted forced expiratory volume in 1 second (FEV1), high body mass index (BMI) (P. J. Agostini et al., 2018) and poor exercise tolerance (Weinstein, Bates, Spaltro, Thaler, & Steingart, 2007). The response to the survey question '*Out of the patients that you refer preoperatively, can you describe why these patients are referred to physiotherapy?*' further highlights this concern as the top two reasons why they refer is related to high-risk patients or patients with borderline fitness for surgery. The main reason cited for not referring to preoperative physiotherapy (exercise intervention) was an urgent need for surgery or short waiting period. The literature to date supports the use of prehabilitation in lung cancer in reducing this postoperative morbidity with a recent systematic review concluding that preoperative exercise intervention halves the rate of postoperative complications (RR 0.52, 95% CI 0.36 – 0.74) and reduces hospital length of stay (MD -2.86 days, 95% CI -5.4 to -0.33) in patients undergoing lung resection (Steffens et al., 2018). Clearly the evidence is emerging, however it is the promotion of the role that physiotherapists can play in modifying patient risk factors and providing interventions that may help reduce postoperative morbidity which needs further work.

Achieving a greater awareness of the role physiotherapists/prehabilitation can play in reducing postoperative morbidity would be assisted by further studies looking specifically at the cost-benefit of providing prehabilitation in lung cancer. Many of the studies to date have examined the effect prehabilitation in lung cancer has on patient and postoperative outcomes, however this may not be measuring the same outcomes that surgeons have identified as being important. In terms of surgical

practice, the top priorities for surgeons include morbidity, mortality and practicing in a way that adds value to their service. If we can prove that prehabilitation demonstrates clear cost saving advantages, for example the dollar value of inpatient hospital resources and reduced postoperative complications, perhaps there would be more acceptance and integration of prehabilitation into current thoracic surgery care pathways. The fact that the surgeons surveyed were able to identify the key benefits of preoperative exercise and that 91.7% of them believe further research into prehabilitation is warranted adds strength to this argument and suggest that we need to provide the most convincing evidence possible, perhaps by focusing on more than feasibility.

There is strong evidence that pulmonary rehabilitation improves exercise tolerance, reduces symptoms and improves quality of life in patients with COPD (McCarthy et al., 2015; Puhan, Gimeno-Santos, Cates, & Troosters, 2016; Rochester, Fairburn, & Crouch, 2014). Growing interest in populations with respiratory disease other than COPD has prompted further research into the benefits of pulmonary rehabilitation in other patient cohorts. Within lung cancer, the symptom burden that patients present with is very similar to COPD (dyspnoea, cough, fatigue, anxiety, depression, impaired QoL, poor exercise tolerance) and may respond to pulmonary rehabilitation type interventions. Studies to date examining the effect of pulmonary rehabilitation in lung cancer have demonstrated improvements in exercise endurance, exercise capacity, muscle strength, shorter hospital length of stay, fewer postoperative pulmonary complications as well as reclassification of operability in patients deemed to be of borderline fitness (Rochester et al., 2014). Despite the evidence, uptake of this service remains low in lung cancer (Marthick.M, 2018). In this survey, 60% of surgeons surveyed identified pulmonary rehabilitation as a service available preoperatively, however only 16.7% reported that preoperative exercise intervention with an allied health professional was readily available. Clearly there is a disconnect between what services are available and which services, if any, surgeons refer to. Also, despite pulmonary rehabilitation existing, being an outpatient service offered by most major tertiary hospitals, only 18% of those surveyed reported that they refer their patients postoperatively as part of

their ongoing care (many of which have co-existing respiratory disease such as COPD). Indeed, many of the prehabilitation programs outlined in the lung cancer literature use the pulmonary rehabilitation model as the basis of their intervention design due to the high level of efficacy it has shown in patients with chronic respiratory disease. It appears that, although these services are available, they are under-utilized, further emphasizing the fact that services providing exercise in lung cancer need to be promoted further so that patients can benefit from them and so that they become part of routine care.

The strongest message this survey uncovered was the overwhelming support for prehabilitation amongst surgeons in order to optimize their 'high-risk' patients preoperatively. 91.3% of cardiothoracic surgeons surveyed would be willing to delay surgery for prehabilitation (depending on the stage/operability of the tumour) indicating that there is potential for prehabilitation to fill a current gap in the lung cancer care pathway, particularly in patients with borderline fitness for surgery. This is corroborated by Li et al's survey of colorectal surgeons who also reported that surgeons would be willing to delay surgery for 2-4 weeks for prehabilitation (M. H. Li et al., 2019). These results clearly demonstrate the recognition that surgeons have of the association between functional capacity and postoperative outcomes, and point toward the acute or urgent need for allied health professionals to work to integrate prehabilitation services into current routine practice.

6.5 SUMMARY

This survey of cardiothoracic surgeons within Australia and New Zealand is the first to test the perceptions and attitudes of these gatekeepers to prehabilitation within lung cancer. The results clearly demonstrate a keen interest in prehabilitation within the thoracic surgical oncology population, with 91.3% of survey respondents willing to delay surgery for prehabilitation, however further evidence is required to provide a convincing argument for its incorporation into routine care within lung cancer surgery. This is evidenced by the fact that 91.7% of respondents agreed that further research into prehabilitation is warranted. Knowledge of the benefits of preoperative exercise and conditioning of patients prior to surgery is well known throughout the surgical and anaesthetic literature. Strong evidence also exists demonstrating the benefits of exercise throughout all stages of the cancer continuum, especially in the preoperative stage. The challenge lies in establishing strong referral pathways, developing good relationships with these gatekeepers and being able to provide well-developed prehabilitation program services in order to deliver these benefits to the patients most debilitated by lung cancer.

The next chapter summarizes the findings of this thesis and discusses the future directions.

CHAPTER 7 CONCLUSION AND FUTURE DIRECTIONS

7.1 SUMMARY OF THESIS FINDINGS

Non-small cell lung cancer (NSCLC) is the fifth most common cancer in Australians and the leading cause of cancer-related mortality, being responsible for more deaths than breast, colorectal and prostate cancer combined (AIHW, 2019). Patients with lung cancer display a complex cluster of symptoms including fatigue, breathlessness, pain, psychological distress and depression, which contribute to the spiral of decline in levels of physical activity. Reduced exercise capacity, combined with the deconditioning induced by cancer, make patients with lung cancer particularly vulnerable, especially at the time of diagnosis, and more likely to experience significant suffering as a result of the burden of their disease. The impact of this on physical activity levels leads to a vicious cycle of inactivity and functional decline (Granger, 2013). Poor fitness prior to surgery increases the likelihood of longer postoperative hospital stay, higher incidence of complications and increased morbidity (Myers, 2016; Richardson et al., 2017). Improving physical activity levels and functional capacity prior to lung cancer surgery may have positive beneficial effects on the complex symptom burden experienced by these individuals as well as reduce postoperative morbidity.

The primary aims of this research were to determine the feasibility of a prehabilitation program for individuals with stage I-IIIa lung cancer undergoing lung resection surgery, this work included a pilot RCT, as well as an online survey to determine the opinions and current beliefs of thoracic surgeons within Australia and New Zealand to prehabilitation. The main findings from the studies included within this thesis are outlined below.

Study 1 (Pilot RCT):

- Prehabilitation prior to lung cancer surgery is safe, partly acceptable and that the exercise program was feasible for some participants to undertake before surgery.
- The trial consent rate was good (75%) but the high drop-out rate was significant (58% by 30 days post-op). Consent and drop-out rates vary greatly within the prehabilitation literature with consent rates ranging from: 12.5% (Sebio-Garcia 2017) to 80.9% (Liu et al., 2019) and drop-out rates ranging from: 5.5% (Huang et al., 2017) to 52.2% (R. Y.-B. Sebio Garcia, M.I; Gimenez Moolhuyzen, E, 2017).
- Given the attrition rate was so high we do not believe that a future scaled-up version of this pilot trial (as an adequately powered RCT) is appropriate in its current form. Instead further research is required to explore why participants are withdrawing/dropping out to be able to effectively address this before conducting an RCT. Additionally research is required to explore the ideal target population who would benefit from prehabilitation. It may be that future trials should focus on the high-risk surgical patients who may not have surgery unless they are fitter.
- The mean time from diagnosis to surgery was 59 days (SD 26) providing adequate timeframes for prehabilitation to occur.
- Adherence to the unsupervised home-based exercise intervention varied. Participants were more compliant with strength training (64%), compared with aerobic training (45%).
- Both intervention and control groups were small (n=7 for each group at final analysis), therefore inferences about secondary physical and patient-reported outcomes cannot be made with certainty as the RCT was not powered to detect such changes.
- From the qualitative interviews, the perceived benefits of prehabilitation for participants were improvements in exercise capacity and mental health.
- Participants were satisfied with the prehabilitation program and felt that it was a 'positive distraction' in their preparation for surgery. Some participants

mentioned the program gave them a 'sense of control' in the period of uncertainty after lung cancer diagnosis and they were motivated to improve their exercise/functional capacity due to the prospects of having to undergo surgery for their cancer.

- Participants reported issues with motivation to exercise, different sources worked for different individuals (internal vs external), social support was vital to maintaining motivation.
- Participants indicated a desire for more information and guidance on ideal levels of physical activity and exercise after a lung cancer diagnosis. Advice to exercise was encouraged by their treating surgeon and this helped to motivate the individuals to take action.
- Participants indicated a need for longer-term follow up, particularly postoperatively after their discharge from hospital. The pilot RCTs endpoint was 30-days post-surgery however patients indicated that once they had started exercising, they were motivated to continue some form of physical activity and would have liked more general advice/guidance for maintenance activities.
- Participants capacity to perform exercise was often limited by their lung cancer symptoms but also their pre-existing comorbidities. Many had other conditions, some of which required other surgery, or were taking medications for chronic health conditions which impacted their tolerance to exercise.

Study 2 (Online survey):

- Respondents to the survey included 28 cardiothoracic surgeons working in Australia and New Zealand, mean age 46 years (SD 12) with mean years of experience 12 (SD 9). Most surgeons practiced a mix of cardiac and thoracic cases with only 23% of the sample performing thoracic surgery exclusively. For their current thoracic surgery practice: the average waiting period between diagnosis and surgery was reported as 20-days, the average postoperative length of stay was reported as 6-7 days.
- The highest factors influencing the surgeons' current practice included: literature/evidence, followed by personal experience and surgical unit structure/practice, followed by staffing and availability of resources.
- When asked if they refer patients to physiotherapy preoperatively, 48% of the sample answered 'no'. Only 17% of the respondents reported that preoperative exercise intervention with an allied health professional was readily accessible.
- Despite 60% of the sample stating that pulmonary rehabilitation was available as a resource to patients with lung cancer, only 18% of the surgeons refer their patients to this program after surgery.
- The main reasons cited as the need for prehabilitation (preoperative exercise intervention) included: high-risk patients, borderline fitness for surgery and standard practice within their unit.
- The main reasons cited for not referring for preoperative physiotherapy include; urgent need for surgery/short waiting period, staffing limitations, minimal perceived need, unsure who to refer to and transport/access issues.
- The main perceived barriers to prehabilitation included: access to allied health professionals, time, patient comorbidities, transport/access issues and costs/financial constraints.
- The main perceived benefits of prehabilitation included: reduced postoperative complications, reduced postoperative length of stay, improved exercise capacity, improved symptom management, improved pulmonary function tests and improved quality of life.

- When asked if they would be willing to delay surgery for prehabilitation, 91% of the sample answered yes (depending on the stage/operability of the cancer).
- 92% of the sample believed that further research into prehabilitation for patients with lung cancer is warranted.

7.2 STRENGTHS AND LIMITATIONS

A very clear strength of this research was that prehabilitation was accepted and appreciated by the sub-group of patients with lung cancer who participated in and completed the program. Feedback from the qualitative interviews of participants was that availability of such a novel program was of utmost benefit in terms of better preparing the individuals for their surgery and actively involving them in their treatment pathway, rather than simply being passive bystanders. Some participants mentioned 'empowerment', a sense of control, a 'positive distraction' as words used to describe their perception of what the prehabilitation program meant to them. Also, the desire expressed by participants for more education, guidance/advice and follow-up that came from the qualitative interview responses indicates that prehabilitation was well received and an option that most patients are interested in.

Results of the online survey study echo this interest in prehabilitation. Many of the surgeons interviewed acknowledged the benefits of prehabilitation for their patients, with just over 91% indicating that they would be willing to consider delaying surgery to conduct prehabilitation on appropriate patients. This also highlights a strength for the work within this thesis, as interest in prehabilitation and what it can offer both patients and surgeons exist, the next step is being able to provide the service as part of standard care in order to cement this interest and optimize the cancer treatment pathway in lung cancer.

A number of limitations in the studies included within this thesis have been identified, review of these limitations may help shape future work in this area of prehabilitation in lung cancer. As the RCT included within this research work was a pilot/feasibility trial the sample size was small therefore the study was not powered

to demonstrate significant changes in any of the secondary outcome measures. Despite the small sample size ($n = 24$), the RCT did achieve its primary outcome of assessing feasibility of prehabilitation within the lung cancer population and found it to be safe but high attrition impacts feasibility before lung resection surgery. Challenges within this area include: recruitment, patient and surgeon 'buy-in' to preoperative exercise programs, providing models of care allowing access for patients in rural areas, as well as stratifying and then targeting the most responsive sub-group of patients who have the most to gain from prehabilitation. Additionally, providing more motivation to exercise and using behavior change techniques in this largely sedentary population may have improved attrition from the program. We have been able to identify potential issues for trial design that can be utilized by other researchers to design subsequent trials.

A further limitation of the RCT was the focus on the single component of exercise in the prehabilitation program. Recent literature has emphasized that multimodal prehabilitation addressing exercise, respiratory training, nutrition optimization, psychological wellbeing and lifestyle modification *collectively* maximizes its effectiveness (Scheede-Bergdahl et al., 2019). Inclusion of respiratory intervention to the exercise program in the RCT may have shown more benefit to this patient population, especially when many of them exhibited co-existing respiratory disease (COPD) for which there is strong evidence for both exercise and inspiratory muscle training (Beaumont, Forget, Couturaud, & Reyckler, 2018; McCarthy et al., 2015).

Lastly, in regard to the online survey, the overall response rate was poor ($n = 28$ cardiothoracic surgeons) at only 14%, this limits the generalizability of the results. Medical professionals are notorious for their poor response rate to surveys, a similar survey study examining the views on prehabilitation amongst anesthetists and colorectal surgeons yielded a response rate of only 18.7%. Despite methods attempting to increase response rate by: being available online as well as in paper format, being distributed on multiple occasions at different timepoints/locations and an email reminder being sent out, the low response rate makes it difficult to gain a full appreciation of the attitudes and perceptions of surgeons to prehabilitation in lung cancer. The results of the survey do show positivity and interest in

prehabilitation, 92% believe that further research in prehabilitation in lung cancer is warranted, so perhaps an alternate research method (such as focus groups or interviews) would have yielded better results.

7.3 FUTURE DIRECTIONS

Current interest in prehabilitation has resulted in the conduct of a large number of studies specifically examining the effect of prehabilitation in the cancer population. Initial studies in prehabilitation examined the safety of exercise within the surgical oncology patient population and concluded that preoperative exercise is safe, feasible and associated with few adverse outcomes (L. E. Jones, N.D; Waner,E; Joy,A.A, 2009; Schmitz K, 2005). Figure 7.1 represents a conceptual diagram outlining the main findings from these prehabilitation studies in oncology along with the current evidence available for lung cancer and potential future work

Within the lung cancer population, 11 systematic reviews (inclusive of 10 randomized controlled trials) have been published in the past eight years which examine the different components of preoperative exercise intervention and their effects on various outcomes (exercise capacity, HRQoL, fatigue levels and symptoms as well as postoperative morbidity). These systematic reviews provide the highest level of evidence in support of prehabilitation (Granger 2011, Crandall 2014, Rodriguez-Larrad 2014, Pouwels 2015, Sebio-Garcia 2016, Mainini 2016, Ni 2017, Dreissen 2017, Steffens 2018, Rosero 2019). Many of these systematic reviews include trials where the exercise intervention occurred both in the pre and postoperative/post cancer treatment stages making it challenging to ascertain the benefits of prehabilitation alone. The trials within these reviews are mostly pilot studies with small sample sizes and only moderate methodological quality. Also, due to the heterogeneity of the exercise interventions included in these studies along with the variability in outcome measures used and time points assessed, meta-analysis has been unable to be performed in all but four of these systematic reviews. Despite this, the studies that have been published provide evidence for prehabilitation in lung cancer suggesting that preoperative exercise intervention

prior to lung resection leads to improvements in postoperative outcomes: 48% decrease in incidence of PPCs (Steffens et al., 2018), decreased hospital length of stay by 3 days (Steffens et al., 2018) and improved exercise capacity. Varied results have been reported for HRQoL, symptoms and changes in pulmonary function test outcomes.

It seems clear that prehabilitation for individuals with lung cancer preparing for lung resection surgery provides numerous benefits, either physical/psychological or both, however what is not currently known is the exact sub-group of patients with lung cancer who respond best to this intervention. Targeting the most frail or sedentary individuals with the lowest baseline functional capacity who have the most to gain from increasing their physical activity levels and functional capacity makes sense. However, the challenge lies in getting 'buy-in' from these patients and providing interventions that are achievable given their multiple comorbidities and current lifestyles. This thesis focused specifically on the exercise component of prehabilitation, the results of the studies forming this work show that preoperative exercise intervention is feasible and is relatively well adhered to when the program is individualised, personalised and supervised/guided by a trained allied health professional. Further to this, there is keen interest by both patients and surgeons in prehabilitation for lung cancer, with both groups indicating that more information/education and preoperative exercise intervention/services should be available. Future studies combining multiple prehabilitation components (for example exercise combined with nutrition, psychological and respiratory interventions) may have a better combined effect for the lung cancer population. Larger multicentre, high-quality trials in lung cancer prehabilitation are also needed to demonstrate improvement in clinical outcomes.

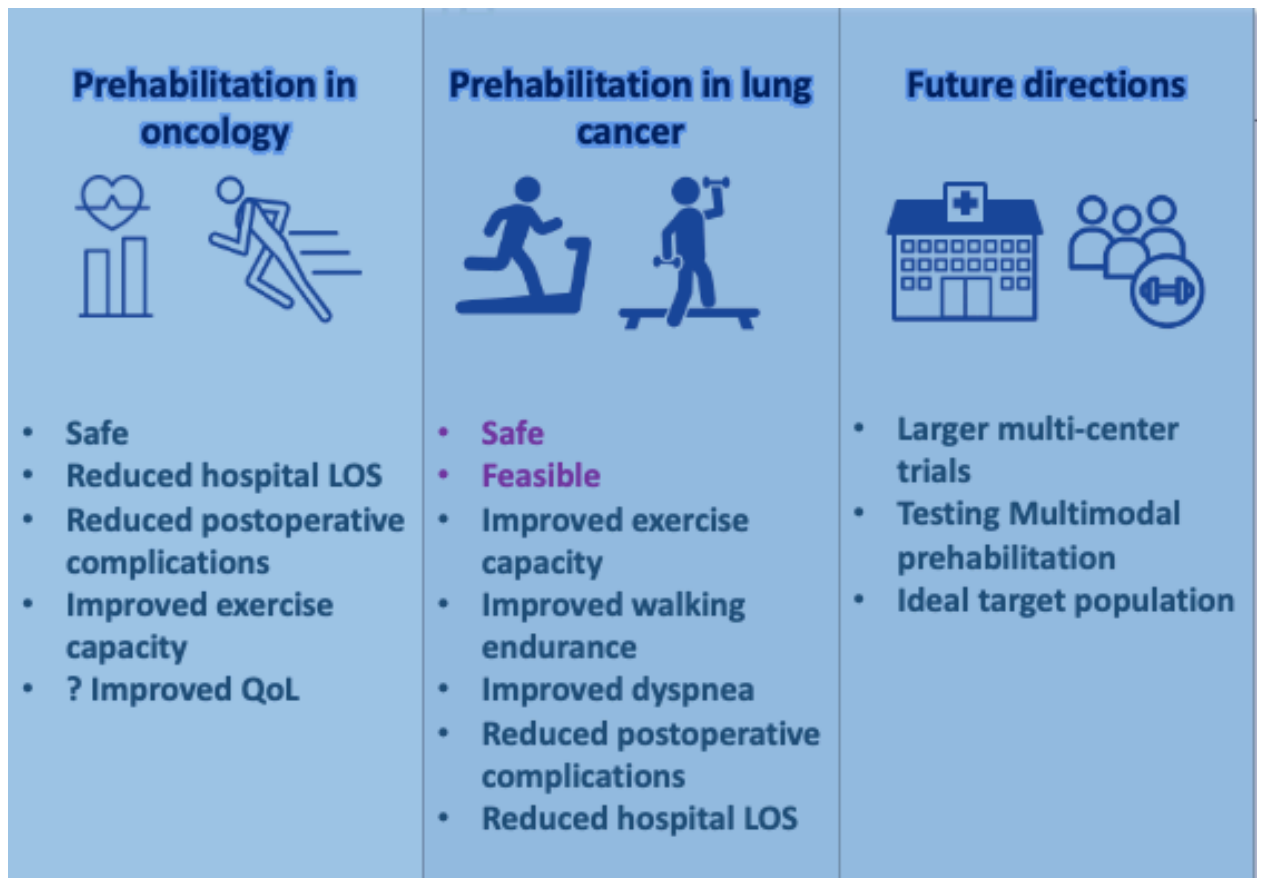
As well as promotion of the beneficial role that prehabilitation can have in the lung cancer patient's journey, exploration of the cost-effectiveness of prehabilitation and the best methods of implementation (translation of research findings into practice) need to occur if future trials are positive. Clarifying which outcomes are important and gaining consensus amongst researchers and clinicians about the ideal models of

prehabilitation and timing of outcome assessment will help strengthen the quality of research within this area and provide the robust evidence required to lead change in current clinical practice. Focused studies examining the dollar cost value of prehabilitation, rather than simply postoperative outcomes (such as morbidity, PPCs and LOS), are needed to prove the worth of multi-modal prehabilitation in terms of value to the patient and clinicians, best use of hospital/organisational resources and/or benefits to the health service.

In light of recent research on the role that patient education plays in improving surgical outcomes, focus of the preoperative education aspects of prehabilitation also need to be addressed. The multicentre randomized controlled trial by Boden et al (2018) demonstrates that just 30-minutes of preoperative physiotherapy education with patients undergoing major open upper abdominal surgery has significant advantages in terms of improved postoperative outcomes. Results of this study showed that the incidence of PPC's was halved (adjusted hazard ratio 0.48, 95% CI 0.30 – 0.75, $p= 0.001$) in the intervention group compared with the control group with an absolute risk reduction of 15% (95% CI 7% - 22%) (Boden et al., 2018). It has yet to be determined the effect that this preoperative education could have when combined with exercise prehabilitation (+/- other components of prehabilitation). This trial demonstrates the potential for preoperative education to have significant impact on postoperative morbidity and provides further strength to the argument for prehabilitation.

To conclude, prehabilitation for individuals undergoing lung cancer surgery is safe and certain aspects are feasible, the work in this thesis adds to the knowledge that we currently have regarding the role of exercise for individuals after a cancer diagnosis. The overall results from the included studies highlight a keen interest in lung cancer prehabilitation both from patients and surgeons, indicating that more work needs to occur in order for this important intervention to become part of the standard preoperative clinical practice for patients with lung cancer.

Figure 7.1: Conceptual diagram – future directions



Purple font represents the findings of this thesis in relation to prehabilitation in lung cancer.

REFERENCES

- Aaronson, N. A., S; Bergman, B. (1993). The European Organisation for the research and treatment of cancer QLQ-C30: a quality of life instrument for the use in international clinical trials in oncology. *Journal of the National Cancer Institute*, 85(5), 365 - 376.
- Abbosh, C., Birkbak, N. J., & Swanton, C. (2018). Early stage NSCLC - challenges to implementing ctDNA-based screening and MRD detection. *Nat Rev Clin Oncol*, 15(9), 577-586. doi:10.1038/s41571-018-0058-3
- Aberle, D. R., DeMello, S., Berg, C. D., Black, W. C., Brewer, B., Church, T. R., . . . National Lung Screening Trial Research, T. (2013). Results of the two incidence screenings in the National Lung Screening Trial. *N Engl J Med*, 369(10), 920-931. doi:10.1056/NEJMoa1208962
- Agostini, P., Cieslik, H., Rathinam, S., Bishay, E., Kalkat, M. S., Rajesh, P. B., . . . Naidu, B. (2010). Postoperative pulmonary complications following thoracic surgery: are there any modifiable risk factors? *Thorax*, 65(9), 815-818. doi:10.1136/thx.2009.123083
- Agostini, P. J., Lugg, S. T., Adams, K., Smith, T., Kalkat, M. S., Rajesh, P. B., . . . Bishay, E. (2018). Risk factors and short-term outcomes of postoperative pulmonary complications after VATS lobectomy. *Journal of Cardiothoracic Surgery*, 13(1). doi:10.1186/s13019-018-0717-6
- AIHW. (2011). *Lung cancer in Australia: an overview* Retrieved from Canberra: <https://www.aihw.gov.au/reports/cancer/lung-cancer-in-australia-overview/contents/table-of-contents>
- AIHW. (2019). *Cancer in Australia 2019*. Retrieved from Canberra: <https://www.aihw.gov.au/reports/cancer/cancer-in-australia-2019/contents/table-of-contents>
- Arnardottir, R. H., Emtner, M., Hedenstrom, H., Larsson, K., & Boman, G. (2006). Peak exercise capacity estimated from incremental shuttle walking test in patients with COPD: a methodological study. *Respir Res*, 7, 127. doi:10.1186/1465-9921-7-127
- Banugo, P., & Amoako, D. (2017). Prehabilitation. *BJA Education*, 17(12), 401-405. doi:10.1093/bjaed/mkx032
- Beaumont, M., Forget, P., Couturaud, F., & Reyckler, G. (2018). Effects of inspiratory muscle training in COPD patients: A systematic review and meta-analysis. *Clin Respir J*, 12(7), 2178-2188. doi:10.1111/crj.12905
- Ben-Aharon, I., Gafer-Gvili, A., Leibovici, L., & Stemmer, S. M. (2012). Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. *Acta Oncol*, 51(8), 996-1008. doi:10.3109/0284186X.2012.709638
- Bendixen, M., Jørgensen, O. D., Kronborg, C., Andersen, C., & Licht, P. B. (2016). Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. *The Lancet Oncology*, 17(6), 836-844. doi:10.1016/s1470-2045(16)00173-x
- Benzo, R., Kelley, G. A., Recchi, L., Hofman, A., & Sciruba, F. (2007). Complications of lung resection and exercise capacity: a meta-analysis. *Respir Med*, 101(8), 1790-1797. doi:10.1016/j.rmed.2007.02.012

- Benzo, R., Wigle, D., Novotny, P., Wetzstein, M., Nichols, F., Shen, R. K., . . . Deschamps, C. (2011). Preoperative pulmonary rehabilitation before lung cancer resection: results from two randomized studies. *Lung Cancer*, 74(3), 441-445. doi:10.1016/j.lungcan.2011.05.011
- Bergman, B. A., N.K; Ahmedzai, S. (1994). The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for the use in lung cancer clinical trials. The EORTC Study Group on Quality of Life. . *European Journal of Cancer*, 30A(5), 635 - 642.
- Bjelland, I. D., A.A; Haug, T.T et al. (2002). The validity of the hospital depression and anxiety scale - an updated literature review. *The Journal of Psychosomatic Research*, 52(2), 69 - 77.
- Boden, I., Skinner, E. H., Browning, L., Reeve, J., Anderson, L., Hill, C., . . . Denehy, L. (2018). Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double blinded, multicentre randomised controlled trial. *BMJ*, 360, j5916. doi:10.1136/bmj.j5916
- Bohannon, R. W., Bubela, D. J., Magasi, S. R., & Gershon, R. C. (2011). Relative reliability of three objective tests of limb muscle strength. *Isokinet Exerc Sci*, 19(2). doi:10.3233/IES-2011-0400
- Bozcuk, H. M., C. (2001). Does treatment delay affect survival in non-small cell lung cancer? A retrospective analysis from a single UK centre. *Lung Cancer*, 34, 243 - 252.
- Bradley, A., Marshall, A., Stonehewer, L., Reaper, L., Parker, K., Bevan-Smith, E., . . . Naidu, B. (2013). Pulmonary rehabilitation programme for patients undergoing curative lung cancer surgery. *Eur J Cardiothorac Surg*, 44(4), e266-271. doi:10.1093/ejcts/ezt381
- Bradley, S. H., Kennedy, M. P. T., & Neal, R. D. (2019). Recognising Lung Cancer in Primary Care. *Adv Ther*, 36(1), 19-30. doi:10.1007/s12325-018-0843-5
- Brenner, D. R., Yannitsos, D. H., Farris, M. S., Johansson, M., & Friedenreich, C. M. (2016). Leisure-time physical activity and lung cancer risk: A systematic review and meta-analysis. *Lung Cancer*, 95, 17-27. doi:10.1016/j.lungcan.2016.01.021
- Brocki, B. C., Andreasen, J., Nielsen, L. R., Nekrasas, V., Gorst-Rasmussen, A., & Westerdahl, E. (2014). Short and long-term effects of supervised versus unsupervised exercise training on health-related quality of life and functional outcomes following lung cancer surgery - a randomized controlled trial. *Lung Cancer*, 83(1), 102-108. doi:10.1016/j.lungcan.2013.10.015
- Brunelli, A., Belardinelli, R., Refai, M., Salati, M., Socci, L., Pompili, C., & Sabbatini, A. (2009). Peak oxygen consumption during cardiopulmonary exercise test improves risk stratification in candidates to major lung resection. *Chest*, 135(5), 1260-1267. doi:10.1378/chest.08-2059
- Brunelli, A., Charloux, A., Bolliger, C. T., Rocco, G., Sculier, J. P., Varela, G., . . . European Society of Thoracic Surgeons joint task force on fitness for radical, t. (2009). ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). *Eur Respir J*, 34(1), 17-41. doi:10.1183/09031936.00184308

- Brunelli, A., Kim, A. W., Berger, K. I., & Addrizzo-Harris, D. J. (2013). Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*, 143(5 Suppl), e166S-e190S. doi:10.1378/chest.12-2395
- Bueno, J., Landeras, L., & Chung, J. H. (2018). Updated Fleischner Society Guidelines for Managing Incidental Pulmonary Nodules: Common Questions and Challenging Scenarios. *Radiographics*, 38(5), 1337-1350. doi:10.1148/rg.2018180017
- Cabilan, C. J., Hines, S., & Munday, J. (2015). The effectiveness of prehabilitation or preoperative exercise for surgical patients: a systematic review. *JBIR Database of Systematic Reviews and Implementation Reports*, 13(1), 146-187. doi:10.11124/jbisrir-2015-1885
- Campbell, K. L., Winters-Stone, K. M., Wiskemann, J., May, A. M., Schwartz, A. L., Courneya, K. S., . . . Schmitz, K. H. (2019). Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. *Med Sci Sports Exerc*, 51(11), 2375-2390. doi:10.1249/MSS.0000000000002116
- Cancer Australia. (2014a). *Cancer Australia Strategic Plan 2014-2019*. Retrieved from Surry Hills, NSW: https://canceraustralia.gov.au/sites/default/files/publications/cancer-australias-strategic-plan-2014-2019/pdf/2014_strategic_plan.pdf
- Cancer Australia. (2014b). *Risk factors for lung cancer: an overview of the evidence*. Retrieved from Surry Hills, NSW:
- Cancer Australia. (2019). Lung cancer statistics: lung cancer in Australia. Retrieved from <http://lung-cancer.canceraustralia.gov.au/statistics>
- Cancer Council Australia. (2018). Clinical practice guidelines for the prevention and diagnosis of lung cancer. Retrieved from http://wiki.cancer.org.au/australia/guidelines:lung_cancer/prevention_and_diagnosis
- Cancer Council Australia. (2020). *Clinical practice guidelines for the treatment of lung cancer*. Retrieved from Sydney: http://wiki.cancer.org.au/australia/Guidelines.lung_cancer
- Cancer Council Victoria. (2014). *Optimal care pathway for people with lung cancer*. Retrieved from Victoria: <http://www.cancervic.org.au>
- Carli, F., & Scheede-Bergdahl, C. (2015). Prehabilitation to enhance perioperative care. *Anesthesiol Clin*, 33(1), 17-33. doi:10.1016/j.anclin.2014.11.002
- Carli, F., Silver, J. K., Feldman, L. S., McKee, A., Gilman, S., Gillis, C., . . . Hirsch, B. (2017). Surgical Prehabilitation in Patients with Cancer: State-of-the-Science and Recommendations for Future Research from a Panel of Subject Matter Experts. *Phys Med Rehabil Clin N Am*, 28(1), 49-64. doi:10.1016/j.pmr.2016.09.002
- Casanova, C., Celli, B. R., Barria, P., Casas, A., Cote, C., de Torres, J. P., . . . Six Minute Walk Distance, P. (2011). The 6-min walk distance in healthy subjects: reference standards from seven countries. *Eur Respir J*, 37(1), 150-156. doi:10.1183/09031936.00194909

- Cavalheri, V., & Granger, C. (2017). Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev*, 6, Cd012020. doi:10.1002/14651858.CD012020.pub2
- Cerfolio, R. J., Ghanim, A. F., Dylewski, M., Veronesi, G., Spaggiari, L., & Park, B. J. (2018). The long-term survival of robotic lobectomy for non-small cell lung cancer: A multi-institutional study. *J Thorac Cardiovasc Surg*, 155(2), 778-786. doi:10.1016/j.jtcvs.2017.09.016
- Chan, B. A., & Hughes, B. G. (2015). Targeted therapy for non-small cell lung cancer: current standards and the promise of the future. *Transl Lung Cancer Res*, 4(1), 36-54. doi:10.3978/j.issn.2218-6751.2014.05.01
- Chen, H. M., Tsai, C. M., Wu, Y. C., Lin, K. C., & Lin, C. C. (2015). Randomised controlled trial on the effectiveness of home-based walking exercise on anxiety, depression and cancer-related symptoms in patients with lung cancer. *Br J Cancer*, 112(3), 438-445. doi:10.1038/bjc.2014.612
- Clavien, P. A., Barkun, J., de Oliveira, M. L., Vauthey, J. N., Dindo, D., Schulick, R. D., . . . Makuuchi, M. (2009). The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg*, 250(2), 187-196. doi:10.1097/SLA.0b013e3181b13ca2
- Coleman, M. P., Quaresma, M., Berrino, F., Lutz, J.-M., De Angelis, R., Capocaccia, R., . . . Young, J. L. (2008). Cancer survival in five continents: a worldwide population-based study (CONCORD). *The Lancet Oncology*, 9(8), 730-756. doi:10.1016/s1470-2045(08)70179-7
- Contrada, R. J., Boulifard, D. A., Hekler, E. B., Idler, E. L., Spruill, T. M., Labouvie, E. W., & Krause, T. J. (2008). Psychosocial factors in heart surgery: presurgical vulnerability and postsurgical recovery. *Health Psychol*, 27(3), 309-319. doi:10.1037/0278-6133.27.3.309
- Craig, C. L., Marshall, A. L., Sjostrom, M., Bauman, A. E., Booth, M. L., Ainsworth, B. E., . . . Oja, P. (2003). International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*, 35(8), 1381-1395. doi:10.1249/01.MSS.0000078924.61453.FB
- Crandall, K., Maguire, R., Campbell, A., & Kearney, N. (2014). Exercise intervention for patients surgically treated for Non-Small Cell Lung Cancer (NSCLC): a systematic review. *Surg Oncol*, 23(1), 17-30. doi:10.1016/j.suronc.2014.01.001
- Dai, C., Shen, J., Ren, Y., Zhong, S., Zheng, H., He, J., . . . He, J. (2016). Choice of Surgical Procedure for Patients With Non-Small-Cell Lung Cancer $\leq$ 1 cm or $>$ 1 to 2 cm Among Lobectomy, Segmentectomy, and Wedge Resection: A Population-Based Study. *J Clin Oncol*, 34(26), 3175-3182. doi:10.1200/JCO.2015.64.6729
- De Koning, H., Van Der Aalst, C., Ten Haaf, K., & Oudkerk, M. (2018). PL02.05 Effects of Volume CT Lung Cancer Screening: Mortality Results of the NELSON Randomised-Controlled Population Based Trial. *Journal of Thoracic Oncology*, 13(10). doi:10.1016/j.jtho.2018.08.012
- De Zoysa, M. K., Hamed, D., Routledge, T., & Scarci, M. (2012). Is limited pulmonary resection equivalent to lobectomy for surgical management of stage I non-small-cell lung cancer? *Interact Cardiovasc Thorac Surg*, 14(6), 816-820. doi:10.1093/icvts/ivs031

- Detterbeck, F. C., Boffa, D. J., Kim, A. W., & Tanoue, L. T. (2017). The Eighth Edition Lung Cancer Stage Classification. *Chest*, 151(1), 193-203. doi:10.1016/j.chest.2016.10.010
- Driessen, E. J., Peeters, M. E., Bongers, B. C., Maas, H. A., Bootsma, G. P., van Meeteren, N. L., & Janssen-Heijnen, M. L. (2017). Effects of prehabilitation and rehabilitation including a home-based component on physical fitness, adherence, treatment tolerance, and recovery in patients with non-small cell lung cancer: A systematic review. *Crit Rev Oncol Hematol*, 114, 63-76. doi:10.1016/j.critrevonc.2017.03.031
- Dunstan, D. W., Howard, B., Healy, G. N., & Owen, N. (2012). Too much sitting--a health hazard. *Diabetes Res Clin Pract*, 97(3), 368-376. doi:10.1016/j.diabres.2012.05.020
- Eldridge, S. (2010). CONSORT 2010 Statement: extension to randomised pilot and feasibility trials. *BMJ*, 355.
- Faithfull, S., Turner, L., Poole, K., Joy, M., Manders, R., Weprin, J., . . . Saxton, J. (2019). Prehabilitation for adults diagnosed with cancer: A systematic review of long-term physical function, nutrition and patient-reported outcomes. *Eur J Cancer Care (Engl)*, 28(4), e13023. doi:10.1111/ecc.13023
- Fayers, P. M. A., N.K.; Bjordal, K. (1995). *The EORTC QLQ-C30 Scoring Manual*. Brussels: European Organisation for Research and Treatment of Cancer.
- Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., . . . Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, 136(5), E359-386. doi:10.1002/ijc.29210
- Field, J. K., Hansell, D. M., Duffy, S. W., & Baldwin, D. R. (2013). CT screening for lung cancer: countdown to implementation. *The Lancet Oncology*, 14(13), e591-e600. doi:10.1016/s1470-2045(13)70293-6
- Forde, C. (2018). *Scoring the International Physical Activity Questionnaire (IPAQ) Exercise prescription for the prevention and treatment of disease*. Retrieved from https://ugc.futurelearn.com/uploads/files/bc/c5/bcc53b14-ec1e-4d90-88e3-1568682f32ae/IPAQ_PDF.pdf
- Ferguson, M. (2007). *Thoracic Surgery Atlas*. England: Saunders.
- Gao, K., Yu, P. M., Su, J. H., He, C. Q., Liu, L. X., Zhou, Y. B., . . . Che, G. W. (2015). Cardiopulmonary exercise testing screening and pre-operative pulmonary rehabilitation reduce postoperative complications and improve fast-track recovery after lung cancer surgery: A study for 342 cases. *Thorac Cancer*, 6(4), 443-449. doi:10.1111/1759-7714.12199
- Global resource for the advancing cancer education (GRACE). (2019). Types of lung surgery: from wedge resection to pneumonectomy. Retrieved from <http://www.cancergrace.org/post/types-lung-surgery-wedge-resection-pneumonectomy>
- Granger. (2013). Functional capacity, physical activity and muscle strength assessment in individuals with non-small cell lung cancer: a systematic review of instruments and their measurement properties. *BMC Cancer*, 13(135).
- Granger, C., McDonald, C. F., Irving, L., Clark, R. A., Gough, K., Murnane, A., . . . Denehy, L. (2014). Low physical activity levels and functional decline in

- individuals with lung cancer. *Lung Cancer*, 83(2), 292-299.
doi:10.1016/j.lungcan.2013.11.014
- Granger, C. L. (2016). Physiotherapy management of lung cancer. *J Physiother*, 62(2), 60-67. doi:10.1016/j.jphys.2016.02.010
- Granger, C. L., Connolly, B., Denehy, L., Hart, N., Antippa, P., Lin, K. Y., & Parry, S. M. (2017). Understanding factors influencing physical activity and exercise in lung cancer: a systematic review. *Support Care Cancer*, 25(3), 983-999. doi:10.1007/s00520-016-3484-8
- Granger, C. L., Denehy, L., Parry, S. M., Martin, J., Dimitriadis, T., Sorohan, M., & Irving, L. (2015). Which field walking test should be used to assess functional exercise capacity in lung cancer? An observational study. *BMC Pulm Med*, 15, 89. doi:10.1186/s12890-015-0075-2
- Granger, C. L., Denehy, L., Remedios, L., Retica, S., Phongpagdi, P., Hart, N., & Parry, S. M. (2016). Barriers to Translation of Physical Activity into the Lung Cancer Model of Care. A Qualitative Study of Clinicians' Perspectives. *Ann Am Thorac Soc*, 13(12), 2215-2222. doi:10.1513/AnnalsATS.201607-540OC
- Granger, C. L., McDonald, C. F., Berney, S., Chao, C., & Denehy, L. (2011). Exercise intervention to improve exercise capacity and health related quality of life for patients with Non-small cell lung cancer: a systematic review. *Lung Cancer*, 72(2), 139-153. doi:10.1016/j.lungcan.2011.01.006
- Granger, C. L., Parry, S. M., Edbrooke, L., & Denehy, L. (2016). Deterioration in physical activity and function differs according to treatment type in non-small cell lung cancer - future directions for physiotherapy management. *Physiotherapy*, 102(3), 256-263. doi:10.1016/j.physio.2015.10.007
- Gunnell, A. S., Joyce, S., Tomlin, S., Taaffe, D. R., Cormie, P., Newton, R. U., . . . Galvao, D. A. (2017). Physical Activity and Survival among Long-term Cancer Survivor and Non-Cancer Cohorts. *Front Public Health*, 5, 19. doi:10.3389/fpubh.2017.00019
- Gurlit, S., & Gogol, M. (2019). Prehabilitation is better than cure. *Curr Opin Anaesthesiol*, 32(1), 108-115. doi:10.1097/ACO.0000000000000678
- Ha, D., Mazzone, P. J., Ries, A. L., Malhotra, A., & Fuster, M. (2016). The Utility of Exercise Testing in Patients with Lung Cancer. *J Thorac Oncol*, 11(9), 1397-1410. doi:10.1016/j.jtho.2016.04.021
- Harrison, S., Stiles, B., & Altorki, N. (2018). What is the role of wedge resection for T1a lung cancer? *J Thorac Dis*, 10(Suppl 10), S1157-S1162. doi:10.21037/jtd.2018.03.188
- Hennon, M. W., & Yendamuri, S. (2012). Advances in lung cancer surgery. *J Carcinog*, 11, 21. doi:10.4103/1477-3163.105341
- Holland, A. E., Spruit, M. A., Troosters, T., Puhan, M. A., Pepin, V., Saey, D., . . . Singh, S. J. (2014). An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. *Eur Respir J*, 44(6), 1428-1446. doi:10.1183/09031936.00150314
- Huang, J., Lai, Y., Zhou, X., Li, S., Su, J., Yang, M., & Che, G. (2017). Short-term high-intensity rehabilitation in radically treated lung cancer: a three-armed randomized controlled trial. *J Thorac Dis*, 9(7), 1919-1929. doi:10.21037/jtd.2017.06.15
- Hunt, I. (2009). *ABC of lung cancer*. Oxford (UK): Wiley-Blackwell.

- Ismail, H., Cormie, P., Burbury, K., Waterland, J., Denehy, L., & Riedel, B. (2018). Prehabilitation Prior to Major Cancer Surgery: Training for Surgery to Optimize Physiologic Reserve to Reduce Postoperative Complications. *Current Anesthesiology Reports*, 8(4), 375-385. doi:10.1007/s40140-018-0300-7
- Iyer, S., Roughley, A., Rider, A., & Taylor-Stokes, G. (2014). The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. *Support Care Cancer*, 22(1), 181-187. doi:10.1007/s00520-013-1959-4
- Jenkins, S., Cecins, N., Camarri, B., Williams, C., Thompson, P., & Eastwood, P. (2009). Regression equations to predict 6-minute walk distance in middle-aged and elderly adults. *Physiotherapy Theory and Practice*, 25(7), 516-522. doi:10.3109/09593980802664711
- Jing, R. (2018). Incidence and risk factors of postoperative pulmonary complications after thoracic surgery for early non-small cell lung cancer.
- Jones, L. E., N.D; Waner,E; Joy,A.A. (2009). Exercise therapy across the lung cancer continuum. *Current Oncology Reports*, 11, 255 - 262.
- Jones, L. W., Hornsby, W. E., Goetzinger, A., Forbes, L. M., Sherrard, E. L., Quist, M., . . . Abernethy, A. P. (2012). Prognostic significance of functional capacity and exercise behavior in patients with metastatic non-small cell lung cancer. *Lung Cancer*, 76(2), 248-252. doi:10.1016/j.lungcan.2011.10.009
- Jones, L. W., Peddle, C. J., Eves, N. D., Haykowsky, M. J., Courneya, K. S., Mackey, J. R., . . . Reiman, T. (2007). Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer*, 110(3), 590-598. doi:10.1002/cncr.22830
- Karenovics, W., Licker, M., Ellenberger, C., Christodoulou, M., Diaper, J., Bhatia, C., . . . Triponez, F. (2017). Short-term preoperative exercise therapy does not improve long-term outcome after lung cancer surgery: a randomized controlled study. *Eur J Cardiothorac Surg*, 52(1), 47-54. doi:10.1093/ejcts/ezx030
- Kato, H., Oizumi, H., Suzuki, J., Hamada, A., Watarai, H., Nakahashi, K., & Sadahiro, M. (2017). Thoracoscopic wedge resection and segmentectomy for small-sized pulmonary nodules. *J Vis Surg*, 3, 66. doi:10.21037/jovs.2017.03.22
- Kobayashi, N., Kobayashi, K., Kikuchi, S., Goto, Y., Ichimura, H., Endo, K., & Sato, Y. (2017). Long-term pulmonary function after surgery for lung cancer. *Interact Cardiovasc Thorac Surg*, 24(5), 727-732. doi:10.1093/icvts/ivw414
- Lai, Y., Huang, J., Yang, M., Su, J., Liu, J., & Che, G. (2017). Seven-day intensive preoperative rehabilitation for elderly patients with lung cancer: a randomized controlled trial. *J Surg Res*, 209, 30-36. doi:10.1016/j.jss.2016.09.033
- Lai, Y., Su, J., Qiu, P., Wang, M., Zhou, K., Tang, Y., & Che, G. (2017). Systematic short-term pulmonary rehabilitation before lung cancer lobectomy: a randomized trial. *Interact Cardiovasc Thorac Surg*, 25(3), 476-483. doi:10.1093/icvts/ivx141
- Lai, Y., Su, J., Yang, M., Zhou, K., & Che, G. (2016). [Impact and Effect of Preoperative Short-term Pulmonary Rehabilitation Training on Lung Cancer Patients with Mild to Moderate Chronic Obstructive Pulmonary Disease: A Randomized Trial]. *Zhongguo Fei Ai Za Zhi*, 19(11), 746-753. doi:10.3779/j.issn.1009-3419.2016.11.05

- Lang-Lazdunski, L. (2013). Surgery for nonsmall cell lung cancer. *Eur Respir Rev*, 22(129), 382-404. doi:10.1183/09059180.00003913
- Le Chevalier, T. (2011). Non-small cell lung cancer: the challenges of the next decade. *Front Oncol*, 1, 29. doi:10.3389/fonc.2011.00029
- Leach, H. J., Devonish, J. A., Bebb, D. G., Krenz, K. A., & Culos-Reed, S. N. (2015). Exercise preferences, levels and quality of life in lung cancer survivors. *Support Care Cancer*, 23(11), 3239-3247. doi:10.1007/s00520-015-2717-6
- Levett, D. Z., Edwards, M., Grocott, M., & Mythen, M. (2016). Preparing the patient for surgery to improve outcomes. *Best Pract Res Clin Anaesthesiol*, 30(2), 145-157. doi:10.1016/j.bpa.2016.04.002
- Levett, D. Z., & Grocott, M. P. (2015). Cardiopulmonary exercise testing, prehabilitation, and Enhanced Recovery After Surgery (ERAS). *Can J Anaesth*, 62(2), 131-142. doi:10.1007/s12630-014-0307-6
- Levett, D. Z. H., & Grimmett, C. (2019). Psychological factors, prehabilitation and surgical outcomes: evidence and future directions. *Anaesthesia*, 74 Suppl 1, 36-42. doi:10.1111/anae.14507
- Levy, N., Grocott, M. P. W., & Carli, F. (2019). Patient optimisation before surgery: a clear and present challenge in peri-operative care. *Anaesthesia*, 74 Suppl 1, 3-6. doi:10.1111/anae.14502
- Li, M. H., Bolshinsky, V., Ismail, H., Burbury, K., Ho, K. M., Amin, B., . . . Riedel, B. (2019). A cross-sectional survey of Australian anesthetists' and surgeons' perceptions of preoperative risk stratification and prehabilitation. *Can J Anaesth*, 66(4), 388-405. doi:10.1007/s12630-019-01297-9
- Li, W. W., Lee, R. L., Lee, T. W., Ng, C. S., Sihoe, A. D., Wan, I. Y., . . . Yim, A. P. (2003). The impact of thoracic surgical access on early shoulder function: video-assisted thoracic surgery versus posterolateral thoracotomy. *Eur J Cardiothorac Surg*, 23(3), 390-396. doi:10.1016/s1010-7940(02)00795-9
- Licker, M., Karenovics, W., Diaper, J., Fresard, I., Triponez, F., Ellenberger, C., . . . Bridevaux, P. O. (2016). Short-Term Preoperative High-Intensity Interval Training in Patients Awaiting Lung Cancer Surgery: A Randomized Controlled Trial. *J Thorac Oncol*, 12(2), 323-333. doi:10.1016/j.jtho.2016.09.125
- Licker, M., Schnyder, J. M., Frey, J. G., Diaper, J., Cartier, V., Inan, C., . . . Tschopp, J. M. (2011). Impact of aerobic exercise capacity and procedure-related factors in lung cancer surgery. *Eur Respir J*, 37(5), 1189-1198. doi:10.1183/09031936.00069910
- Lima, L. P., Leite, H. R., Matos, M. A., Neves, C. D. C., Lage, V., Silva, G. P. D., . . . Mendonca, V. A. (2019). Cardiorespiratory fitness assessment and prediction of peak oxygen consumption by Incremental Shuttle Walking Test in healthy women. *PLoS One*, 14(2), e0211327. doi:10.1371/journal.pone.0211327
- Liu, Z., Qiu, T., Pei, L., Zhang, Y., Xu, L., Cui, Y., . . . Huang, Y. (2019). Two-Week Multimodal Prehabilitation Program Improves Perioperative Functional Capability in Patients Undergoing Thoracoscopic Lobectomy for Lung Cancer: A Randomized Controlled Trial. *Anesth Analg*. doi:10.1213/ANE.00000000000004342
- Louie, B. E. (2017). Catastrophes and complicated intraoperative events during robotic lung resection. *J Vis Surg*, 3, 52. doi:10.21037/jovs.2017.02.05

- Luckett, T. B., P.N; King, M.T et al. (2010). A review and recommendations for the optimal outcome measures of anxiety, depression and general distress in studies evaluating psychological interventions for english-speaking adults with heterogenous cancer diagnoses. *Supportive Care in Cancer*, 18(10), 1241 - 1262.
- MacMillan Cancer Support. (2018). Macmillan cancer rehabilitation pathways. Retrieved from <http://www.macmillan.org.uk/assets/macmillan-cancer-rehabilitation-pathways.pdf>
- Mainini, C., Rebelo, P. F., Bardelli, R., Kopliku, B., Tenconi, S., Costi, S., . . . Fugazzaro, S. (2016). Perioperative physical exercise interventions for patients undergoing lung cancer surgery: What is the evidence? *SAGE Open Med*, 4, 2050312116673855. doi:10.1177/2050312116673855
- Mans, C. M., Reeve, J. C., & Elkins, M. R. (2015). Postoperative outcomes following preoperative inspiratory muscle training in patients undergoing cardiothoracic or upper abdominal surgery: a systematic review and meta analysis. *Clin Rehabil*, 29(5), 426-438. doi:10.1177/0269215514545350
- Marthick, M. (2018). Pulmonary rehabilitation and eHealth practices for patients undetgoing surgical treatment for lung cancer - a survey of multidisciplinary yeam sites in Australia. *The Australian Journal of Cancer Nursing*, 19(2), 14 - 20.
- Martin, H. J., Yule, V., Syddall, H. E., Dennison, E. M., Cooper, C., & Aihie Sayer, A. (2006). Is hand-held dynamometry useful for the measurement of quadriceps strength in older people? A comparison with the gold standard Bodex dynamometry. *Gerontology*, 52(3), 154-159. doi:10.1159/000091824
- Martin-Ucar, A. E., & Socci, L. (2017). Thoracic incisions for open surgery. *Shanghai Chest*, 1, 20-20. doi:10.21037/shc.2017.05.11
- Mazzola, M., Bertoglio, C., Boniardi, M., Magistro, C., De Martini, P., Carnevali, P., . . . Ferrari, G. (2017). Frailty in major oncologic surgery of upper gastrointestinal tract: How to improve postoperative outcomes. *Eur J Surg Oncol*, 43(8), 1566-1571. doi:10.1016/j.ejso.2017.06.006
- McCarthy, B., Casey, D., Devane, D., Murphy, K., Murphy, E., & Lacasse, Y. (2015). Pulmonary rehabilitation for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews*(2). doi:10.1002/14651858.CD003793.pub3
- McDonald, F., De Waele, M., Hendriks, L. E., Faivre-Finn, C., Dingemans, A. C., & Van Schil, P. E. (2017). Management of stage I and II nonsmall cell lung cancer. *Eur Respir J*, 49(1). doi:10.1183/13993003.00764-2016
- McIsaac, D. I., Saunders, C., Hladkiewicz, E., Bryson, G. L., Forster, A. J., Gagne, S., . . . McCartney, C. J. L. (2018). PREHAB study: a protocol for a prospective randomised clinical trial of exercise therapy for people living with frailty having cancer surgery. *BMJ Open*, 8(6), e022057. doi:10.1136/bmjopen-2018-022057
- Mercieca-Bebber, R., Costa, D. S., Norman, R., Janda, M., Smith, D. P., Grimison, P., . . . King, M. T. (2019). The EORTC Quality of Life Questionnaire for cancer patients (QLQ-C30): Australian general population reference values. *Med J Aust*, 210(11), 499-506. doi:10.5694/mja2.50207
- Minnella, E. M., Awasthi, R., Gillis, C., Fiore, J. F., Jr., Liberman, A. S., Charlebois, P., . . . Carli, F. (2016). Patients with poor baseline walking capacity are most

- likely to improve their functional status with multimodal prehabilitation. *Surgery*, 160(4), 1070-1079. doi:10.1016/j.surg.2016.05.036
- Mishra. (2012). Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst Rev*(8).
- Mitchell, A. M., N; Symonds, P. (2010). Diagnostic validity of the hospital anxiety and depression scale (HADS) in cancer and palliative settings: a meta-analysis. *Journal of Affective Disorders*, 126(3), 335 - 348.
- Molina, J. (2008). Non-small cell lung cancer: epidemiology, risk factors, treatment and survivorship. *Mayo Clinic Proceedings*, 83(5), 584.
- Moore, J. A., Conway, D. H., Thomas, N., Cummings, D., & Atkinson, D. (2017). Impact of a peri-operative quality improvement programme on postoperative pulmonary complications. *Anaesthesia*, 72(3), 317-327. doi:10.1111/anae.13763
- Morano M, T. (2014). Comparison of the effects of pulmonary rehabilitation with chest physical therapy on the levels of fibrinogen and albumin in patients with lung cancer awaiting lung resection: a randomized clinical trial.
- Moseley, A. M., Herbert, R. D., Maher, C. G., Sherrington, C., & Elkins, M. R. (2011). Reported quality of randomized controlled trials of physiotherapy interventions has improved over time. *J Clin Epidemiol*, 64(6), 594-601. doi:10.1016/j.jclinepi.2010.08.009
- Mustian, K. M., Alfano, C. M., Heckler, C., Kleckner, A. S., Kleckner, I. R., Leach, C. R., . . . Miller, S. M. (2017). Comparison of Pharmaceutical, Psychological, and Exercise Treatments for Cancer-Related Fatigue: A Meta-analysis. *JAMA Oncol*, 3(7), 961-968. doi:10.1001/jamaoncol.2016.6914
- Myers. (2016). The impact of fitness on surgical outcomes: the case for prehabilitation. *Current Sports Medicine Reports*, 15(4), 282 - 289.
- Myles, P. (2015). *Complications of Thoracic Surgery* (P. M. Alston, P.S; Ranucci, M. Ed.). Online: Oxford University Press.
- National Academies of Sciences, E. a. M. (2018). *Long-term survivorship care after cancer treatment: proceedings of a workshop* (9780309472982 0309472989). Retrieved from Washington (DC): <https://www.ncbi.nlm.nih.gov/pubmed/29738209>
- Ni, H. J., Pudasaini, B., Yuan, X. T., Li, H. F., Shi, L., & Yuan, P. (2017). Exercise Training for Patients Pre- and Postsurgically Treated for Non-Small Cell Lung Cancer: A Systematic Review and Meta-analysis. *Integr Cancer Ther*, 16(1), 63-73. doi:10.1177/1534735416645180
- NICE. (2019). *NICE Guideline, lung cancer: diagnosis and management* Retrieved from <http://www.nice.org.uk/guidance/ng122>
- Nigam, Y., Knight, J., Bhattacharya, S., & Bayer, A. (2012). Physiological changes associated with aging and immobility. *J Aging Res*, 2012, 468469. doi:10.1155/2012/468469
- Nwosu, A. C., Bayly, J. L., Gaunt, K. E., & Mayland, C. R. (2012). Lung cancer and rehabilitation--what are the barriers? Results of a questionnaire survey and the development of regional lung cancer rehabilitation standards and guidelines. *Support Care Cancer*, 20(12), 3247-3254. doi:10.1007/s00520-012-1472-1

- O'Doherty, A. F., West, M., Jack, S., & Grocott, M. P. (2013). Preoperative aerobic exercise training in elective intra-cavity surgery: a systematic review. *Br J Anaesth*, 110(5), 679-689. doi:10.1093/bja/aes514
- Older, P. O., & Levett, D. Z. H. (2017). Cardiopulmonary Exercise Testing and Surgery. *Ann Am Thorac Soc*, 14(Supplement_1), S74-S83. doi:10.1513/AnnalsATS.201610-780FR
- Osarogiagbon, R. U., Veronesi, G., Fang, W., Ekman, S., Suda, K., Aerts, J. G., & Donington, J. (2019). Early-Stage NSCLC: Advances in Thoracic Oncology 2018. *J Thorac Oncol*, 14(6), 968-978. doi:10.1016/j.jtho.2019.02.029
- Parreira, V. F., Janaudis-Ferreira, T., Evans, R. A., Mathur, S., Goldstein, R. S., & Brooks, D. (2014). Measurement Properties of the Incremental Shuttle Walk Test. *Chest*, 145(6), 1357-1369. doi:10.1378/chest.13-2071
- PEDro. (1999). PEDro Scale. Retrieved from https://www.pedro.org.au/wp-content/uploads/PEDro_scale.pdf
- Philip, E. J., Coups, E. J., Feinstein, M. B., Park, B. J., Wilson, D. J., & Ostroff, J. S. (2014). Physical activity preferences of early-stage lung cancer survivors. *Support Care Cancer*, 22(2), 495-502. doi:10.1007/s00520-013-2002-5
- Piriaux, E., Caty, G., & Reychler, G. (2018). Effects of preoperative combined aerobic and resistance exercise training in cancer patients undergoing tumour resection surgery: A systematic review of randomised trials. *Surg Oncol*, 27(3), 584-594. doi:10.1016/j.suronc.2018.07.007
- Port, J. L., Mirza, F. M., Lee, P. C., Paul, S., Stiles, B. M., & Altorki, N. K. (2011). Lobectomy in octogenarians with non-small cell lung cancer: ramifications of increasing life expectancy and the benefits of minimally invasive surgery. *Ann Thorac Surg*, 92(6), 1951-1957. doi:10.1016/j.athoracsur.2011.06.082
- Pouwels, S., Fiddelaers, J., Teijink, J. A., Woorst, J. F., Siebenga, J., & Smeenk, F. W. (2015). Preoperative exercise therapy in lung surgery patients: A systematic review. *Respir Med*, 109(12), 1495-1504. doi:10.1016/j.rmed.2015.08.009
- Puhan, M. A., Gimeno-Santos, E., Cates, C. J., & Troosters, T. (2016). Pulmonary rehabilitation following exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*, 12, CD005305. doi:10.1002/14651858.CD005305.pub4
- Quarterman, R. L., McMillan, A., Ratcliffe, M. B., & Block, M. I. (2003). Effect of preoperative delay on prognosis for patients with early stage non-small cell lung cancer. *J Thorac Cardiovasc Surg*, 125(1), 108-113; discussion 113-104. doi:10.1067/mtc.2003.93
- Quist, M., Adamsen, L., Rorth, M., Laursen, J. H., Christensen, K. B., & Langer, S. W. (2015). The Impact of a Multidimensional Exercise Intervention on Physical and Functional Capacity, Anxiety, and Depression in Patients With Advanced-Stage Lung Cancer Undergoing Chemotherapy. *Integr Cancer Ther*, 14(4), 341-349. doi:10.1177/1534735415572887
- Reeve, J. C., Nicol, K., Stiller, K., McPherson, K. M., Birch, P., Gordon, I. R., & Denehy, L. (2010). Does physiotherapy reduce the incidence of postoperative pulmonary complications following pulmonary resection via open thoracotomy? A preliminary randomised single-blind clinical trial. *Eur J Cardiothorac Surg*, 37(5), 1158-1166. doi:10.1016/j.ejcts.2009.12.011

- Richardson, K., Levett, D. Z. H., Jack, S., & Grocott, M. P. W. (2017). Fit for surgery? Perspectives on preoperative exercise testing and training. *Br J Anaesth*, 119(suppl_1), i34-i43. doi:10.1093/bja/aex393
- Rochester, C. L., Fairburn, C., & Crouch, R. H. (2014). Pulmonary rehabilitation for respiratory disorders other than chronic obstructive pulmonary disease. *Clin Chest Med*, 35(2), 369-389. doi:10.1016/j.ccm.2014.02.016
- Rodriguez-Larrad, A., Lascrain-Aguirrebena, I., Abecia-Inchaurregui, L. C., & Seco, J. (2014). Perioperative physiotherapy in patients undergoing lung cancer resection. *Interact Cardiovasc Thorac Surg*, 19(2), 269-281. doi:10.1093/icvts/ivu126
- Rosenberger, P. H. (2006). Psychological factors and surgical outcomes: an evidence-based literature review. *J Am Acad Orthop Surg*, 14, 397 - 405.
- Rosero, I. D., Ramirez-Velez, R., Lucia, A., Martinez-Velilla, N., Santos-Lozano, A., Valenzuela, P. L., . . . Izquierdo, M. (2019). Systematic Review and Meta-Analysis of Randomized, Controlled Trials on Preoperative Physical Exercise Interventions in Patients with Non-Small-Cell Lung Cancer. *Cancers (Basel)*, 11(7). doi:10.3390/cancers11070944
- Santa Mina, D., Clarke, H., Ritvo, P., Leung, Y. W., Matthew, A. G., Katz, J., . . . Alibhai, S. M. (2014). Effect of total-body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy*, 100(3), 196-207. doi:10.1016/j.physio.2013.08.008
- Santa Mina, D., Scheede-Bergdahl, C., Gillis, C., & Carli, F. (2015). Optimization of surgical outcomes with prehabilitation. *Appl Physiol Nutr Metab*, 40(9), 966-969. doi:10.1139/apnm-2015-0084
- Scheede-Bergdahl, C., Minnella, E. M., & Carli, F. (2019). Multi-modal prehabilitation: addressing the why, when, what, how, who and where next? *Anaesthesia*, 74 Suppl 1, 20-26. doi:10.1111/anae.14505
- Scherr, J., Wolfarth, B., Christle, J. W., Pressler, A., Wagenpfeil, S., & Halle, M. (2013). Associations between Borg's rating of perceived exertion and physiological measures of exercise intensity. *Eur J Appl Physiol*, 113(1), 147-155. doi:10.1007/s00421-012-2421-x
- Schmitz K, H. J., Courneya K. (2005). Controlled physical activity trials in cancer survivors: A systematic review and meta-analysis. *Cancer Epidemiology, Biomarkers & Prevention*, 14(7), 1588 - 1595.
- Schofield, P., Ugalde, A., Carey, M., Mileskin, L., Duffy, M., Ball, D., & Aranda, S. (2008). Lung cancer: challenges and solutions for supportive care intervention research. *Palliat Support Care*, 6(3), 281-287. doi:10.1017/S1478951508000424
- Sebio Garcia, R., Yanez Brage, M. I., Gimenez Moolhuyzen, E., Granger, C. L., & Denehy, L. (2016). Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*, 23(3), 486-497. doi:10.1093/icvts/ivw152
- Sebio Garcia, R. Y.-B., M.I.; Gimenez Moolhuyzen, E. (2017). Preoperative exercise training prevents functional decline after lung resection surgery: a randomized, single-blind controlled trial. *Clinical Rehabilitation*, 31(8), 1057 - 1067. doi:DOI: 10.1177/0269215516684179

- Shin, D. W., Cho, J., Kim, S. Y., Guallar, E., Hwang, S. S., Cho, B., . . . Park, J. H. (2013). Delay to curative surgery greater than 12 weeks is associated with increased mortality in patients with colorectal and breast cancer but not lung or thyroid cancer. *Ann Surg Oncol*, 20(8), 2468-2476. doi:10.1245/s10434-013-2957-y
- Silver, J. K. (2015). Cancer prehabilitation: important lessons from a best practices model. *The Oncology Nurse*, 8(2), 7 - 14.
- Silver, J. K., & Baima, J. (2013). Cancer Prehabilitation. *American Journal of Physical Medicine & Rehabilitation*, 92(8), 715-727. doi:10.1097/PHM.0b013e31829b4afe
- Simoglou, C. (2017). Video-assisted thorascopic surgery (VATS). *Scientific Chronicles*, 22(2), 150 - 159.
- Sinclair, R. C., Batterham, A. M., Davies, S., Cawthorn, L., & Danjoux, G. R. (2012). Validity of the 6 min walk test in prediction of the anaerobic threshold before major non-cardiac surgery. *Br J Anaesth*, 108(1), 30-35. doi:10.1093/bja/aer322
- Singh, S., Morgan, M., Hardman, A., Rowe, C., & Bardsley, P. (1994). Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. *European Respiratory Journal*, 7(11), 2016-2020.
- Singh, S., Morgan, M., Scott, S., Walters, D., & Hardman, A. (1992). Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax*, 47, 1019-1024.
- Snowden, C. P., Prentis, J. M., Anderson, H. L., Roberts, D. R., Randles, D., Renton, M., & Manas, D. M. (2010). Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Ann Surg*, 251(3), 535-541. doi:10.1097/SLA.0b013e3181cf811d
- Sorensen, L. T. (2012). Wound healing and infection in surgery: the pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: a systematic review. *Ann Surg*, 255(6), 1069-1079. doi:10.1097/SLA.0b013e31824f632d
- Speck, R. M., Courneya, K. S., Masse, L. C., Duval, S., & Schmitz, K. H. (2010). An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *J Cancer Surviv*, 4(2), 87-100. doi:10.1007/s11764-009-0110-5
- Stefanelli, F., Meoli, I., Cobuccio, R., Curcio, C., Amore, D., Casazza, D., . . . Rocco, G. (2013). High-intensity training and cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease and non-small-cell lung cancer undergoing lobectomy. *European Journal of Cardio-Thoracic Surgery*, 44(4), e260-e265. doi:10.1093/ejcts/ezt375
- Steffens, D., Beckenkamp, P. R., Hancock, M., Solomon, M., & Young, J. (2018). Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer. *Br J Sports Med*, 52(5), 344. doi:10.1136/bjsports-2017-098032
- Stout, N. L., Silver, J. K., Raj, V. S., Rowland, J., Gerber, L., Cheville, A., . . . Chan, L. (2016). Toward a National Initiative in Cancer Rehabilitation:

- Recommendations From a Subject Matter Expert Group. *Arch Phys Med Rehabil*, 97(11), 2006-2015. doi:10.1016/j.apmr.2016.05.002
- Tew, G. A., Ayyash, R., Durrand, J., & Danjoux, G. R. (2018). Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery. *Anaesthesia*, 73(6), 750-768. doi:10.1111/anae.14177
- The.National.Lung.Screening.Trial.Research.Team. (2011). Reduced lung cancer mortality with low-dose computer tomographic screening. *The New England Journal of Medicine*, 365(5), 395 - 409.
- Tonnesen, H., Nielsen, P. R., Lauritzen, J. B., & Moller, A. M. (2009). Smoking and alcohol intervention before surgery: evidence for best practice. *Br J Anaesth*, 102(3), 297-306. doi:10.1093/bja/aen401
- Torre, L. A., Bray, F., Siegel, R. L., Ferlay, J., Lortet-Tieulent, J., & Jemal, A. (2015). Global cancer statistics, 2012. *CA Cancer J Clin*, 65(2), 87-108. doi:10.3322/caac.21262
- Tracey, E., McCaughan, B., Badgery-Parker, T., Young, J., & Armstrong, B. (2015). Survival of Australian lung cancer patients and the impact of distance from and attendance at a thoracic specialist centre: a data linkage study. *Thorax*, 70(2), 152-160. doi:10.1136/thoraxjnl-2014-205554
- Treanor, C., Kyaw, T., & Donnelly, M. (2018). An international review and meta-analysis of prehabilitation compared to usual care for cancer patients. *Journal of Cancer Survivorship*, 12(1), 64-73. doi:10.1007/s11764-017-0645-9
- Tsimopoulou, I., Pasquali, S., Howard, R., Desai, A., Gourevitch, D., Tolosa, I., & Vohra, R. (2015). Psychological Prehabilitation Before Cancer Surgery: A Systematic Review. *Ann Surg Oncol*, 22(13), 4117-4123. doi:10.1245/s10434-015-4550-z
- Valkenet, K. v. d. P., I; Dronkers, J. (2011). The effects of preoperative exercise therapy on postoperative outcome: a systematic review. *Clinical Rehabilitation*, 25, 99 - 111.
- Villamizar, N., & Swanson, S. J. (2014). Lobectomy vs. segmentectomy for NSCLC (T<2 cm). *Ann Cardiothorac Surg*, 3(2), 160-166. doi:10.3978/j.issn.2225-319X.2014.02.11
- Wakelee. (2016). Lung cancer in people who have never smoked. *Caring ambassadors lung cancer choices*. 3rd Edition. Retrieved from <http://www.cancer.lungcancercap.org>
- Walker, M. S., Pohl, G. M., Houts, A. C., Peltz, G., Miller, P. J. E., Schwartzberg, L. S., . . . Marciniak, M. (2017). Analysis of the psychological impact of cancer-related symptoms on patients with non-small cell lung cancer. *Psychooncology*, 26(6), 755-762. doi:10.1002/pon.4071
- Walters, S., Maringe, C., Coleman, M. P., Peake, M. D., Butler, J., Young, N., . . . Group, I. M. W. (2013). Lung cancer survival and stage at diagnosis in Australia, Canada, Denmark, Norway, Sweden and the UK: a population-based study, 2004-2007. *Thorax*, 68(6), 551-564. doi:10.1136/thoraxjnl-2012-202297
- Wei, B., & Cerfolio, R. J. (2016). Clinical pathway for thoracic surgery in the United States. *J Thorac Dis*, 8(Suppl 1), S29-36. doi:10.3978/j.issn.2072-1439.2015.11.21

- Weinstein, H., Bates, A. T., Spaltro, B. E., Thaler, H. T., & Steingart, R. M. (2007). Influence of preoperative exercise capacity on length of stay after thoracic cancer surgery. *Ann Thorac Surg*, 84(1), 197-202. doi:10.1016/j.athoracsur.2007.02.003
- Wilson, R. J., Davies, S., Yates, D., Redman, J., & Stone, M. (2010). Impaired functional capacity is associated with all-cause mortality after major elective intra-abdominal surgery. *Br J Anaesth*, 105(3), 297-303. doi:10.1093/bja/aeq128
- Wolfgang, K. (2019). Telemedicine Expands Oncology Care Options. *Oncology Times*, 41(8), 13,19. doi:10.1097/01.Cot.0000557852.06846.47
- Wong, J., Lam, D. P., Abrishami, A., Chan, M. T., & Chung, F. (2012). Short-term preoperative smoking cessation and postoperative complications: a systematic review and meta-analysis. *Can J Anaesth*, 59(3), 268-279. doi:10.1007/s12630-011-9652-x
- Wright, G., Manser, R. L., Byrnes, G., Hart, D., & Campbell, D. A. (2006). Surgery for non-small cell lung cancer: systematic review and meta-analysis of randomised controlled trials. *Thorax*, 61(7), 597-603. doi:10.1136/thx.2005.051995
- Wynter-Blyth, V., & Moorthy, K. (2017). Prehabilitation: preparing patients for surgery. *BMJ*, 358, j3702. doi:10.1136/bmj.j3702
- Zhang, Z., Zhang, Y., Feng, H., Yao, Z., Teng, J., Wei, D., & Liu, D. (2013). Is video-assisted thoracic surgery lobectomy better than thoracotomy for early-stage non-small-cell lung cancer? A systematic review and meta-analysis. *Eur J Cardiothorac Surg*, 44(3), 407-414. doi:10.1093/ejcts/ezt015
- Zigmond, A. S. S., R.P. (1983). The Hospital Anxiety and Depression Scale. *Acta Psychiatry Scand*, 67(6), 361 - 370.

LIST OF APPENDICES

APPENDIX I – Outcome Measure Booklet

Participant trial number: _____

Inclusion Criteria for Recruitment:		
	Yes	No
Lung Cancer?	☐	☐
Preoperative scheduled to receive surgical treatment?	☐	☐
Age $\geq$ 18 years?	☐	☐
Able to understand English?	☐	☐

Trial dates:

Date of consent: _____/_____/201_

Date of recruitment: _____/_____/201_

BASELINE DEMOGRAPHICS

Age			
Gender	1 = MALE	2 = FEMALE	
Histological type	1 = squamous	2 = adenocarcinoma	
	3 = large cell	4 = other (please specify) _____	
Stage	1 = stage IA <i>includes: T1a/bN0M0</i> 2 = stage IB <i>includes: T2aN0M0</i> 3 = stage IIA <i>includes: T2bN0M0; T1a/bN1M0; T2aN1M0</i> 4 = stage IIB <i>Includes: T2bN1M0; T3N0M0</i> 5 = stage IIIA <i>Includes: T1a/bN2M0; T2a/bN2M0; T3N1/2M0; T4N0/1M0</i> 6 = stage IIIB <i>Includes: Any T N3 M0; T4 any N M0</i> 7 = stage IV		

RFT (in litres and percentage predicted)

FEV1 =

FVC=

TLCO =

Date of test

___/___/ 201__

Colinet Score



total score

= (please add up scores on right)

☐

TOBACCO CONSUMPTION

- lifelong consumption of at least 100 cigs

7 points

☐

DIABETES MELLITUS

- treated with oral hypoglycaemic or insulin

5 points

☐

RENAL INSUFFICIENCY

- creatine clearance lower than 60ml

4 points

☐

RESPIRATORY

- 1 or more of the following:

history of TB, PE or pneumonia, asthma, pulmonary embolism, chronic COPD, (FEV1) <1.5l

1 point

☐

CARDIOVASCULAR

- 1 or more of the following:

congestive HF, ischaemic cardiomyopathy +/- MI, severe cardiopathy, arrhythmia requiring chronic tx, hx of cerebrovascular disease, hypertension or peripheral vascular disease

1 point

☐

NEOPLASTIC

- Previous Hx of cancer excluding; basal cell carcinoma of the skin and in situ carcinoma of the cervix.

1 point

☐

ALCOHOLISM -

> 80g (4-7 sd) per day Men

> 40g (2-4 sd) per day Women

1 point

Date of diagnosis ___/___/ 201__

Date of surgery ___/___/ 201_

Length of hospital stay _____
(in days – inc day admitted and day discharge)

Discharge destination _____

Type of surgery

- 1 = lobectomy
 - 1 = pneumonectomy
 - 2 = segmentectomy
 - 3 = wedge
 - 4 = other
-

Type of incision

Type of postoperative analgesia

Postoperative complications (list date and details):

Cancer treatment

1 = chemo + radio

2 = radio palliative < 5
fractions

3 = radio HD (radical)

4 = chemo only

5 = tarceva or iressa

6 = no anti-cancer

Weight _____ kg

Height _____ m

Incremental Shuttle Walk Test: Protocol and recording sheet

The ISWT measures the distance (in meters) an individual can walk around a 10m shuttle course paced according to an incremental speed dictated by an audio recording. The test speed increases every minute and the test finishes when the participant can no longer maintain the desired speed. The test result can predict VO_2peak (Singh, Morgan, Hardman, Rowe, & Bardsley, 1994; Singh, Morgan, Scott, Walters, & Hardman, 1992).



INCREMENTAL SHUTTLE WALKING TEST RECORDING SHEET*(accessed from the Pulmonary Rehabilitation Toolkit <http://www.pulmonaryrehab.com.au>)***Age:** _____**Predicted HRmax (220-age):** _____**Walk 1**

Time: _____

Bronchodilator/time since last dose: _____
last dose: _____**Walk 2**

Time: _____

Bronchodilator/time since _____

BP ____/____ mmHg	Supplemental Oxygen _____ l/min	Gait Aid _____
-------------------------	---------------------------------------	-------------------

BP ____/____ mmHg	Supplemental Oxygen _____ l/min	Gait Aid _____
-------------------------	---------------------------------------	-------------------

Time mins	SpO ₂	HR	Dyspnoea
Rest			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Recovery 1			
2			

Time mins	SpO ₂	HR	Dyspnoea
Rest			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
Recovery 1			
2			

Number of shuttles completed: _____

Number of shuttles completed: _____

Distance (number of shuttles x 10): _____

Distance (m): _____

Limiting factor to the test:SOB ☐Low SpO₂ ☐Leg fatigue ☐

Other: _____

Limiting factor to the test:SOB ☐Low SpO₂ ☐

Other: _____

Tick shuttles completed during test:

Level 1	☐	☐	☐									
Level 2	☐	☐	☐	☐								
Level 3	☐	☐	☐	☐	☐							
Level 4	☐	☐	☐	☐	☐	☐						
Level 5	☐	☐	☐	☐	☐	☐	☐					
Level 6	☐	☐	☐	☐	☐	☐	☐	☐				
Level 7	☐	☐	☐	☐	☐	☐	☐	☐	☐			
Level 8	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐		
Level 9	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	
Level 10	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Clinical notes for using the recording sheet:

You do not need to record SpO₂%, heart rate and dyspnoea every minute but there is space on the table above if you wish to.

The box diagram above is designed to make sure you don't lose track of the number of shuttles completed. Tick a box each time the patient reaches a cone.

Strength test: protocol and recording sheet

Perform procedure using a Power track II Commander

Following the following steps for each strength test listed in the table below. Leave a minimum of 30 seconds between each test.

1. Participant positioned as per chart below
2. Participant is told to keep hips on plinth/chair and minimize unwanted trunk movement
3. Handheld dynamometer is placed as per chart below – using wide force plate
4. Examiner applies resistance in a direction inwards perpendicular to bone
5. Subjects are asked to try to straighten their knee/lift their arm outwards but not to move maximally against the force plate and examiner for 5 seconds while examiner counts to five (2 seconds to generate a maximum force and then 3 seconds as hard as possible)
6. One practice trial against examiners hand
7. One practice trial against dynamometer
8. Three actual consecutive efforts are made with 5 seconds rest in between each repetition with verbal encouragement from examiner
9. Record all three efforts, highest force generated is ultimately used for database
10. Repeat test with other arm/leg – with a minimum of 30 seconds between the opposite side strength test

TEST	Starting position	Testing position	Dynamometer placement
Quadriceps (knee extension)	Supine, arms by side relaxed, legs shoulder width apart, testing knee flexed 35° over rolled towel, other leg straight resting on bed	Knee at 35° flexion while testing	Posterior aspect of lower leg just proximal to ankle
Rotator cuff (shoulder abduction)	Sitting back against a chair, feet flat on floor, shoulder adducted and neutrally rotated, elbow flexed 90degrees, forearm in neutral position, wrist 0 degrees extension and 0 degrees ulnar deviation. Arm NOT supported on arm rest		Posterior aspect of lower triceps
Grip strength	Sitting back against a chair, feet flat on floor, shoulder adducted and neutrally rotated, elbow flexed 90degrees, forearm in neutral position, wrist 0 degrees extension and 0 degrees ulnar deviation. Arm NOT supported on arm rest		In hand

STRENGTH RECORDING SHEET

Trial Number:

Date:

Time Point (please circle):

Time 1

Time 2

Time 3

STRENGTH	RIGHT			LEFT		
TEST	1 (LBS)	2 (LBS)	3 (LBS)	1 (LBS)	2 (LBS)	3 (LBS)
Knee Extension						
Rotator cuff						
Grip						

Dominant hand: Right / Left

PARTICIPANT QUESTIONNAIRE BOOKLET

Trial number: _____

Date: ____/____/ 201_

Time point

Time 1

☐

Time 2

☐

Time 3

☐

SECTION ONE

In this section we are interested in getting some background information about you. The information that you provide will remain strictly confidential.

Which of the following best describes your social situation?

- | | | |
|----|--------------------------------|-----------------------|
| 1. | Home alone, independent | ☐ |
| 2. | Home with family | ☐ |
| 3. | Home with supports | ☐ |
| 4. | Retirement village | ☐ |
| 5. | Nursing home – low level care | ☐ |
| 6. | Nursing home – high level care | ☐ |
| 7. | Other _____ | ☐ |

Which of the following best describes your current employment status?

- | | | |
|----|--|-----------------------|
| 1. | Working full time | ☐ |
| 2. | Working part time | ☐ |
| 3. | Sick leave/ leave of absence – temporary | ☐ |
| 4. | Sick leave/ leave of absence – permanent | ☐ |
| 5. | Not employed/ taking time off work | ☐ |
| 6. | Retired | ☐ |
| 7. | Home duties | ☐ |
| 8. | Studying | ☐ |
| 9. | Other _____ | ☐ |

Which of the following best describes your smoking status?

- | | | |
|----|--------------------------------------|-----------------------|
| 1. | Never smoked | ☐ |
| 2. | Quit smoking longer than 8 weeks ago | ☐ |
| 3. | Current smoker | ☐ |

How many years have you/ did you smoked for? _____

How many packets per day on average do you / did you smoke? _____

What is the highest level of formal education that you obtained?

- | | | |
|-----|--|-----------------------|
| 1. | No formal schooling | ☐ |
| 2. | Some primary schooling | ☐ |
| 3. | Finished primary schooling | ☐ |
| 4. | Some secondary or high school | ☐ |
| 5. | Completed secondary or high school | ☐ |
| 6. | Some trade, community or TAFE college | ☐ |
| 7. | Completed trade, community, TAFE college | ☐ |
| 8. | Some university | ☐ |
| 9. | Completed Bachelors degree | ☐ |
| 10. | Completed Masters or PhD degree | ☐ |
| 11. | Other | ☐ |

How active are you at present?

- | | | |
|----|---|-----------------------|
| 0. | Fully active | ☐ |
| 1. | Walking, but only can do light work | ☐ |
| 2. | Rest in bed LESS than half the day, do not work but can care for self | ☐ |
| 3. | Rest in bed MORE than half the day, and only partially cares for self | ☐ |
| 4. | Bedridden | ☐ |

Do you have any limitations to walking as far as you need to at present?

- | | | |
|----|------------|-----------------------|
| 1. | No | ☐ |
| 2. | Yes, if so | ☐ |

How far can you walk on average?_____meters

Do you need an aid to walk with at present?

- | | | |
|----|-----------------------------|-----------------------|
| 1. | No | ☐ |
| 2. | Walking stick outdoors only | ☐ |
| 3. | Walking stick | ☐ |
| 4. | Walking frame | ☐ |
| 5. | Other | ☐ |

**THE INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE (IPAQ)
(PAST 7 DAYS, SHORT-FORM)**

Your physical activity in the past 7 days

The next questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

___ **days per week**

☐

No vigorous physical activities →

Skip to question 3

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?

___ **hours per day**

___ **minutes per day**

☐

Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.

☐

___ **days per week**

No moderate physical activities → ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

___ **hours per day**

___ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

___ **days per week**

☐ No walking → *Skip to question 7*

6. How much time did you usually spend **walking** on one of those days?

___ **hours per day**

___ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on **weekdays** during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **weekday**?

___ **hours per day**

___ **minutes per day**

☐ Don't know/Not sure

**THE EUROPEAN ORGANIZATION FOR RESEARCH & TREATMENT OF CANCER
QUALITY OF LIFE QUESTIONNAIRE (EORTC QLQ-C30-LC13)**

We are interested in some things about you and your health. Please answer all of the questions yourself by **circling** the number that best applies to you. There are no "right" or "wrong" answers.

		Not at all	A Little	Quite a bit	Very much
1	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4	Do you need to stay in bed or a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at all	A Little	Quite a bit	Very much
6	Were you limited in doing either your work or other daily activities?	1	2	3	4
7	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8	Were you short of breath?	1	2	3	4
9	Have you had pain?	1	2	3	4
10	Did you need to rest?	1	2	3	4
11	Have you had trouble sleeping?	1	2	3	4
12	Have you felt weak?	1	2	3	4
13	Have you lacked appetite?	1	2	3	4
14	Have you felt nauseated?	1	2	3	4
15	Have you vomited?	1	2	3	4

During the past week:		Not at all	A Little	Quite a bit	Very much
16	Have you been constipated?	1	2	3	4
17	Have you had diarrhea?	1	2	3	4
18	Were you tired?	1	2	3	4
19	Did pain interfere with your daily activities?	1	2	3	4
20	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21	Did you feel tense?	1	2	3	4
22	Did you worry?	1	2	3	4
23	Did you feel irritable?	1	2	3	4
24	Did you feel depressed?	1	2	3	4
25	Have you had difficulty remembering things?	1	2	3	4
26	Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27	Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29 How would you rate your overall health during the past week?

1	2	3	4	5	6	7	
Very poor						Excellent	

30 How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7	
Very poor							Excellent

During the past week:		Not at all	A Little	Quite a bit	Very much
31	How much did you cough?	1	2	3	4
32	Did you cough up blood?	1	2	3	4
33	Were you short of breath when you rested?	1	2	3	4
34	Were you short of breath when you walked?	1	2	3	4
35	Were you short of breath when you climbed stairs?	1	2	3	4
36	Have you had a sore mouth or tongue?	1	2	3	4
37	Have you had trouble swallowing?	1	2	3	4
38	Have you had tingling hands or feet?	1	2	3	4
39	Have you had hair loss?	1	2	3	4
40	Have you had pain in your chest?	1	2	3	4
41	Have you had pain in your arm or shoulder?	1	2	3	4
42	Have you had pain in other parts of your body?	1	2	3	4

If yes, where _____

43 Did you take any medicine for pain?

1 No **2 Yes**

If yes, how much did it help? 1 2 3 4

HOSPITAL ANXIETY AND DEPRESSION SCALE

Please choose one response from the four given for each question. Give an immediate response and don't think too long about your answers. Please answer this how it currently describes your feelings.

A	I feel tense or 'wound up':	
	Most of the time	3
	A lot of the time	2
	From time to time, occasionally	1
	Not at all	0
D	I still enjoy the things I used to enjoy:	
	Definitely as much	0
	Not quite so much	1
	Only a little	2
	Hardly at all	3
A	I get a sort of frightened feeling as if something awful is about to happen:	
	Very definitely and quite badly	3
	Yes, but not too badly	2
	A little, but it doesn't worry me	1
	Not at all	0
D	I can laugh and see the funny side of things:	
	As much as I always could	0
	Not quite so much now	1
	Definitely not so much now	2
	Not at all	3
A	Worrying thoughts go through my mind:	
	A great deal of the time	3
	A lot of the time	2
	From time to time, but not too often	1
	Only occasionally	0
D	I feel cheerful:	
	Not at all	3
	Not often	2
	Sometimes	1
	Most of the time	0

A	I can sit at ease and feel relaxed:	
	Definitely	0
	Usually	1
	Not Often	2
	Not at all	3
D	I feel as if I am slowed down:	
	Nearly all the time	3
	Very often	2
	Sometimes	1
	Not at all	0
A	I get a sort of frightened feeling like 'butterflies' in the stomach:	
	Not at all	0
	Occasionally	1
	Quite Often	2
	Very Often	3
D	I have lost interest in my appearance:	
	Definitely	3
	I don't take as much care as I should	2
	I may not take quite as much care	1
	I take just as much care as ever	0
A	I feel restless as I have to be on the move:	
	Very much indeed	3
	Quite a lot	2
	Not very much	1
	Not at all	0
D	I look forward with enjoyment to things:	
	As much as I ever did	0
	Rather less than I used to	1
	Definitely less than I used to	2
	Hardly at all	3
A	I get sudden feelings of panic:	
	Very often indeed	3
	Quite often	2
	Not very often	1
	Not at all	0
D	I can enjoy a good book or radio or TV program:	
	Often	0
	Sometimes	1
	Not often	2
	Very seldom	3

BLINDING OF OUTCOME ASSESSOR QUESTIONS

1. Did the patient directly tell you which group they were allocated to?

2. Did the patient inadvertently give away information that allowed you to work out which group they were allocated to?

3. Are you otherwise aware of which group the patient has been allocated to (i.e. from other sources)? If yes, what was the source of information?

Outcome assessor name: _____

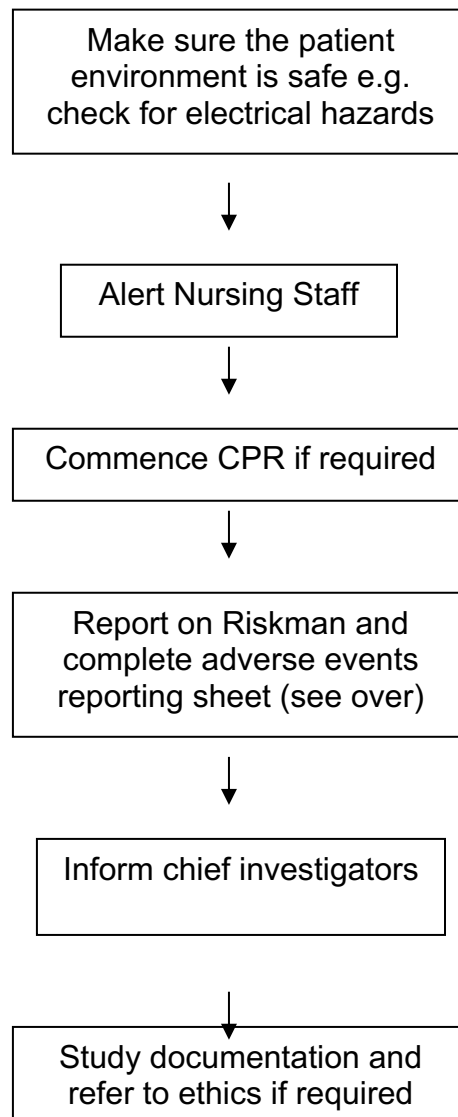
Safety and Adverse Events Protocol

The following adverse events must be reported if they occur during or up to one hour post study intervention or study outcome assessment for all intervention and control subjects. If any of these events occur during exercise/testing, exercise should be ceased. Oxygen saturation is to be measured on all participants prior to the commencement of exercise/testing.

- Heart rate is < 50 or >140 beats/minute and / or a new arrhythmia developed (including frequent ventricular ectopics or new onset atrial fibrillation)
- Patient suffers a fall or collapse
- Patient becomes pale and sweaty and/or the patient specifically requested to stop due to feeling acutely unwell
- Patient complained on new onset chest pain
- Patient suffered a 10% oxygen desaturation below their resting SpO₂ or if SpO₂ <85%. Exercise/testing can be recommenced when SpO₂ returns to resting level of the same FiO₂
- Patient respiratory rate >35 beats/minute. Exercise/testing can be recommenced when the respiratory rate is within 5 breaths of resting rate
- Patient temperature >38 degrees

Action Required During a Serious Adverse Event

“Serious adverse events” are defined as adverse events which result in medical intervention e.g. admission to a critical care area, surgical intervention or a neurological episode. Serious adverse events could include: death, a fall resulting in injury, cardiac arrest or stroke.



Adverse Events Reporting Sheet

Subject Number:

Date:

Describe incident:

Immediate action taken:

Have CI's been notified? YES / NO

Reported by:

APPENDIX II - Exercise Program and Recording Sheet for Intervention Group

This program is flexible and should be adapted for the individual patient. It is a combination of resistance and cardiovascular training. The overall aim is to complete 20 to 30 minutes of cardiovascular interval exercise, working at an intensity of BORG 4. This can be achieved through a combination of cycling and treadmill walking as adapted for the individual patient. The patient is also to complete a generalised strengthening program adapted for the individual patient based upon ACSM strengthening guidelines.

Ambulation

- Duration: 20 - 30minutes interval training
- Speed: commence at 80% VO₂peak
 - Prescribed from 6MWT
- Intensity: progressively increase speed / incline to achieve BORG 4

Cycling

- Duration: 20 - 30minutes
- Resistance: commence 70% W_{Peak} either based on:
 - Prescribed based upon 6MWT
$$W_{\max} (W) = (0.122 \times 6MWD [m]) + (72.683 \times \text{height [m]}) - 117.109$$
 - Distance: maximum achievable in set time with set intensity

Resistance

- 3 sets x (8 -15 reps)
- Intensity: RPE 13
- Commence at 80% 1RM
- Progression: increase repetitions then weight (drop back repetitions) as per standard ACSM strength training to achieve RPE 13
- Exercises (can be flexible) for example
 - Resisted leg press
 - Calf raises (with hand held weights)
 - Wall Squats (with hand held weights)
 - Step ups (with hand held weights)
 - Chest press
 - Seated row
 - Triceps extension (with theraband)

Upper limb and Thoracic Stretches

- Thoracic mobility exercises
 - 10 repetitions bilaterally
 - Continue until full range achieved

Example recording sheet

NAME

DATE	CARDIOVASCULAR				RESISTANCE						STRETCHES					
	RESTING		TREADMILL			BIKE		POST								
	HR	SpO2	mins	KPH	incl	mins	W	HR	SpO2	weight x no.						

APPENDIX III - Patient Handout and Exercise Diary (Intervention Group Only)

**Prehabilitation for individuals having lung cancer surgery: a pilot
randomized controlled trial**

Information booklet and exercise diary

Why is exercise important?

Exercise has many benefits, it helps to:

- increases energy levels
- improve sleep
- increase strength
- tone muscles
- allow you to relax
- decrease depression
- decrease stress and anxiety
- improve self confidence
- control weight and blood pressure
- decrease the risk of many diseases including stroke, heart disease and some types of cancer
- keep bones and joints healthy

In relation to cancer, physical activity helps to:

- reduce cancer fatigue
- reduce other cancer symptoms (including breathlessness)
- improve quality of life
- improve fitness
- and in breast and colon cancer physical activity may prolong life.

How much should I do?

The Australian government physical activity guidelines recommend that people aged between 18 and 64 years should do between 150 to 300 minutes of moderate intensity or 75 to 150 minutes of vigorous intensity physical activity a week.

In those over 65 years it is recommended that people should do at least 30 minutes of physical activity on five or more days of the week.

For people with cancer the guidelines are very similar. The guidelines recommend that people perform 30 minutes of moderate intensity physical activity on five or more days of the week.

How do I start?

As part of this research study, your physiotherapist will ask you about your current level of physical activity and any goals you may have. Your physiotherapist will work with you to develop a rehabilitation program.

How hard should I be exercising?

We recommend you engage in moderate intensity physical activity to begin with. With this type of exercise it is normal to become a little breathless, but not so short of breath that you can't talk. If you start to feel uncomfortable, slow down and concentrate on relaxed breathing. When you are in control again, go on with the exercise, but maybe at a slightly slower pace. You should be getting slightly more breathless while you are exercising (compared to resting) to ensure you are training your body.

You may be familiar with the Borg scale – a scale that rates the difficulty of your breathing. When you are exercising, you should be aiming to be working **around 4**.

Rate your difficulty of breathing:

0 - Nothing at all

1 - Very light

2 - Fairly light

3 - Moderate

4 - Somewhat hard

5 - Hard

6

7 - Very hard

8

9

10 - Very, very hard

Safety

Please do not exercise if you have a **temperature (above 38.0 C)** or **any new chest pain**.

If you have any concerns regarding your exercise program please contact Anna Shukla.

If you have any medical concerns please contact your general practitioner.

Overcoming barriers

Fatigue

One of the side effects of cancer is feeling fatigued. While you may think that being active would make you more tired, research shows that physical activity actually decreases fatigue in people with cancer. The key is to start small and work up. Breaking up your physical activity into small blocks over the day (even as short as 10 minutes at a time) can help you still achieve your physical activity goals on days when fatigue levels are high. Make sure you get adequate rest as well.

Breathlessness

Like in fatigue, physical activity has been shown to decrease the symptoms of breathlessness. The key to managing your breathlessness when being physically active is choosing the right level of activity for you. You should aim at exercise at an intensity that is somewhat hard, without making you completely breathless or unable to talk in sentences. Over time your level of breathless should reduce for the same intensity of physical activity.

Nausea and pain

Physical activity has also been shown to decrease pain and nausea in people with cancer. The key to managing these symptoms is making sure that the activities you perform do not exacerbate the symptoms. If you are nauseous or dizzy avoid activities which require a lot of turning your head or standing up and sitting down. Rather take a walk in a quiet environment or do some stretching or light strengthening in your home, may be a good place to start. If you find your physical activity program is making your pain worse, reduce the amount of activity you do on the following day – this will help you trial what level of activity suits your body's needs. If you find your symptoms get worse, consider calling your physiotherapist (number under safety section) to discuss.

The weather

Perfect days are hard to come by. Sometimes it rains, other times it is too hot or too cold. You can be physically active inside your house by doing simple exercises or cleaning, or you can even go to the local shopping centre and walk around. If it is raining or very hot you could walk in a long hallway at home or in a shopping centre.

Staying motivated

Staying motivated when you initially start a new activity is hard, but there are easy ways to make it easier.

1. Positive thinking! Remember that staying active is good for you. You will start to feel better, both physically and mentally after you persist at this.
2. Find people who will keep you motivated and get the involved. Family, friends and pets are great sources of motivation. You can even get them being active with you. If you don't have anyone close to you, join a local walking group or go walking in the local shopping center where you can meet people.
3. Vary your workouts. Doing the same workout every day can get boring. Try varying your program: you could consider walking around the neighbourhood one day, walking around the shopping center the next, and then walking around a local sports oval another time.
4. Keep a diary. This is an excellent way to keep track of your physical activity and help you see improvements as the weeks go on. This provides positive feedback about what you are doing. We have included an exercise diary for you to use in this booklet. If you are someone who has a Smart Phone you could consider using an app to track and record your activity.

Our physiotherapist will contact you on the days you are not coming into the hospital gymnasium to see how you are going with your program.

Exercise diary

On these pages please record your daily exercise – it is very important that you complete this so we have a good idea of how much exercise you have been doing. We will collect this diary from you at the end of the rehabilitation program.

Week ____

Date: ____/____/201

Exercise prescribed (set by your physiotherapist):

Other notes:

Diary

	Day1*	Day2*	Day3*	Day4*	Day5*	Day6*	Day7*
Exercises - - - - -							
Issues / Difficulties							

* Tick box if completed (✓)

APPENDIX IV - Online Survey

Introduction and explanation

PERCEPTIONS AND ATTITUDES TO PRHABILITATION SURVEY

This survey is being conducted to determine the acceptability and perceived benefit of prehabilitation amongst Thoracic surgeons throughout Australia.

Your help in completing this survey is greatly appreciated. It is hoped that the results of this survey will assist the direction of future research into exercise interventions for patients with lung cancer.

It is anticipated this survey will take approximately 10 -15 minutes to complete. Responses to this survey are anonymous and will remain confidential. All responses are voluntary. Completion of the survey will indicate your consent to participate.

For further information or assistance with completing this survey please contact Anna Shukla (Senior Cardiorespiratory Physiotherapist – St Vincent’s Hospital, Melbourne):
Email: anna.shukla@svha.org.au
Phone: 0414 686 235
Work: 9231 2211 (pager 216)

If you have any concerns about the conduct of this study, you can contact the executive officer, Human Research Ethics at the University of Melbourne (Ethics I.D 1646932.1).

Yours sincerely

Ms Anna Shukla	Master’s student, The University of Melbourne Cardiorespiratory Physiotherapist St Vincent’s Melbourne
Professor Linda Denehy	Head of the Melbourne School of Health Sciences The University of Melbourne
Dr Catherine Granger	Lecturer, The University of Melbourne NHMRC Translating Research into Practice Fellow

Introduction

Non-small cell lung cancer (NSCLC) is the second most common cancer in Australia. It is the leading cause of cancer-related mortality, being responsible for more deaths than breast, colorectal and prostate cancer combined and has an overall 5-year survival rate of 14%. Pulmonary resection provides the best chance of cure for patients with early stage operable lung cancer; survival for this patient group is between 38-76%. There is a growing body of evidence that supports prehabilitation as a means of preparing patients with newly diagnosed cancer for treatment by optimizing their health preoperatively.

Prehabilitation

Prehabilitation is not a new concept. Recent research provides evidence that higher physical activity levels after cancer diagnosis are associated with reduced cancer-specific and all-cause mortality in breast, colon and prostate cancer. Prehabilitation has been utilized successfully in patients with colon cancer. In this population positive outcomes have been achieved within short preoperative time frames (1-4 weeks), including 81% return to baseline function in the intervention (prehabilitation) group compared with 40% in the control group at 8 weeks after surgery. Use of prehabilitation for patients with lung cancer is an emerging area and is defined as *a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment that, in the perioperative setting, aims to enhance functional capacity of the individuals to enable them to withstand the stress associated with a procedure*. Prehabilitation includes a care bundle incorporating smoking cessation, diet optimization, psychosocial support and exercise, and aims to identify impairments and deliver targeted interventions that improve patient outcomes. It provides an opportunity to decrease treatment-related morbidity, increase available treatment options for patients who would not otherwise be surgical candidates and facilitate return of patients to the highest possible functional level.

Systematic reviews and other existing literature demonstrate ‘proof of principle’ supporting the safety and feasibility of prehabilitation in lung cancer that may also be associated with improved exercise capacity and patient reported outcomes.

Therefore, the aims of this research are to

1. Determine the acceptability of prehabilitation before lung cancer resection amongst thoracic surgeons
2. Determine the perceived benefits of prehabilitation
3. Investigate timing of preoperative interventions

Survey questions

A) PERSONAL CHARACTERISTICS:

1) Age: _____

2) **Principle state of thoracic surgery practice** in Australia;

- | | |
|--------------------------------------|--------------------------------|
| ☐ VIC | ☐ Qld |
| ☐ NSW | ☐ N.T |
| ☐ S.A | ☐ TAS |
| ☐ W.A | ☐ A.C.T |
| ☐ Other _____ | |

3) **Years of experience** as a Cardiothoracic Consultant: _____

- 4) **Clinical caseload** ☐ Cardiac only
- ☐ Cardiac and thoracic
- ☐ Thoracic only

5) **Number of Hospitals** at which you perform Cardiothoracic surgery: _____

6) What percentage of your **patient population** for thoracic surgery are surgical **oncology** patients?

- ☐ 0 -25%
- ☐ 25 – 50%
- ☐ 50 – 75%
- ☐ 75 – 100%

B) PLEASE COMPLETE THE FOLLOWING IN RELATION TO YOUR CURRENT MAIN PLACE OF THORACIC SURGICAL WORK:

7) **Main place** of work:

- ☐ Public
- ☐ Private
- ☐ Combination of public + private
- ☐ other (please comment) _____

8) Is there a **dedicated thoracic surgery unit** within your main place of work?

- ☐ Yes
- ☐ No
- ☐ other _____

9) Total **number** of thoracic surgical resection cases for NSCLC per week in your main place of work:

Thoracotomy	0 – 25%
	25 – 50%
	50 – 75%
	75 – 100%

10) Please circle the number which most closely resembles the **percentage of cases performed** via minimally invasive **VATS** and open **Thoracotomy** in your unit each week;

VATs	0 – 25%
	25 – 50%
	50 – 75%
	75 – 100%

C) PREOPERATIVE MANAGEMENT

11) Do you refer patients to a **Physiotherapist** preoperatively?

- ☐ No (go to question 14)
- ☐ Yes what percentage of patients? _____
- ☐ sometimes
- ☐ Refer to an exercise Physiologist

12) Of the patients that **you refer preoperatively**, can you describe *why* these patients are referred to Physiotherapy?

- ☐ High-risk patients
- ☐ Standard practice in our unit
- ☐ Borderline fitness for surgery

- ☐ Surgeon/anaesthetist preference
- ☐ Patient request
- ☐ other _____

13) Can you outline the main reasons *why* patients undergoing lung resection surgery are **not referred** to Physiotherapy preoperatively (circle all that apply);

- ☐ Staffing limitations
- ☐ Urgent need for surgery/short waiting period
- ☐ Minimal perceived need
- ☐ Lack of evidence supporting preoperative intervention
- ☐ Transport or access issues
- ☐ Minimal resources available
- ☐ Unsure who to refer to
- ☐ other (please comment) _____

14) What standard **preoperative work-up** do lung cancer patients undergoing lung resection surgery receive in your unit? (Circle all that apply):

- ☐ CXR
- ☐ CT scan/PET
- ☐ MRI
- ☐ Bronchoscopy
- ☐ PFT
- ☐ Cardiopulmonary exercise testing
- ☐ 6 min walk test
- ☐ Stair climb test
- ☐ Pre-op clinic appointment
- ☐ Discussion on multidisciplinary meeting
- ☐ Cardiac screening (ECG, ECHO, Thallium scan)
- ☐ other _____

15) What is the **average waiting period** for patients with NSCLC consented for lung resection surgery from diagnosis to surgery within your unit?

- ☐ 10 days
- ☐ 20 days
- ☐ 30 days
- ☐ 40 days
- ☐ 50 days
- ☐ other _____

16) Please rank how much each of the following **influence your preoperative practice** for patients with lung cancer undergoing lung resection surgery;

	No influence				High influence	
	1	2	3	4	5	Comment
Personal experience						
Literature/evidence						
Surgical Unit structure/practice						
Staffing						
Waiting lists						
Availability of resources						
Patient type: public vs. private						
Financial constraints						

D) POST OPERATIVE CARE

17) What **Standard Post op care** do lung cancer patients receive in your unit? (Circle all that apply);

- ☐ Respiratory Physiotherapy during inpatient stay
- ☐ Pulmonary rehabilitation after discharge
- ☐ Specific Thoracic surgery clinical pathway
- ☐ Outpatient clinic follow up
- ☐ other (please comment)

18) What is the **average length of stay** for patients with NSCLC undergoing lung resection in your unit?

- ☐ 0 – 5 days
- ☐ 5 – 7 days
- ☐ 7 – 10 days
- ☐ 10+ days

E) QUESTIONS RELATING TO EXERCISE INTERVENTION

19) Of the following, which do you perceive to be the **main Barriers** to preoperative exercise for patients with stage I-IIIb NSCLC (circle all that apply):

- ☐ Dyspnoea
- ☐ Access to allied health professionals
- ☐ Fatigue
- ☐ Pain
- ☐ Time
- ☐ Patient beliefs
- ☐ Advice not to exercise
- ☐ Side effects of adjunct cancer treatment
- ☐ Patient comorbidities
- ☐ costs/financial
- ☐ transport or access issues
- ☐ other

20) How **accessible** is **preoperative exercise intervention** with allied health professionals within your unit?

- ☐ Readily available
- ☐ Available but difficult to refer
- ☐ Not accessible
- ☐ Unsure
- ☐ other _____

21) What preoperative **resources/interventions are currently available** for your patients with lung cancer (i.e. patients that you identify as moderate risk or borderline fitness for surgery)?

- ☐ Pulmonary rehabilitation
- ☐ Physiotherapy outpatient appointment
- ☐ Private exercise classes/clinic
- ☐ Home-based intervention (Physiotherapy, exercise physiologist)
- ☐ other _____

22) What do you perceive to be the main **benefits of preoperative exercise**?

- ☐ Reduced postoperative complications
- ☐ Reduced postoperative LOS
- ☐ Improved exercise capacity
- ☐ Improved symptom management
- ☐ Improved pulmonary function test results
- ☐ Improved quality of life
- ☐ All of the above
- ☐ other _____

23) Would you be willing to **delay surgery** in this patient population in order to optimise them for surgical intervention?

- ☐ Yes
- ☐ No
- ☐ Unsure

24) Do you believe **further research into prehabilitation** for patients for lung cancer is warranted?

- ☐ Yes
- ☐ No
- ☐ Unsure

Thank you for your participation in this survey

APPENDIX V – Attitudes and perceptions to prehabilitation in lung cancer

Attitudes and Perceptions to Prehabilitation in Lung Cancer

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and Linda Denehy, BAppSc, PhD^{1,5}

Abstract

Background: Prehabilitation to maximize exercise capacity before lung cancer surgery has the potential to improve operative tolerability and patient outcomes. However, translation of this evidence into clinical practice is limited. **Aims:** To determine the acceptability and perceived benefit of prehabilitation in lung cancer among thoracic surgeons. **Procedure:** 198 cardiothoracic surgeons within Australia and New Zealand were surveyed to evaluate their attitudes and perceived benefits of prehabilitation in lung cancer. **Results:** Response rate was 14%. A moderate proportion of respondents reported that there is a need to refer lung resection patients to preoperative physiotherapy/prehabilitation, particularly high-risk patients or those with borderline fitness for surgery. 91% of surgeons were willing to delay surgery (as indicated by cancer stage/type) to optimize patients via prehabilitation. The main barriers to prehabilitation reported were patient comorbidities and access to allied health professionals, with 33% stating that they were unsure who to refer to for prehabilitation in thoracic surgery. This is despite 60% of the cohort reporting that pulmonary rehabilitation is available as a preoperative resource. 92% of respondents believe that further research into prehabilitation in lung cancer is warranted. **Conclusion:** The benefits of prehabilitation for the oncology population have been well documented in the literature over recent years and this is reflected in the perceptions surgeons had on the benefits of prehabilitation for their patients. This survey demonstrates an interest among cardiothoracic surgeons in favor of prehabilitation, and therefore further research and demonstration of its benefit is needed in lung cancer to facilitate implementation into practice.

Keywords

lung cancer, exercise, prehabilitation, surgery, exercise capacity, survey

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Background

Prehabilitation is described as a

process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and severity of current and future impairments (p. 716).¹

Prehabilitation programs may include one or more of the following: exercise, smoking cessation, dietary intervention, psychological assessment, and medical optimization; however, the optimal combination of these components in the context of lung cancer remains unknown. In the context of lung cancer, prehabilitation programs usually target patients who are awaiting lung resection and the primary goal of the

program is to increase functional exercise capacity. Interventions that aim to maximize functional exercise capacity in the time available before surgery (prehabilitation) have the potential to improve operative tolerability and this is supported by emerging evidence. Systematic reviews demonstrate “proof of principle” supporting the safety and feasibility of prehabilitation in several cancer tumor streams including lung cancer and show that prehabilitation may also

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be associated with improved functional exercise capacity and patient-reported outcomes.²

Prehabilitation in lung cancer provides an opportunity for physiological assessment of the patient and multidisciplinary workup prior to surgery. It is known that individuals with lung cancer experience a high symptom burden and present with reduced levels of physical activity prior to surgery.³ This poses a significant risk for patients with operable lung cancer, as it is recognized that low cardiorespiratory fitness prior to lung surgery is predictive of poor postoperative outcomes.^{4,5} This presents a strong case for prehabilitation, as improved fitness prior to lung cancer surgery is shown to halve the rate of postoperative complications and reduce hospital length of stay.^{2,6,7} Despite this evidence, and current randomized controlled trials (6 international studies registered on ClinicalTrials.gov) attempting to determine the ideal mode, optimal timing, and patient selection for prehabilitation in lung cancer, translation into practice remains stagnant.

Barriers to the implementation of robust prehabilitation programs for patients with lung cancer include the traditional hurdles of funding, clinician knowledge, and acceptability, as well as healthcare system-related factors such as access to programs.^{8,9} Another factor to consider is the referral basis for prehabilitation, with thoracic surgeons acting as the main “gatekeepers” to this service. Since the inception of prehabilitation, little research has been dedicated to uncovering the perceptions or attitudes to prehabilitation among these gatekeepers. Only one article to date examined the perceptions of both anesthesiologists and colorectal surgeons to prehabilitation in the colorectal cancer patient population.¹⁰ The results of this research demonstrate clear recognition of the association between functional capacity and postoperative outcomes among both anesthesiologists and surgeons. This cross-sectional survey concluded that there is a “window of opportunity” for prehabilitation within the colorectal cancer cohort of 2 to 4 weeks after cancer diagnosis and recommended that further multicenter or implementation studies are required.

Purpose

This study aimed to determine the acceptability and perceived benefit of prehabilitation in lung cancer among thoracic surgeons throughout Australia and New Zealand. It was postulated that responses from the survey could be used to gain further insight into the referral pathways and reasons why surgeons choose or do not choose to utilize prehabilitation for patients with lung cancer prior to surgery. The survey also aimed to gather data on the perceived interest in prehabilitation among these gatekeepers to establish if, along with the evidence currently being generated, implementation of prehabilitation into standard care was a common goal within the thoracic surgical oncology field.

Procedure

Ethical approval was obtained from the University of Melbourne (Ethics ID: 1646932).

The survey was conducted as an online survey, with paper versions of the survey also being available (see Supplemental file available online). A 24-item survey was specifically designed for this investigation and was piloted on 2 thoracic surgeons prior to distribution among the larger target population. An email invitation with the link to the survey was sent to 198 fellows of the Royal Australasian College of Cardiothoracic Surgeons; as thoracic surgery is not a stand-alone specialty in Australia, it was not possible to target pure thoracic surgeons. After the initial invitation, 2 further email invitations were distributed via college newsletters and digital press. The survey invitation was sent with a cover letter briefly outlining the purpose of the survey along with instructions and intended use of the survey results. The survey was also distributed in printed format at the Australian and New Zealand Society of Cardiothoracic Surgery Annual Scientific Meeting. Consent was implied by participation in the survey. Following completion of the survey, demographic data and responses to the survey were collated on the online portal Survey Monkey (www.surveymonkey.com; Palo Alto, CA). Data were analyzed descriptively.

Results

Twenty-eight surgeons responded to the survey; the response rate was 14%. The highest response rate was received from surgeons in the state of Victoria 61% ($n = 16$). Respondents to the survey included cardiothoracic surgeons working in tertiary public and private hospitals throughout Australia and New Zealand. The mean age of the surgeons was 46 years (range = 32–56 years), with a mean level of experience in cardiothoracic surgery of 12.5 years. Most of the surgeons completed an average of 3.4 thoracic cases per week (range = 1–8; Table 1).

Only 23% of respondents practiced thoracic surgery exclusively (most surgeons performed a mix of cardiac and thoracic cases) (Table 2). The most common waiting period between diagnosis and surgery reported was reported to be 20 days by 38% of the sample, and the most common postoperative length of stay was reported as 6 to 7 days (55% of respondents). All surgeons reported that respiratory physiotherapy was delivered as part of the standard postoperative care, and 63% reported that a thoracic surgery pathway was utilized in their hospital unit. Only 18% of those surveyed reported that they refer lung cancer patients post lung resection for outpatient pulmonary rehabilitation as part of their ongoing care (Table 3).

The majority of respondents reported that there is a perceived need to refer lung resection patients to preoperative physiotherapy or prehabilitation, particularly high-risk patients

Table 1. Participant Demographics.

Characteristic	Mean (SD)
Age (years)	46 (12.3)
Experience (years)	12.5 (8.6)
Volume of thoracic surgery (cases/week)	3.4 (1.9)
Number of hospitals operating	2.6 (0.9)

Abbreviation: SD, standard deviation.

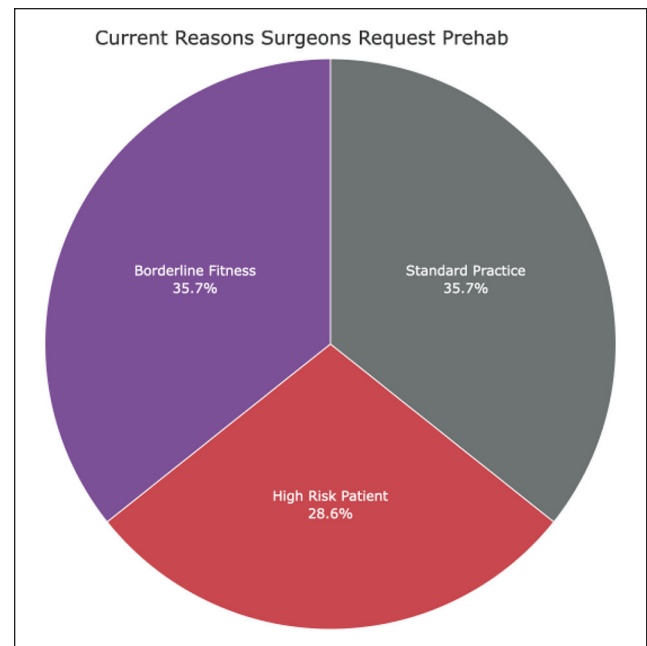
Table 2. Work Characteristics of Respondents.

Thoracic Surgeons, N = 28	n (%)
State of practice	
Victoria	16 (61.5%)
New South Wales	2 (7.7%)
South Australia	0 (0%)
Western Australia	2 (7.7%)
Queensland	2 (7.7%)
Northern Territory	0 (0%)
Tasmania	1 (3.9%)
Australian Capital Territory	0 (0%)
New Zealand	0 (0%)
Clinical caseload	
Cardiac + thoracic	20 (76.9%)
Thoracic only	6 (23%)
Public versus private	
Public	11 (42.3%)
Private	1 (3.9%)
Combination	14 (53.9%)
Dedicated thoracic unit	
Yes	10 (40%)
No	15 (60%)
Average waiting period (diagnosis to surgery)	
10 days	5 (19.2%)
20 days	10 (38.5%)
30 days	6 (23%)
40 days	3 (11.5%)
50 days	1 (3.9%)

or those with borderline fitness for surgery (Figure 1). In fact, 91% of surgeons were willing to delay surgery (as indicated by cancer stage/type) to optimize patients via prehabilitation. The main perceived benefits of prehabilitation (% of respondents that reported the variable) included the following: reduced postoperative complications (86%), reduced postoperative length of stay (76%), improved exercise capacity (67%), improved quality of life (57%), and improved symptom management (52%; Figure 2). The respondents reported that prehabilitation programs were either not accessible, or available and difficult to refer to (Figure 3). The main barriers to prehabilitation recorded were access to allied health professionals (57%), patient comorbidities (57%), transport or access issues (52%), time (48%), and costs/financial constraints (33%). Despite

Table 3. Pre- and Postoperative Referral for Lung Cancer Patients Undergoing Surgery.

Pre- and Postoperative Care	n (%)
Preoperative referral to physiotherapy	
Yes	8 (32%)
Sometimes	4 (12%)
No	13 (52%)
What preoperative resources are available for lung cancer patients?	
Pulmonary prehabilitation	12 (60%)
Physiotherapy outpatient appointment	6 (30%)
Private exercise class/clinic	5 (25%)
Home-based intervention	2 (10%)
Other	6 (30%)
Standard postoperative care of thoracic patients	
Respiratory physiotherapy as inpatient	22 (100%)
Thoracic surgery pathway as inpatient	14 (63.6%)
Outpatient pulmonary rehabilitation following hospital discharge	4 (18%)
Outpatient clinic follow up	21 (95.5%)

**Figure 1.** Reasons why surgeons request prehabilitation. Data reported in percentage of responders.

these difficulties, the perceived benefits of prehabilitation were clear and 92% of respondents believed that further research into prehabilitation in lung cancer is warranted.

Discussion

This was the first study in the Australian setting examining the attitudes and perceptions of thoracic surgeons to prehabilitation

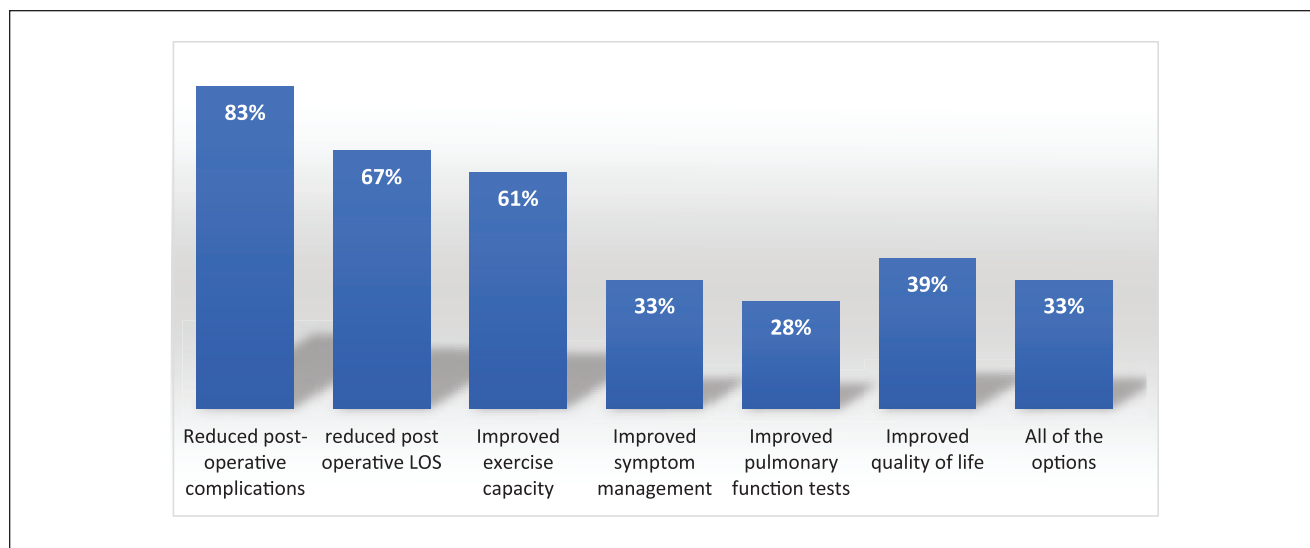


Figure 2. Surgeon's perceived benefits of prehabilitation. Data reported in percentage of responders. Responders could choose more than one option. LOS, length of stay.

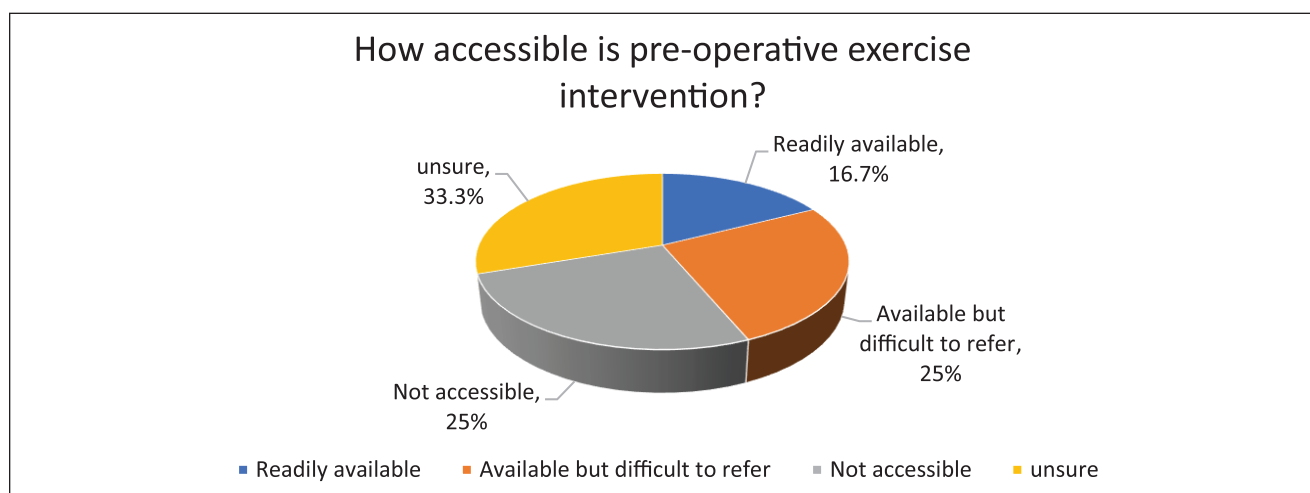


Figure 3. Accessibility of preoperative exercise interventions. Data reported in percentage of responders.

in lung cancer. The results of this study are consistent with those of a recent survey performed with colorectal surgeons and anesthesiologists, which concluded that surgeons recognize the clear association between functional capacity and postoperative outcomes, robust evidence for prehabilitation is currently lacking and that surgeons would be willing to delay surgery (up to 2 weeks) in order to optimize their patients.¹⁰

We surveyed 198 cardiothoracic surgeons; however, the response rate was poor with only 28 responses (of a potential 198), yielding a response rate of 14%. A recent online survey of thoracic surgeons in the United States examining the pre-operative management of thoracic surgery patients who were smokers reported a similar low response rate of 13% with this population.¹¹ Within the medical profession, in particular

surgery, time to participate in additional nonclinical tasks, such as a survey, is limited and may explain some of the inadequate capture of the wider target population despite multiple methods and modes to increase response rate. Another limitation that must be considered is the language and motivations of the survey and how they align with those of the surgeons. Surgeons are often driven by results and invest in strategies that will improve the outcomes for their patients. Unless prehabilitation can demonstrate clear benefits for their patients through robust evidence, it is unlikely to become part of their standard referral practices. Of the surgeons interviewed, a large proportion were from the state of Victoria. This state has a strong bias toward surgeons who practice thoracic surgery as its own specialty, in comparison to cardiothoracic

surgeons who perform both cardiac and thoracic surgery and may therefore be more representative of the attitudes and opinions, which are most relevant for prehabilitation prior to lung cancer surgery.

Despite the results of the survey demonstrating that the majority of cardiothoracic surgeons practice minimally invasive techniques (video-assisted thoracoscopic surgery), postoperative morbidity remains a concern for many surgeons. The incidence of postoperative pulmonary complications such as pneumonia, atelectasis, acute respiratory distress syndrome, pulmonary edema, and respiratory failure after lung resection ranges from 4.8% to 55%.¹² The response to the survey question, "Out of the patients that you refer preoperatively, can you describe why these patients are referred to Physiotherapy?" further highlights this concern; as 2 of the 3 reasons for referral were related to factors that are associated with higher postoperative morbidity (high-risk patients or patients with borderline fitness for surgery; Figure 1). The main reason cited for not referring to preoperative physiotherapy (exercise intervention) was urgent need for surgery or short waiting period. The literature to date supports the use of prehabilitation in lung cancer in reducing this postoperative morbidity with a recent systematic review concluding that preoperative exercise intervention halves the rate of postoperative complications (risk ratio = 0.52, 95% confidence interval = 0.36 to 0.74) and reduces hospital length of stay (MD = -2.86 days, 95% confidence interval = -5.4 to -0.33) in patients undergoing lung resection.⁷ Clearly the evidence is emerging; however, promotion of the role that physiotherapists can play in modifying patient risk factors and providing interventions that may help reduce postoperative morbidity needs further attention.

Achieving greater awareness of the role physiotherapists and prehabilitation can play in reducing postoperative morbidity would be assisted by further studies looking specifically at the cost-benefit of providing prehabilitation to patients with lung cancer. Many of the studies to date have examined the effect of prehabilitation on postoperative outcomes; however, these endpoints may not be "speaking the same language" as the surgeons. In terms of surgical practice, the top priorities for surgeons include morbidity, mortality, and practicing in a way that adds value to their service. If we can provide evidence that prehabilitation demonstrates clear cost saving advantages for both the patient and health care system, as well as more data on postoperative morbidity rather than simply the incidence of complications, perhaps there would be more acceptance and integration of prehabilitation into current thoracic surgery care pathways. This has been well researched in a larger study of general surgery patients having preoperative physiotherapy education to reduce postoperative complications.¹³ The fact that the surgeons surveyed in our

study were able to identify the key benefits of preoperative exercise and that nearly all believe further research into prehabilitation is warranted provides evidence to undertake more research in this patient population.

The strongest message this survey uncovered was the overwhelming support for prehabilitation among surgeons in order to optimize their "high-risk" patients (those with multiple comorbidities, advanced age, positive smoking status/respiratory disease, and/or obesity) preoperatively. Over 90% of cardiothoracic surgeons surveyed would be willing to delay surgery for prehabilitation (depending on the stage/operability of the tumor) indicating that there is potential for prehabilitation to fill a current gap in the lung cancer care pathway, particularly in patients with borderline fitness for surgery (as defined by measures of cardio-pulmonary function VO_{2max} and pulmonary function tests). This is corroborated by Li et al's survey of colorectal surgeons who also reported that surgeons would be willing to delay surgery for 2 to 4 weeks for prehabilitation.¹⁰ These results clearly demonstrate the recognition that surgeons have of the association between functional capacity and postoperative outcomes, and point toward the acute need for allied health professionals to work to integrate prehabilitation services into current routine practice. Further randomized controlled trial research is required to determine the efficacy of delaying surgery for high-risk patients, as at present data do not support delaying surgery for patients already deemed fit for surgery,² but rather prehabilitation is timed opportunistically in the waiting period of these patients prior to their surgery.

Finally, it is important to explore alternate means of delivering prehabilitation for patients with lung cancer, such as via telehealth with virtual/online exercise platforms, which could allow delivery of programs to patients in their home setting. A home-based model would be appealing, particularly for patients who are unable to access the traditional center-based programs who often report barriers such as living too far away from the center or lack of transport.⁹ The trials testing preoperative exercise programs in lung cancer to date predominately use supervised, center-based exercise programs and these may offer advantages to patients in terms of their ability to enhance patient motivation and adherence.² However, there are emerging data to suggest that home-based exercise is also effective in this population, with a recent trial demonstrating a 2-week home-based multimodal prehabilitation program, supported with telephone calls, improved functional exercise capacity in patients before lung resection.¹⁴ Further research is needed to compare the effectiveness of home-based programs compared with center-based programs in lung cancer,² as well as the optimal home-based exercise models and how these could be supported with technology,¹⁵ which has been relatively underresearched in this field to date.

The Future

This survey of cardiothoracic surgeons within Australia and New Zealand is the first to explore the perceptions and attitudes of these gatekeepers to prehabilitation within lung cancer. Results demonstrate a keen interest in prehabilitation within the thoracic oncology population, with 91% of survey respondents willing to delay surgery for prehabilitation. The poor response rate of 14% is a limitation to this study; however, as the majority of responses were from surgeons practicing thoracic surgery exclusively, the attitudes and perceptions reported closely represent current thoracic surgery practice. The attitudes and perceptions of the 86% of “non-responders” remains unknown and may demonstrate a lack of receptiveness to prehabilitation in lung cancer. Further evidence is required to provide a convincing argument for prehabilitation and to target the “non-responders” who may not, due to low thoracic caseload mix or lack of exposure, had the benefit of experience with such preoperative programs and therefore be willing to incorporate prehabilitation into routine care within lung cancer surgery. The challenges for prehabilitation that must be overcome include enhancing its promotion (through education and research), establishing strong referral pathways, developing good relationships with the surgeon gatekeepers, and being able to provide best evidence prehabilitation services in order to provide optimal care to patients most debilitated by lung cancer.

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Supplemental Material

Supplemental material for this article is available online.

References

1. Silver JK, Baima J. Cancer prehabilitation: an opportunity to decrease treatment related morbidity, increase cancer treatment options and improve physical and psychological health outcomes. *Am J Phys Med Rehabil*. 2014;92:715-727.
2. Cavalheri V, Granger CL. Preoperative exercise training for patients with non-small cell lung cancer. *Cochrane Database Syst Rev*. 2017;(6):CD012020. doi:10.1002/14651858.CD012020.pub2
3. Granger CL, McDonald CF, Irving L, et al. Low physical activity levels and functional decline in individuals with lung cancer. *Lung Cancer*. 2014;83:292-299.
4. Santa Mina D, Clarke H, Ritvo P, et al. Effect of total body prehabilitation on postoperative outcomes: a systematic review and meta-analysis. *Physiotherapy*. 2014;100:196-207.
5. Myers JN, Fonda H. The impact of fitness on surgical outcomes: the case for prehabilitation. *Curr Sports Med Rep*. 2016;15:282-289.
6. Garcia RS, Brage MIY, Moolhuyzen EG, Granger CL, Denehy L. Functional and postoperative outcomes after preoperative exercise training in patients with lung cancer: a systematic review and meta-analysis. *Interact Cardiovasc Thorac Surg*. 2016;23:486-497.
7. Steffens D, Beckenkamp PR, Hancock M, Solomon M, Young J. Preoperative exercise halves the postoperative complication rate in patients with lung cancer: a systematic review of the effect of exercise on complications, length of stay and quality of life in patients with cancer. *Br J Sports Med*. 2018;52:344.
8. Granger CL, Denehy L, Remedios L, et al. Barriers to translation of physical activity into the lung cancer model of care: a qualitative study of clinicians' perspectives. *Ann Am Thorac Soc*. 2016;13:2215-2222.
9. Granger CL, Connolly B, Denehy L, et al. Understanding factors influencing physical activity and exercise in lung cancer: a systematic review. *Support Care Cancer*. 2017;25:983-999.
10. Li MHG, Bolshinsky V, Ismail H, et al. Cross-sectional survey of Australian anesthetists and surgeons' perceptions of preoperative risk stratification and prehabilitation. *Can J Anesth*. 2019;66:388-405.
11. Marino KA, Little MA, Bursac Z, Sullivan JL, Klesges R, Weksler B. Operating on patients who smoke: a survey of thoracic surgeons in the United States. *Ann Thorac Surg*. 2016;102:911-916.
12. Jing R, He S, Dai H, et al. Incidence and risk factors of postoperative pulmonary complications after thoracic surgery for early non-small cell cancer. *Int J Clin Exp Med*. 2018;11:285-294.
13. Boden I, Skinner EH, Browning L, et al. Preoperative physiotherapy for the prevention of respiratory complications after upper abdominal surgery: pragmatic, double-blinded, multi-center randomized controlled trial. *BMJ*. 2018;360:j5916.
14. Liu ZT, Qiu L, Pei Y, et al. Two-week multimodal prehabilitation program improves perioperative functional capability in patients undergoing thoracoscopic lobectomy for lung cancer: a randomized controlled trial [published online July 23, 2019]. *Anesth Analg*. doi:10.1213/ANE.0000000000004342
15. Cox A, Lucas G, Marcu A, et al. Cancer survivors' experience with telehealth: a systematic review and thematic analysis. *J Med Internet Res*. 2017;19:e11.

