UNIVERSIDADE DA CORUÑA

Preoperative pulmonary rehabilitation in lung cancer patients undergoing lung resection surgery

Tesis Doctoral

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A Adrián y a Marisé

“Lack of activity destroys the good condition of every human being, while movement and methodological physical exercise, save it and preserve it”.

Plato (427 – 347 B.C)

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ABSTRACT

INTRODUCTION: Lung resection surgery (LRS) remains the treatment of choice for early stages of lung cancer but significant morbidity is associated, especially among patients with poor preoperative status. Preoperative exercise training (PET) has been proposed as an effective way of optimizing patients' condition before surgery and enhancing postoperative recovery. However, it remains unknown whether or not similar results can be achieved after video-assisted thoracic surgery (VATS). Therefore, the aim of this thesis is to determine the feasibility, safety and efficacy of a preoperative pulmonary rehabilitation program (PPRP) on the functional and postoperative outcomes on patients undergoing VATS.

MATERIALS AND METHODS: This thesis was structured in three studies: 1) a systematic review and meta-analysis of the effects PET on the functional and postoperative outcomes after LRS; 2) a small pilot investigation to assess the feasibility, safety and preliminary effects of a PPRP in patients awaiting VATS; and 3) a randomized controlled trial examining the effects of the PPRP after VATS for lung cancer on selected postoperative and functional outcomes in comparison to the standard care.

RESULTS: Results from the study #1 show that PET improves pulmonary function before surgery and hastens postoperative recovery by reducing postoperative complications and hospital length of stay. In study #2, we concluded that a PPRP is safe and feasible and can potentially improve functional fitness. Finally, study #3, confirmed that a PPRP significantly improves exercise capacity, muscle strength and health-related quality of life while minimizing the impact of LRS during the first 3 months after VATS.

CONCLUSIONS: We conclude that preoperative exercise-based interventions in patients with lung cancer awaiting VATS are feasible, safe and can significantly improve exercise and functional performance and enhance postoperative recovery.

RESUMEN

INTRODUCCION: La cirugía de resección pulmonar (CRP) continúa siendo el tratamiento de elección en estadios iniciales del cáncer de pulmón pero la morbilidad asociada continúa siendo elevada, especialmente en pacientes con peor condición física. La Rehabilitación Pulmonar Preoperatoria (RPP) podría constituir una herramienta útil a la hora de disminuir el riesgo perioperatorio y optimizar la recuperación postoperatoria. Sin embargo, dichos programas no han sido probados en pacientes operados por videocirugía. Así pues, el objetivo de esta tesis es investigar la viabilidad, seguridad y eficacia de un programa de RPP en pacientes sometidos a resección pulmonar por videocirugía.

MATERIAL Y METODOS: Esta tesis está estructurada en tres estudios: 1) revisión sistemática y meta-análisis sobre la eficacia del ejercicio preoperatorio en pacientes sometidos a CRP en cuanto a mejorar el estado funcional de los pacientes y acelerar la recuperación postoperatoria; 2) estudio piloto centrado en la viabilidad, seguridad y eficacia preliminar de la RPP en pacientes sometidos a videocirugia; y 3) un ensayo controlado aleatorizado sobre la eficacia de la RPP en los outcomes funcionales y postoperatorios en pacientes sometidos a videocirugia en comparación con el tratamiento estándar.

RESULTADOS: Los resultados obtenidos en el estudio #1 muestran que el ejercicio preoperatorio mejora la función pulmonar y acelera la recuperación postoperatoria al reducir la estancia hospitalaria y el número de complicaciones; con el estudio #2 se comprobó que la RPP es viable, segura y potencialmente eficaz a la hora de incrementar la capacidad funcional, mientras que el estudio #3 corroboró los resultados anteriores demostrando que la RPP incrementa la tolerancia al esfuerzo, la fuerza muscular y la calidad de vida al tiempo que optimiza la recuperación postoperatoria los tres primeros meses tras videocirugia.

CONCLUSION: La RPP en pacientes con cáncer de pulmón sometidos a videocirugia es viable, segura y eficaz a la hora de incrementar el estado funcional preoperatorio de los pacientes así como optimizar la recuperación postoperatoria.

RESUMO

INTRODUCCION: A cirurxía de resección pulmonar (CRP) constitue o tratamiento de elección en pacientes con cancro de pulmón en estadios iniciáis pero a morbilidade asociada continua a ser elevada especialmente en pacientes con peor condición física de base. Neste contexto, a Rehabilitación Pulmonar Preoperatoria (PRP) podería considerarse como unha ferramenta útil para disminuir o risco quirúrxico e optimizar o estado funcional dos pacientes. Non obstante, desconecese o rol destos programas nos pacientes operados por videocirurxía. Así pois, o obxectivo desta tese de doutoramento e estudar a viabilidade, seguridade e eficacia da Rehabilitación Pulmonar Preoperatoria (RPP) en pacientes con cancro de pulmón sometidos a resección pulmonar por videocirurxía.

MATERIAL E METODOS: Esta tese está estructurada en tres estudos: 1) revisión sistemática e meta-analice da efectividade da RPP en pacientes con cancro de pulmón sometidos a CRP para mellorar o estado funcional e acelerar a recuperación postoperatoria; 2) estudo piloto sobre a viabilidade, seguridade e eficacia preliminar da RPP en pacientes operados por videocirurxía e 3) ensaio clínico aleatorizado sobre o impacto da RPP sobre a tolerancia o esforzo, a capacidade funcional e a tolerancia o esforzo no postoperatorio de CRP en comparación co tratamento estándar.

RESULTADOS: Os resultados obtidos no estudo #1 mostraron que o exercicio preoperatorio en pacientes sometidos a CRP mellora a función pulmonar e acelera a recuperación postoperatoria ao reducir o número de complicacións postoperatorias e a estadía hospitalaria; no estudo #2 quedo comprobada a viabilidade da intervención así como a ausencia de eventos adversos así como o potential da intervención para mellorar a funcionalidade dos pacientes; finalmente, o estudo #3 corroborou a efectividade da RPP para optimizar o estado funcional

dos pacientes previo a cirurxía e disminuir o impacto ocasionado pola CRP durante os tres primeiros meses tras videocirurxía.

CONCLUSIÓNS: A RPP en pacientes con cancro de pulmón sometidos a videocirurxía e viable, segura e eficaz para incrementar a tolerancia o estado funcional previo a cirurxía e optimizar a recuperación postoperatoria.

THESIS OVERVIEW

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LIST OF ABBREVIATIONS, ACRONYSMS AND SYMBOLS

± = Plus or minus

≤ = Equal or less than

≥ = Equal or greater than

↑ = increase

↓ = reduction

95% CI = Confident Interval at 95%

6MWT = Six Minute Walk Test

ACCP = American College of Chest Physicians

ATP = Adenosine Triphosphate

ATS = American Thoracic Society

CCI = Charlson Comorbidity Index

CCS = Colinet Comorbidity Score

CINAHL = Cumulative Index to Nursing and Allied Health Literature

CONSORT = Consolidate Standards of Reporting Trials

COPD = Chronic Obstructive Pulmonary Disease

CPET = Cardiopulmonary Exercise Testing

CRF = Cancer-related fatigue

CT = Computed Tomography

CXR = Chest x-ray

EBUS = Endobronchial Ultrasound

EGFR = Epidermal Growth Factor Receptor

EMBASE = Excerpta Medica Database

EORTC = European Organization for Research and Treatment of Cancer

ERS = European Respiratory Society

ESTS = European Society of Thoracic Surgeons

ESWT = Endurance Shuttle Walk Test

FEV_1 = Forced Expiratory Volume in the 1 second

FVC = Forced Vital Capacity

HR = Heart Rate

HR_{max} = Maximal Heart Rate

HRQoL = Health-Related Quality of Life

IASLC = International Association for the Study of Lung Cancer

ICU = Intensive Care Unit

IMT = Inspiratory Muscle Training

IQR = Inter-quartil range

ISWT = Incremental Shuttle Walk Test

LCTD = Low Computed Tomography Dose

LVRS = Lung Volume Resection Surgery

MCS = Mental Health Summary

MCID = Minimally Clinical Important Difference

MEDLINE = Medical Literature Analysis and Retrieval System Online

MEP = Maximal Expiratory Pressure

MD = Mean Difference

MGS = Melbourne Group Scale

MIP = Maximal Inspiratory Pressure

NSCLC = Non-Small Cell Lung Cancer

NOS = Newcastle – Ottawa Quality Assessment Scale

OR = Odds Ratio

PEDro = Physiotherapy Evidence Database

PET = Positron Emission Tomography

PCS = Physical Component Summary

PORT = Post-operative Radiotherapy

PPRP = Preoperative Pulmonary Rehabilitation Program

PR = Pulmonary Rehabilitation

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO = International Prospective Register of Systematic Reviews

PTPS = Post-thoracotomy Pain Syndrome

PUBMED = National Library of Medicine's collection database

RCT = Randomized Controlled Trial

RR = Risk Ratio

RRR = Relative Risk Reduction

SBRT = Stereotactic Body Radiotherapy

SCLC = Small Cell Lung Cancer

SCC = Squamous Cell Carcinoma

SCT = Stair Climbing Test

SD = Standard Deviation

SEPAR = Spanish Society of Respiratory Medicine and Thoracic Surgery

SF36 = Short Form 36 Health Survey

SMD = Standardized Mean Difference

VATS = Video-Assisted Thoracic Surgery

VO_{2peak} = Peak of Oxygen Consumption

WHO = World Health Organization

W_{max} = Maximal Workload

W_{peak} = Peak workload

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A) Publications

- ✓ **Sebio García R,** Yáñez Brage Mi; Efecto de la rehabilitación pulmonar preoperatoria en pacientes con cáncer de pulmón; *Rehabilitación; 2013;47:229-37*
- ✓ **Sebio Garcia R.,** Yáñez Brage MI., Giménez Moolhuyzen E., Valenza MC., Reychler G., Cahalin LP.; Impact of a Pre-operative Pulmonary Rehabilitation Program on Exercise Tolerance after Video-Assisted Thoracic Surgery (VATS) for lung malignancies; *Arch Bronconeumol* – ahead of pub

B) Conference Papers

- ✓ **Sebio Garcia R.,** Preoperative exercise training in lung cancer: systematic review and meta-analysis; Cardiorespiratory Research Network Forum; Melbourne, September 2015 (Oral Presentation).
- ✓ **Sebio García R.,** Giménez Moolhuyzen E., Salorio Riobo M., Borro Mate JM.; Efecto de la rehabilitación pulmonar preoperatoria en pacientes con neoplasias pulmonares operados por videocirugía; II Encuentro Científico Gallego de estudiantes y profesionales de enfermería y fisioterapia; A Coruña, 2014 (Oral Presentation).
- ✓ **Sebio García R,** Gimenez Moolhuyzen E, Sanesteban Hermida Y, Ripamondi A, Yáñez Brage MI; Exercise capacity after Video-Assisted Thoracic Surgery for lung cancer; European Respiratory Society International Congress; Munich, September 2014 (Poster – Exhibition).
- ✓ **Sebio García R.,** Lista Paz A., Yáñez Brage MI., Sanesteban Hermida Y., Efecto de la rehabilitación pulmonar preoperatoria en pacientes con cáncer de pulmón; 47

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- ✓ **Sebio García R**., Lista Paz A., Yáñez Brage MI., Sanesteban Hermida Y., López Calviño B., Efectividad de un programa de rehabilitación pulmonar preoperatorio en pacientes operados por videocirugía; 47 Congreso Nacional Sociedad Española de Neumología y Cirugía Torácica (SEPAR); Bilbao, Junio 2014 (Poster – Exhibition).

INTRODUCTION

Lung cancer is the most common diagnosed malignancy in the world (American Cancer Society, 2015). An estimated 1.8 million new cases occurred in 2012 accounting for 13% of all cancer diagnoses. Lung cancer is a pandemic disease, with a high burden and elevated economic cost. Individuals with lung cancer often experience significant levels of symptom distress, anxiety, depression and low quality of life. Furthermore, the overall five-year survival rates are among the lowest of all cancer types (ranging between 10 and 18 %) (Siegel et al., 2015, De Angelis et al., 2014). Unsurprisingly, survival is higher for those diagnosed with early stages, increasing to 55% for localized disease (stages I and II), thereby highlighting the importance of an early diagnosis and adequate therapeutic management (Amer et al., 2011).

Approximately 85% of lung cancers correspond to non-small-cell type (NSCLC). Surgery remains the gold treatment for stages I and II of lung cancer (Molina et al., 2008). Unfortunately, patients diagnosed with resectable disease represent only 20 to 25 % of all cases (Howington et al., 2013, Brunelli et al., 2013a). In addition, lung cancer patients frequently exhibit low cardiopulmonary fitness, impaired pulmonary function, associated chronic co-morbidities and advanced age, which are known to negatively impact on surgical tolerability and increase the risk of post-operative mortality and morbidity (Brunelli et al., 2013a, Beckles et al., 2003, Mazzone, 2012). In addition, all forms of cancer therapy are associated with some degree of physical and psychological impairment (Jones et al., 2009a). In particular, after surgical resection, patients experience a significant decrease in exercise capacity, pulmonary function, health-related quality of life (HRQoL) and self-care (Win et al., 2007, Granger et al., 2014, Kenny et al., 2008). As a result, several perioperative strategies have been proposed in recent years to reduce post-operative complications, enhance post-operative recovery and minimize the impact of local and systemic therapies. One of the most important advances in thoracic surgery has been the introduction and

further optimization of a minimally invasive approach. Video-assisted thoracic surgery (VATS) was first introduced for the management of lung cancer in the early 90s and its use has been steadily increasing ever since. Among the numerous benefits associated with this approach are a reduction in post-operative pain (Handy et al., 2009, Cheng et al., 2007), fewer post-operative complications, shortened hospital length of stay (Cao, 2012, Cheng et al., 2007, Whitson et al., 2008) and enhanced post-operative recovery (Che et al., 2013, Demmy and Nwogu, 2008). Furthermore, VATS has allowed patients of an advanced age or poor cardiopulmonary fitness, who would previously have been denied surgery, to undergo lung resection, thereby improving their prognosis and survival. Although both cardiopulmonary fitness and pulmonary function are strong independent predictors of post-operative pulmonary complications (PPCs) after thoracic surgery, adequate preoperative evaluation and management of these patients should be undertaken to minimize post-operative morbidity and prevent further deterioration.

A recent review conducted by a panel of experts recommended pulmonary rehabilitation as part of the preoperative measures to optimize functional status before thoracic surgery (Jones et al., 2013). Pulmonary rehabilitation (PR) is a non-pharmacological, cost-effective intervention aimed at improving the physical and psychological status of people with chronic respiratory disease (Spruit et al., 2013, Rochester et al., 2015). Exercise training (especially endurance training) is regarded as the cornerstone of the whole intervention and it can be argued that it is the most effective therapy for improving dyspnoea, exercise tolerance and HRQoL in chronic obstructive pulmonary disease (COPD) (Casaburi, 2008). Recent research conducted in the context of lung cancer suggests that exercise training delivered both pre- and postoperatively is safe and can also improve exercise capacity, pulmonary function, HRQoL and global functioning (Granger et al., 2011, Nagarajan et al., 2011). However, the majority of the research has been conducted in patients undergoing conventional thoracotomy. With the widespread use of videothoracoscopic resection

in the management of lung cancer, it is unknown whether patients undergoing VATS for lung lesions can benefit from a PR intervention in a similar way to those operated on by thoracotomy. Additionally, there is still some controversy regarding the impact of the surgical approach on the short- and long-term outcomes, particularly those related to functional and psychological well-being. Finally, very few randomized controlled trials have been undertaken to assess the effectiveness of a preoperative intervention on functional outcomes in comparison to the standard care. Therefore, it's the purpose of this thesis to fill those gaps in the literature and to provide a solid foundation for further research.

SIGNIFICANCE OF RESEARCH

Lung cancer is the second most common malignant diagnosis among Spanish men and the fourth among women (GLOBOCAN, 2012). According to the latest report of the Spanish Bureau of Statistics, 21,664 people died of lung cancer in 2013, which translates into a 0.8% increase in comparison to previous data. Despite this increment in raw mortality, the five-year overall survival rates have been slowly increasing in recent decades, especially among patients with localized disease (De Angelis, 2014). About 50 to 68 % of those patients diagnosed with stage I and II NSCLC would become lung cancer survivors each year (living five or more years after diagnosis). However, a high percentage of them still experience some degree of dyspnoea and fatigue for a long time after treatment cessation, which could lead to low physical activity levels and poor HRQoL (Ostroff et al., 2011, Coups et al., 2009, Feinstein et al., 2010). Although post-operative rehabilitation has been successfully undertaken in this population to restore functional capacity (Crandall et al., 2014, Cavalheri et al., 2014), the appropriate timing for exercise has not been established yet. Furthermore, it is common for patients after lung resection to undergo adjuvant chemo- or radiotherapy, which may limit the subject's capacity and willingness to engage in an exercise-based programme. In this scenario, prehabilitation of patients awaiting surgery may

be a better way to reduce post-operative morbidity and accelerate recovery than post-operative interventions, especially in elderly patients and individuals with poor preoperative status (Gillis et al., 2014, Debes et al., 2014).

OBJECTIVES

The aims of this thesis were:

a) To identify, synthesize and analyse the current body of evidence regarding the effectiveness of a preoperative exercise-based intervention for improving functional capacity, exercise tolerance, HRQoL and post-operative outcomes in lung cancer patients.
b) To assess the feasibility, safety and tolerability of a supervised pulmonary rehabilitation programme in individuals awaiting lung resection surgery by VATS.
c) To examine the efficacy of the preoperative intervention for enhancing exercise capacity, functional capacity, muscle strength and HRQoL and hastening post-operative recovery.
d) To provide a solid foundation for further research involving patients in the preoperative period of diverse cancer types to reduce post-operative morbidity and accelerate functional and psychological recovery.

THESIS STRUCTURE

I. Chapter one provides an overview of lung cancer including the latest trends and advances in epidemiology, aetiology, diagnosis, treatment and prognosis, with a special focus on NSCLC. This chapter plays an important role in stating the magnitude of the problem and the need for further research in this field.

II. Chapter two looks more deeply into the clinical and socio-economic impact of lung cancer in our society, providing a detailed description of the lung cancer patient including major signs and symptoms, associated co-morbidities and other findings related to the disease and its background.

III. Chapter three presents a description of the perioperative management of the patient being considered for lung resection surgery, including the potential risks associated with surgery and the impact of the treatment on the short- and long-term outcomes.

IV. Chapter four contains the results of a systematic review and meta-analysis of the effects of a preoperative exercise-based intervention on post-operative and functional outcomes in patients with lung cancer. This piece of research is fundamental to set the current body of knowledge in the topic as well as the limitations and research gaps.

V. Chapter five reports on the results of a pilot investigation conducted in a small sample of individuals with lung malignancies awaiting VATS to assess the viability of the research project in terms of feasibility, tolerability and safety.

VI. Chapter six details the results of the main study of this thesis, a randomized single-blinded controlled trial undertaken in patients with suspected or confirmed lung cancer undergoing VATS. Post-operative morbidity, functional exercise capacity, muscle strength and health-related quality of life were analysed pre- and post-intervention and in comparison to the standard care to determine the effectiveness of the intervention for enhancing physical functioning and accelerating recovery.

VII. Finally, chapter seven summarizes the main findings yielded by this thesis as well as recommendations for future research.

CHAPTER ONE: LUNG CANCER – AN OVERVIEW

1.1 Brief history of lung cancer

Lung cancer was once a rare disease. In the early 1900s, only about 140 cases had been published in the medical literature (Proctor, 2012). One of those was the case of Mary Benbow, a woman who was admitted to Guy's Hospital in London complaining of shortness of breath, haemoptysis and a dry cough. She had been presenting symptoms for at least two years and she died only a couple of months after being admitted to the hospital with her doctors not knowing what to do to save her life. It was not until the autopsy was carried out that the doctors saw a proliferation of cells in her lung similar to that seen in other malignant diseases (Timmermann, 2014). In 1840 there were only 2,786 cases of cancer reported in England and Wales. By 1905, the number of diagnosed cases had increased tenfold (Adler, 1980). This led physicians to acknowledge that the disease was becoming more common and they started to look for a cause. The American doctor Isaac Adler was the first to strongly suggest that smoking and alcohol abuse were the main causes of lung cancer. By the end of World War II, the link between smoking and lung cancer incidence was evident, with the first epidemiological studies showing the likelihood of tobacco smoking leading to the development of lung cancer. These first impressions were later confirmed with animal experimentation and with the discovery of cancer-causing agents present in cigarette smoke (Proctor, 2012).

If there is any hope for a cure for lung cancer, Adler wrote in 1912, he expected it to come from surgeons (Timmermann, 2014). That same year, Dr. Morriston Davies, a surgeon from the London Chest Hospital, was the first to perform what is today considered the first successful dissection lobectomy. However, the patient barely made it through the surgery and died on the 8th post-operative day of an empyema (Timmermann, 2014). The first lung cancer lobectomy was performed in 1933 by Evarts Graham and was later recognized as the most dramatic contribution

to pulmonary resection (Meade, 1961). Only a few months later, Dr. Edward Archibald at the Royal Victoria Hospital in Montreal performed the first successful hilar dissection pneumonectomy for a sarcoma of the left upper lobe (Deslauriers et al., 2011). Thanks to further advances in anaesthesia, the development of modern mechanical ventilators and most importantly the widespread use of penicillin, lung cancer became successfully treated. By 1990, surgery was universally acknowledged as the gold treatment for lung cancer and it has remained so ever since.

In 1992, Landreneau and colleagues described the first lobectomy using a minimally invasive technique (Landreneau et al., 1992). Two decades later, video-assisted thoracic surgery (VATS) has become the treatment of choice for stage I NSCLC, and as the technique evolves further, the percentage of thoracic surgeries performed by VATS continues to rise. Thanks to this minimally invasive approach, patients with poor pulmonary function, high body mass index (BMI), poor performance status and/or severe cardiovascular and respiratory co-morbidities have been surgically treated improving their prognosis and survival.

Despite the advantages in local and systemic therapies, lung cancer continues to be the leading cause of cancer-related death worldwide and is expected to surpass cardiovascular diseases as the top cause of overall death. In this chapter, an overview of lung cancer epidemiology, aetiology, diagnosis and current treatment modalities is provided to establish the magnitude of the problem and the need for further research.

1.2 Epidemiology of lung cancer: incidence, mortality and five-year survival rates

1.2.1 Incidence of lung cancer

With an estimated 1.8 million new cases around the world, lung cancer is the most frequently diagnosed cancer accounting for 13% of all diagnoses (Torre et al., 2015, American Cancer Society, 2015). In males, lung cancer is both the most frequent malignancy and the most fatal, resulting in more than 1 million deaths in 2012. In more developed countries, lung cancer is also the leading cause of cancer death in females, being responsible for 209,900 deaths in 2012 (Figure 1.1). In the US, lung cancer accounts for more deaths than breast, prostate and colorectal cancers combined (approximately 27% of all cancer deaths) (Siegel et al., 2015).

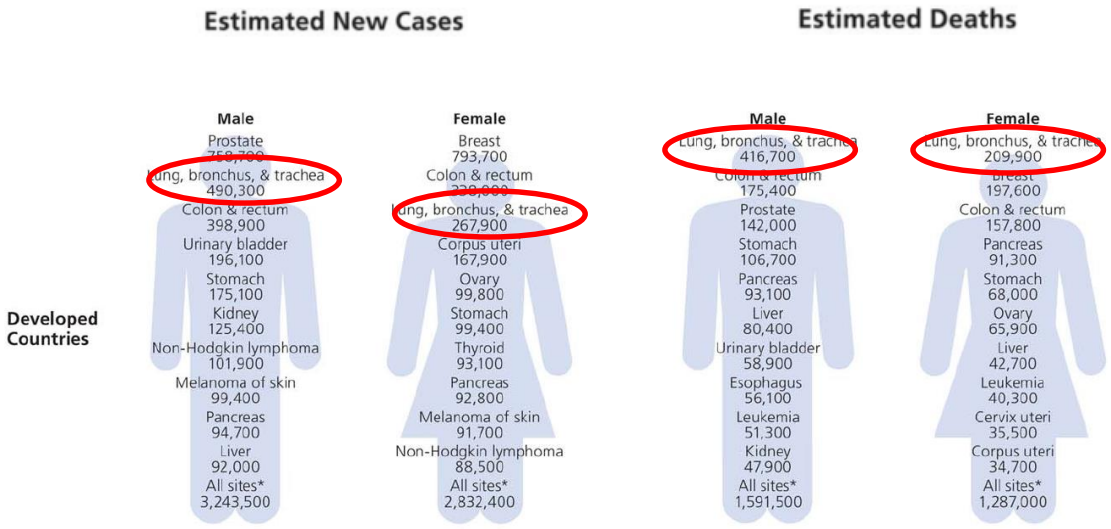


Figure 1.1: Incidence and mortality in developed countries; GLOBOCAN, 2012.

The highest incidence of lung cancer is currently found in more developed countries, and is particularly frequent in Australia and New Zealand, where it is the most common type of cancer diagnosed in both sexes, and in southern Europe (Torre et al., 2015) (Figure 1.2). The incidence of lung cancer in women is generally lower than in men, and appears to be markedly influenced by geographical location. For instance, in eastern Asia, lung cancer is relatively common among women despite the lower prevalence of smoking (International Agency for Research Cancer, 2012).

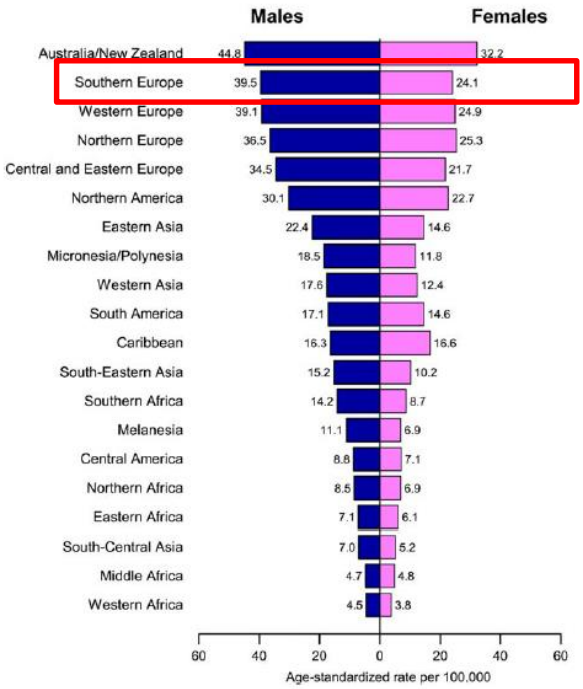


Figure 1.2: Lung Cancer Incidence Rates by sex and World Area; GLOBOCAN, 2012.

In Spain, numbers are consistent with the other Western developed countries. Data derived from the GLOBOCAN study show that lung cancer is the second most common malignancy among men and the fourth among women, accounting for 12.4% of all diagnoses (Table 1.1) (Sociedad Española de Oncologia Medica, 2014). The raw incidence rates varied between regions ranging from 51.5 to 102 in men (with the maximum incidence reported in 1997–1999) and from 2.4 to 20 in women (Sánchez De Cos Escuín, 2009).

	Hombre	Mujer	Ambos Sexos
1°	Próstata	Mama	Colorrectal
2°	Pulmón	Colorrectal	Próstata
3°	Colorrectal	Cuerpo de Útero	Pulmón
4°	Vejiga	Pulmón	Mama
5°	Estómago	Ovario	Vejiga

Table 1.1: Most common cancer types diagnosed in Spain; GLOBOCAN, 2012.

International variations in lung cancer rates and trends are a reflection of the geographical and sex differences in the tobacco epidemic (Torre et al., 2015). In developed countries, lung cancer incidence has started to plateau as a result of the anti-tobacco politics and consequent reduction in smoking prevalence, while in less developed countries, the incidence continues to grow. In the US, for instance, where tobacco consumption peaked in the mid-1960s, lung cancer incidence has been steadily declining since 1980 in males and more recently in females (Figure 1.3) (Houston et al., 2014). In contrast, in Spain, lung cancer incidence has started to decline in men but continues to rise in females (Figures 1.4) (Sánchez et al., 2010, Linares et al., 2015). The male-to-female ratio has also experienced a significant change in recent years due to the increase in smoking prevalence among women; in the US, the ratio is approaching the unity (1.5:1) (Houston et al., 2014), while in Spain, although the difference is still significant, the gap is slowly closing (from 7:1 in 2006 to 4:1 in 2012) (Sánchez et al., 2010).

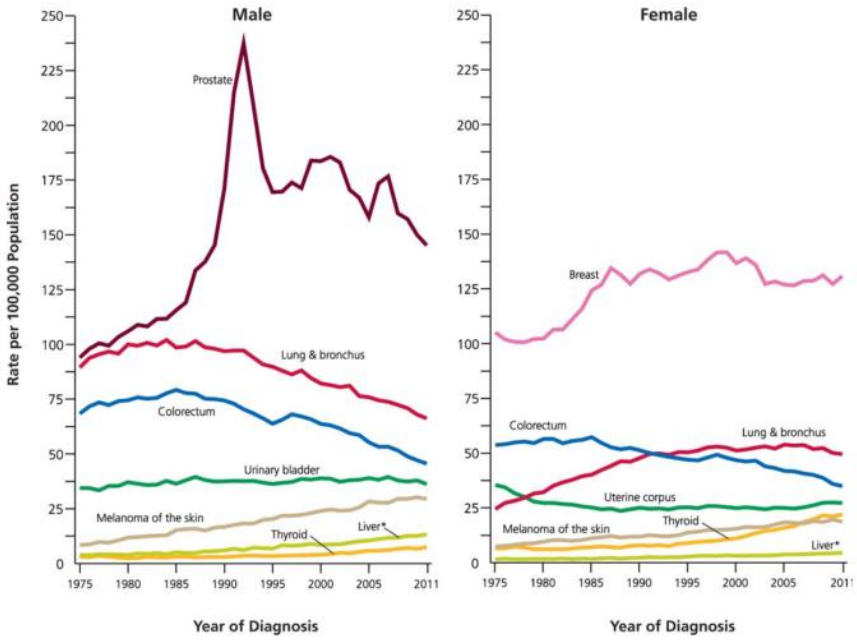


Figure 1.3: Cancer Incidence trends in US in males and females; Torre et al., 2015.

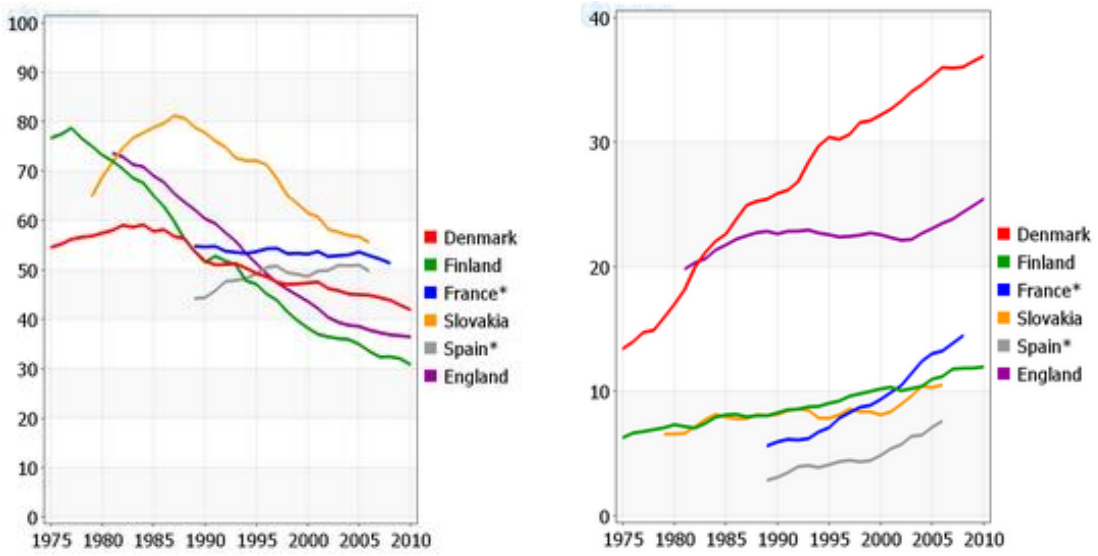


Figure 1.4: Cancer Incidence trends in males (A) and females (B) in some European Countries; SEOM, 2014.

1.2.2 Prevalence of lung cancer

Prevalence refers to the number of people diagnosed with lung cancer who are alive regardless of the time from diagnosis. Prevalence is determined by two factors: incidence and survival. In 2008, the estimated five-year prevalence of lung cancer in Spain was 4.8%, which means that 28,148 people were alive after a lung cancer diagnosis (Bray et al., 2013). The five-year most prevalent cancers in our country are breast (17.9%) and prostate (31.4%) in females and males, respectively.

1.2.3 Mortality and five-year survival rates

Lung cancer is the leading cause of cancer-related death worldwide (Torre et al., 2015). According to the latest report of the National Bureau of Statistics, in Spain, 21,664 people died of lung cancer in 2013 accounting for 20.6% of all cancer deaths (Sociedad Española de Oncologia Medica, 2014). By gender, lung cancer was the leading cause of cancer-related deaths in males and

the second in women. This represents a small reduction of -0.7% for men but a significant increase of 7.3% for females (Instituto Nacional de Estadistica, 2015).

Globally, mortality from lung cancer has been declining over the past two decades in males but has increased in women (Cayuela et al., 2008) (Figure 1.5). This variation is caused by historical differences in tobacco consumption between males and females, with women achieving peak tobacco consumption about a decade later than men. In Spain, even though tobacco consumption has been steadily reducing in recent years, it is expected that we must wait around 10 to 15 years to actually see a reduction in lung cancer incidence and mortality (Hernández et al., 2006).

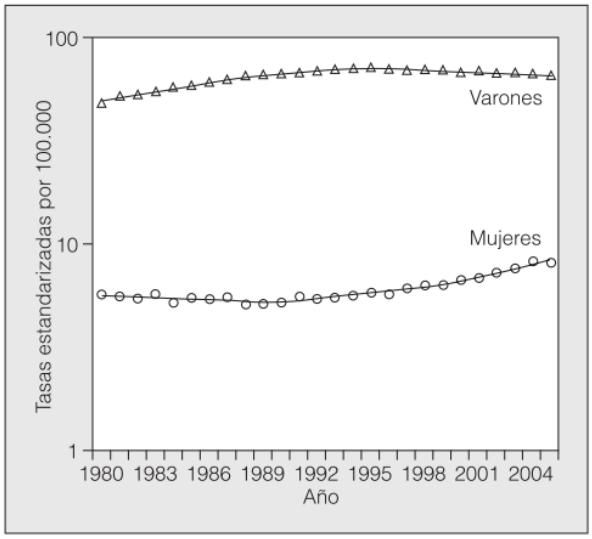


Figure 1.5: Mortality trends in Spain for males and females (1985–2005); Hernández et al., 2006.

The elevated mortality registered for lung cancer is mostly due to the tardiness in the detection of the disease. At the time of diagnosis, approximately 70% of patients will present with advanced disease (Hernández et al., 2006), which accounts for the lowest survival rate. The overall five-year survival rates for lung cancer are 18% in the US (Siegel et al., 2015), around 13% across European countries and 10.7% in our environment (De Angelis et al., 2014). Likewise for many cancer types, the five-year survival rates for lung cancer are stage-dependent: 78.6% for stages IA and IB, 54% for stages I and II combined, 39.8% for stage IIIB and only 4% for advanced, distance

disease (Hernández et al., 2006, Jones et al., 2009a, Alberg et al., 2013). In light of these figures, patients at high risk of developing lung cancer (heavy smokers, patients with COPD) should be monitored closely to enable an early diagnosis and optimize treatment.

1.3 Aetiology of lung cancer

1.3.1 Tobacco exposure

The most dramatic aspect of lung cancer is that 90% of related deaths are entirely preventable (Proctor, 2012). Tobacco smoking is, by far, the leading cause of lung cancer in developed countries. The World Health Organization (WHO) estimates that 70% of the lung cancer diagnoses worldwide are caused by cigarette smoking. In developed countries, smoking is responsible for up to 90% of lung cancer cases (Alberg et al., 2013, León-Atance et al., 2011). The relationship between smoking and lung cancer was first suggested by Isaac Adler in the first decade of the twentieth century and it became more obvious in the mid-1900s, when two large observational studies conducted in the US found that 96.5% of lung cancer diagnoses occurred in those who had been moderate to heavy smokers for many years (Wynder and Graham, 1950). In fact, compared with those who have never smoked, current smokers have a tenfold increased risk of developing lung cancer (Sánchez De Cos Escuín, 2009, Alberg et al., 2013). Although the risk decreases gradually after quitting, even for those who gave up smoking 40 years ago, the risk of lung cancer remains higher than for lifetime non-smokers (Alberg et al., 2013).

The risk of lung cancer in smokers is strongly correlated with the number of cigarettes smoked per day as well as the number of years smoking (De la Cruz et al., 2011). Heavy smokers have a 20- to 30-fold increased risk of developing lung cancer than lifetime non-smokers. Other factors such as age of onset and depth of inhalation also influence the risk of developing the disease (De la Cruz et al., 2011). In addition, changes in cigarette composition, including less nicotine and

the use of filters, have affected smoking patterns and now smokers tend to smoke more vividly with deeper inhalations to satisfy their nicotine needs (De la Cruz et al., 2011). Despite the strong link between smoking and lung cancer, only one out of nine smokers will develop the disease in the course of their lifetimes (De la Cruz et al., 2011), suggesting that there are also other powerful factors involved.

Pipe and cigar smoking have also been associated with an increased risk of lung cancer but the relationship seems weaker than with cigarette smoking, possibly due to the differences in smoking frequency and/or depth of inhalation (De la Cruz et al., 2011, Alberg et al., 2013). Although an association between smoking marijuana or other opioids and lung cancer is likely to exist, there is currently no evidence to back up this assumption (Alberg et al., 2013).

Smoking is also the main risk factor for lung cancer in our country (Hernández et al., 2006). The prevalence of smoking among individuals recently diagnosed with lung cancer has been reported to be as high as 95% in several national series (León-Atance et al., 2011, Montero et al., 2003, Gullón et al., 2012). All lung cancer types are associated with smoking; however, there are some differences across the histological types. For example, it has been demonstrated that small-cell lung cancer (SCLC) has the strongest association with tobacco consumption while some histological types of NSCLC are more common among non-smokers. Furthermore, lung cancer among non-smokers is almost considered a different entity since it exhibits a completely different behaviour affecting primarily women and is strongly associated with geographic location (De la Cruz et al., 2011).

1.3.2 Second-hand smoke exposure

Tobacco can also cause lung cancer indirectly in lifetime non-smokers. Second-hand smoke exposure is responsible for 1.6% of all cases of lung cancer and 21,400 deaths annually (Molina et

al., 2008, Alberg et al., 2013). Living together with a smoker is highly associated with lung cancer in non-smokers as it is has been shown to increase the risk of developing lung cancer in 30% (Alberg et al., 2013). More importantly, researchers believe that second-hand smoke exposure during childhood and early adolescence is responsible for approximately 17% of the lung cancer cases in non-smokers (De la Cruz et al., 2011). The studies also suggest that the longer the exposure, the higher the risk.

1.3.3 Environmental and occupational carcinogens

Environmental and/or occupational exposure to certain carcinogens is the other major cause of lung cancer and is estimated to be responsible for 10% of all diagnoses in developed countries (Alberg et al., 2013). Many work settings involve being exposed to several well-known carcinogens (Table 1.2). Asbestos is derived from silicate minerals and is the most common occupational agent associated with lung cancer (De la Cruz et al., 2011). It is not clear, however, whether it is the exposure itself or the consequent asbestosis after being repeatedly exposed to asbestos that actually causes lung cancer (De la Cruz et al., 2011). Radon contamination is another common occupational carcinogen and is estimated to be responsible for at least 15% of all lung cancer diagnoses in the US and 11% of deaths (Alberg et al., 2013, De la Cruz et al., 2011). In lifetime non-smokers, the effects of radon contamination are especially noticeable (accounting for 70% and 30% of incidence and deaths, respectively).

Table 1.2: Common carcinogens found in the workplace; Alberg et al., 2013.

Agents, mixture, circumstance	Main industry, use
Arsenic and arsenic compounds	Glass, metals, pesticides
Asbestos	Insulation, filters, textiles
Beryllium and beryllium compounds	Aerospace
Bis(chloromethyl)ether and	
Chloromethyl methyl ether	Chemical intermediate
Cadmium and cadmium compounds	Dye/pigment
Chromium[VI] compounds	Metal plating, dye/pigment
Dioxin (TCDD)	Chemical industry
Nickel compounds	Metallurgy, alloy, catalyst
Plutonium-239	Nuclear
Radon-222 and its decay products	Mining
Silica, crystalline	Stone cutting, mining, glass, paper
Talc containing asbestiform fibers	Paper, paints
X- and gamma-radiation	Medical, nuclear
Coal-tar pitches	Construction, electrodes
Coal-tars	Fuel
Soots	Pigments
Exposure circumstances	
Aluminum production	
Coal gasification	
Coke production	
Haematite mining (underground)	
with exposure to radon	
Iron and steel founding	
Painter (occupational exposure)	

Outdoor and indoor pollution derived from the combustion of fossil and natural fuels has also been linked to an increase in lung cancer risk, especially in heavily industrialized countries such as the US, Japan and China. In Europe, the proportion of lung cancer diagnoses attributable to outdoor pollution is estimated to be around 11% (Molina et al., 2008). In less developed areas such as southern Asia, outdoor and especially indoor pollution are the most common causes of lung cancer in women, causing approximately 80% of all diagnoses (De la Cruz et al., 2011). The precarious working conditions reported in those countries, including overcrowding and the absence of ventilation systems, could mainly explain the high percentage of lung cancer found in this population. Nonetheless, a large fraction of cases of lung cancer in non-smokers don't respond to any of the aforementioned causes, which means that in this population, there might be intrinsic,

lifestyle and environmental factors determining the likelihood of developing lung cancer, which will be covered in the next subsections.

1.3.4 Genetic factors

Genetic factors are deemed to play an important role in the risk of developing lung cancer. In a meta-analysis of 41 cohort and case-control studies, the authors concluded that having a family history of lung cancer (two or more relatives) was associated with a 1.7-fold increase in lung cancer risk (95% CI: 1.6–1.9) (Lissowska et al.). Given the potential association between genetics and lung cancer, several studies have focused on candidate susceptibility to developing lung cancer targeting the genes involved in the absorption, metabolism and accumulation of tobacco and other known carcinogens (De la Cruz et al., 2011). Mutations in the epidermal growth factor receptor (EGFR) have been associated with an increased risk of several cancer types, including lung cancer. Gene polymorphism factor has been reported as being an important factor that increases the susceptibility of lung cancer (Feng et al., 2014). In 40% to 80% of NSCLC patients, EGFR is overexpressed, which is associated with a poor prognosis. This finding has led researchers to investigate new targeted therapies, with several EGFR inhibitors being currently tested (Molina et al., 2008).

1.3.5 Age, gender and other non-modifiable factors

Aging is the single biggest risk factor for cancer. For many years, cancer was a disease associated with the elderly and nowadays, with our lifespan being constantly extended, the number of patients over 80 years old who are diagnosed with lung cancer has noticeably increased. In fact, currently, more than 50% of individuals diagnosed with lung cancer are over 70 years old (De la Cruz et al., 2011). Aging is a natural process that occurs as a result of cell senescence. The precise pathways involved in the relationship between aging and carcinogenesis are not entirely known and are beyond the scope of this thesis. In brief, aging is associated with multiple events occurring

at a molecular, cellular and physiologic level that influence carcinogenesis and ease cancer growth. Three major hypotheses have been proposed to explain the association between age and cancer. The first holds that the link between the two processes is a mere consequence of the duration of the exposure to carcinogens. The second maintains that the natural changes occurring at a cellular and physiologic level during aging provide a more favourable environment for already existent but otherwise latent malignant cells to grow. Finally, the last theory is fundamentally a combination of both the previous hypotheses (Anisimov, 2007).

Lung cancer has been traditionally associated with male gender. However, lung cancer among women has exponentially increased over the past two decades and has now surpassed breast cancer as the leading cause of cancer death in more developed countries (Torre et al., 2015). The increase in lung cancer incidence and mortality among women has been attributed to the historical differences in smoking patterns between the sexes (women started smoking later than men and peak consumption was reached one decade later) but also to the premise that women are more susceptible to the adverse effects of smoking than men. A study using National Health Foundation data in the US found that the relative risk of lung cancer was consistently higher in women than in men even after adjusting for cigarette consumption (Zang and Wynder, 1996). This presumption has also been used to explain the increase in COPD incidence among women in recent years. However, there is still much controversy around the topic and no definitive conclusions can be drawn.

Significant variations in the incidence and mortality of lung cancer have been reported among different races and ethnicities. Black race has been associated with high incidence of lung cancer and poor prognosis in several epidemiological studies even though white Americans smoke in larger quantities than black Americans (De la Cruz et al., 2011). The five-year survival rates have also been reported to be substantially lower for black Americans than their white counterparts

(Siegel et al., 2015). Conversely, the risk of lung cancer seems to be lower among other non-Caucasian races such as Hispanic and Asian at equal smoking dosage.

1.3.6 Lifestyle and other modifiable factors

The presence of an underlying respiratory disease can increase the risk of developing lung cancer. Chronic obstructive pulmonary disease (COPD) is strongly associated with lung cancer, especially in men, though it is not clear whether the co-occurrence is in fact a cause-effect relationship, since both of them are closely linked to tobacco consumption. In a study comparing smokers with and without COPD, authors found that individuals with COPD had a six-fold increased risk of developing lung cancer than those without COPD, which indicates that there might be some pathophysiological factors in COPD beyond smoking implicated in the risk of developing lung cancer (Young et al., 2009). This finding is consistent with other investigations that have shown that there is a strong association between chronic airflow obstruction and lung cancer after controlling for smoking habits, with a 2.8-fold increase in the lung cancer risk in those individuals with moderate or severe pulmonary obstruction (95% CI: 1.8–4.4) (Mannino et al., 2003). In this line of research, asthma has been identified as an independent risk factor associated with lung cancer particularly for non-adenocarcinomas (Santillan et al., 2003). Other common respiratory diseases that have been associated with lung cancer are tuberculosis and idiopathic pulmonary fibrosis (Alberg et al., 2013).

Diet and physical activity have also been extensively studied regarding their protective effect in several cancer types. So far, the intake of fruits and vegetables is the only dietary factor associated with a low risk of lung cancer (De la Cruz et al., 2011, Alberg et al., 2013). It is believed that the antioxidants contained in them could play an important role in preventing several cancers. In particular, vitamin A and beta-carotenes were associated with a decrease in lung cancer risk (De la Cruz et al., 2011). Cruciferous vegetables such as broccoli and cauliflower have also been found

to be independently associated with a decrease in lung cancer risk (Alberg et al., 2013). In particular, this reduction seems to be stronger for certain histological types (non-squamous cell carcinoma) (Deng et al., 2013). On the other hand, it has been suggested that a diet rich in saturated fats derived from animal sources increases lung cancer risk but the evidence is limited to a few observational studies. Even so, it has been suggested that for individuals with a high risk of developing lung cancer, a diet low in red meat and processed meat might be preferable (Deng et al., 2013). Alcohol intake in large amounts has also been associated with an increase in lung cancer risk (De la Cruz et al., 2011).

Last but not least, physical activity has been strongly associated with a reduction in the risk of several cancer types, especially breast and colon, and an improvement in cancer-related and overall mortality in cancer survivors. Moderate to high physical activity can significantly reduce cancer risk by approximately 16% to 30% (Tardon et al., 2005, Shi et al., 2015, Emaus and Thune, 2011). After a cancer diagnosis, maintaining appropriate levels of physical activity results in a significant reduction in mortality and disease recurrence (Li et al., 2015, Zhong et al., 2014, Je et al., 2013, Meyerhardt et al., 2006). In the lung cancer setting, moderate to high levels of physical activity have been shown to reduce the risk of lung cancer by 13% and 23%, respectively (OR = 0.87; 95% CI: 0.83–0.90 and OR = 0.77; 95% CI: 0.73–0.81, respectively) (Sun et al., 2012). Some studies have reported different results for males and females. Emus et al., in a systematic review conducted in 2011, reported that while four out of six studies had found a statistically significant reduction in lung cancer risk among physically active men, only one of the four studies reported the same association among women (Emaus and Thune, 2011). However, these differences could be just due to the histological type of lung cancer, the percentage of smokers versus non-smokers in both males and females and other confounding factors.

1.4 Classification of lung cancer

Tumours of the lung include a wide range of different histopathological features. The WHO and the International Association for the Study of Lung Cancer (IASLC) distinguish four main histological types, which are divided into small- and non-small-cell lung cancer. The former accounts for around 15% of all lung cancer diagnoses and has been traditionally classified as limited disease or extensive disease. Non-small-cell lung cancer encompasses several histological types, with the most common being adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma (Figure 1.6). Squamous-cell carcinoma (SCC) was traditionally the most frequent histologic type but recently there has been a shift and adenocarcinoma has now replaced SCC as the most diagnosed type of lung cancer, especially among women, accounting for approximately 40% of all NSCLCs (Houston et al., 2014, Leiro-Fernández et al., 2014) (Figure 1.7). Carcinoid tumours are neuroendocrine growths that can also be found in the lungs, although they represent a minority of lung cancer diagnoses (2%) (Iglesias et al., 2004). This slow-growing tumour is more likely to affect young people and is frequently found in non-smokers. The prognosis is very good and most patients manage to survive 15 years and more (Iglesias et al., 2004).

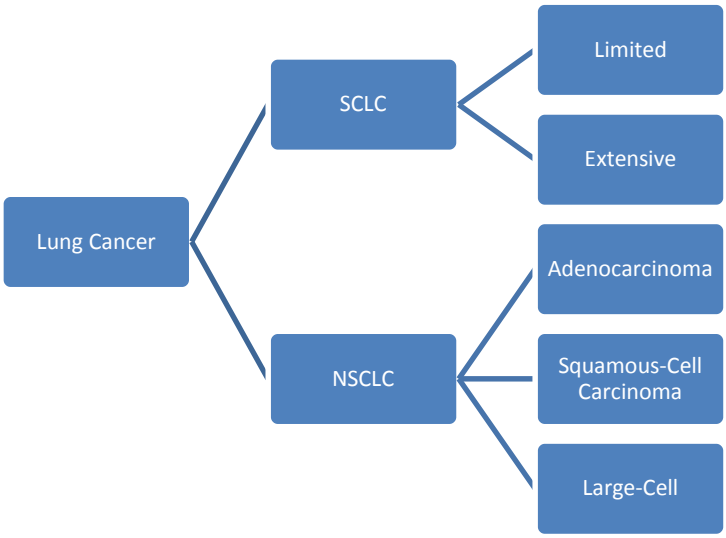


Figure 1.6: Classification of lung cancer.

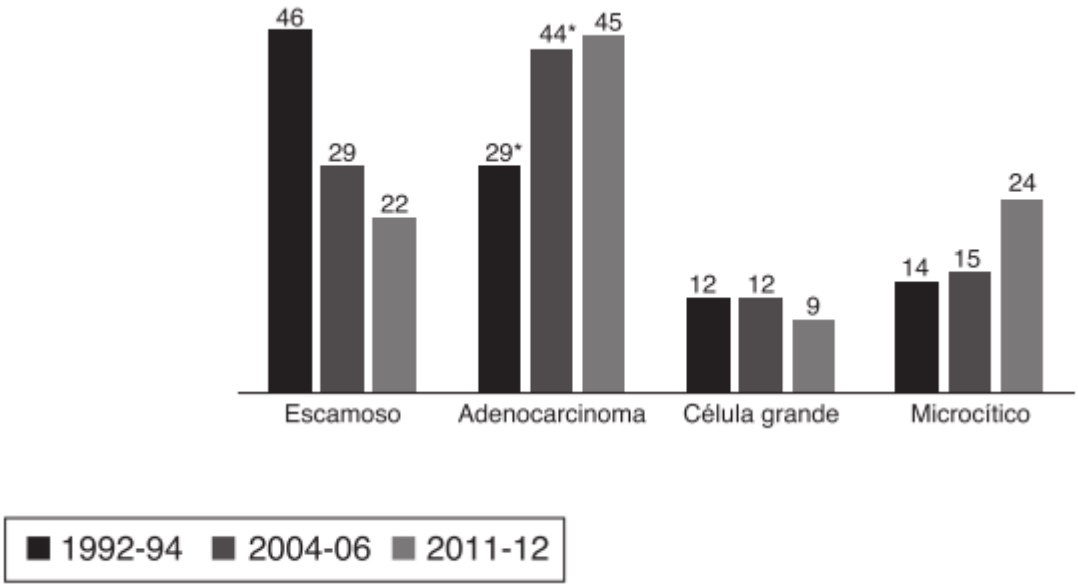


Figure 1.7: Changes in histological features over two decades in Spain; Leiro-Martinez, 2014.

NSCLC is further classified according to the TNM Staging System developed by the IASLC, which takes into consideration three parameters: tumour size (T), number of lymph nodes affected (N) and the presence of distant metastases (M). A summary of the description of each component is shown in Table 1.3.

Table 1.3: 7th edition of the TNM staging system

Descriptors	Definitions
T	Primary tumour
Tx	The primary tumour cannot be measured
Tis	Tumour *in situ*
T0	No primary tumour
T1	Tumour ≤ 3 cm, surrounded by lung or visceral pleura, not more proximal than the lobar bronchus
T1a	Tumour ≤ 2 cm
T1b	Tumour ≥ 2 cm but ≤ 3 cm
T2	Tumour > 3 cm but ≤ 7 cm or tumour with any of the following: invades visceral pleural, involves main bronchus ≥ 2 cm distal to the carina, atelectasis/obstructive pneumonia extending to hilum but not involving the entire lung
T2a	Tumour > 3 cm but ≤ 5 cm
T2b	Tumour > 5 cm but ≤ 7 cm
T3	Tumour > 7 cm or invading chest wall, diaphragm, phrenic nerve, mediastinal pleural or parietal pericardium; or tumour in the main bronchus < 2 cm distal to the carina; or atelectasis/obstructive pneumonitis of the entire lung or separate tumour nodules in the same lobe
T4	Tumour of any size with invasion of heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body or carina, or separate tumour nodules in a different ipsilateral lobe
N	Regional lymph nodes
Nx	Lymph nodes cannot be assessed
N0	No evidence of regional node metastasis
N1	Metastasis in ipsilateral peribronchial and/or perihilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastases in ipsilateral mediastinal and/or subcarinal lymph nodes
N3	Metastases in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph nodes
M	Distant metastases
Mx	Distant metastases cannot be assessed
M0	No evidence of distant metastases
M1a	Separate tumour nodules in contralateral lobe or tumour with pleural nodules or malignant pleural dissemination
M1b	Distant metastases

The current TNM classification was updated in 2009 with the introduction of some changes in the T and N components. Compared to the previous version, the new TNM included a subdivision of the T1 and T2 classification resulting in 5 different categories, and a reclassification of some special conditions (Table 1.4).

Table 1.4: Updates in the 7th TNM Staging System

Component	Changes
T	T1: T1a: ≤ 2 cm T1b: > 2 cm ≤ 3 cm T2: T2a: > 3 cm ≤ 5 cm T2b: > 5 cm ≤ 7 cm T2 > 7 cm changes to T3 T4 for additional nodule(s) in the same lobe changes to T3 T4 for malignant pleural effusion changes to M1a M1 for additional nodule(s) in the ipsilateral side changes to T4
N	No change
M	M1: M1a: additional nodule(s) in the contralateral side or malignant pleural effusion M1b: distant metastases

Once the tumour size, lymph nodes affected and the presence of metastases have been assessed, the TNM system provides a distribution of the tumours for stages of the disease. This classification was made according to the prognosis and five-year survival rates for each category and is summarized in Table 1.5 and Figures 1.8 and 1.9 (Detterbeck et al., 2013a).

Table 1.5: TNM Staging System; ACCP, 2013

T/M	N0	N1	N2	N3
T1a T1b	IA IA	IIA IIA	IIIA IIIA	IIIB IIIB
T2a T2b	IB IIA	IIA IIB	IIIA IIIA	IIIB IIIB
T3	IIB	IIIA	IIIA	IIIB
T4	IIIA	IIIA	IIIB	IIIB
M1	IV	IV	IV	IV

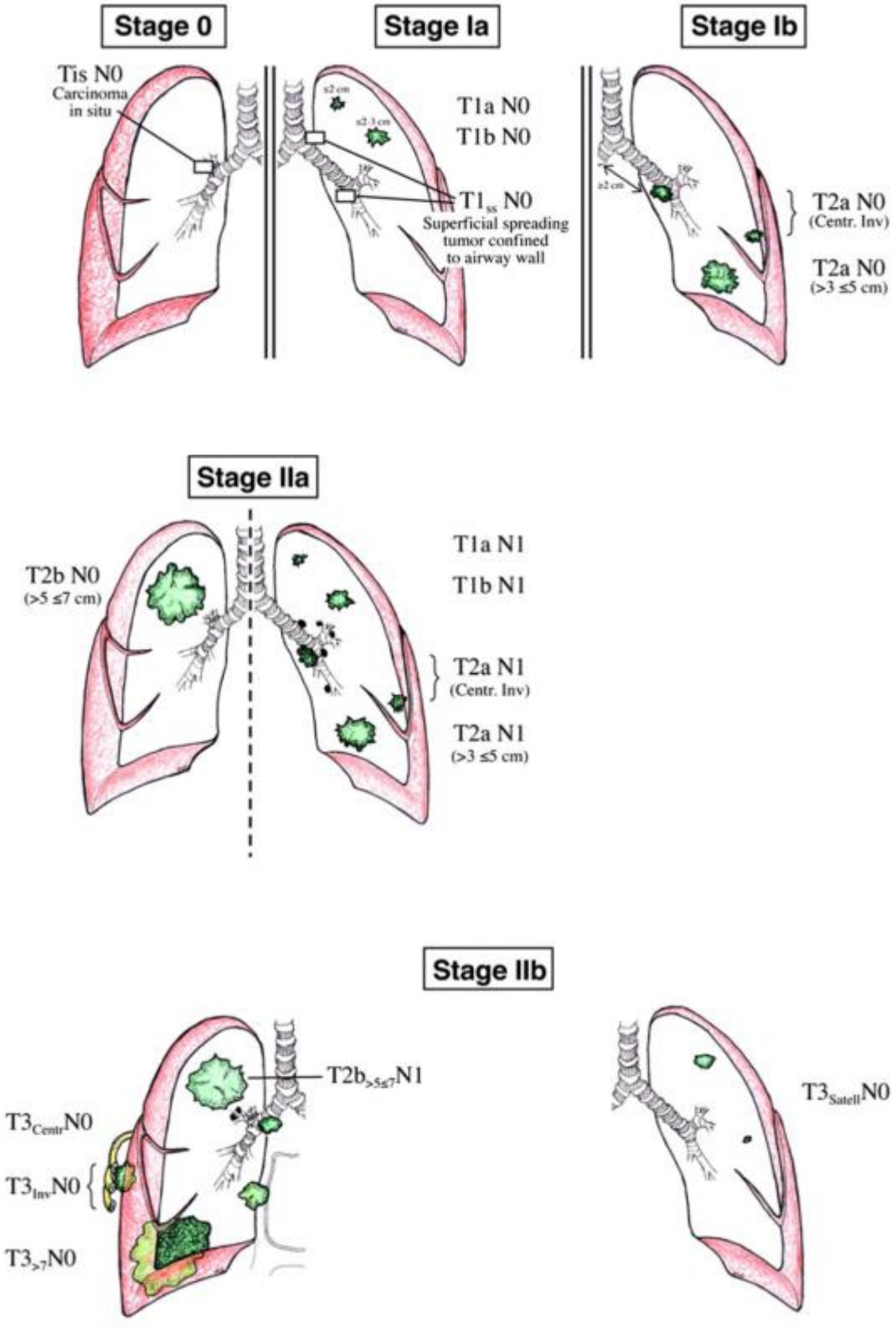


Figure 1.8: Illustration of localized disease (stage I and II) according to the 7th edition of the TNM classification; Detterbeck, 2013.

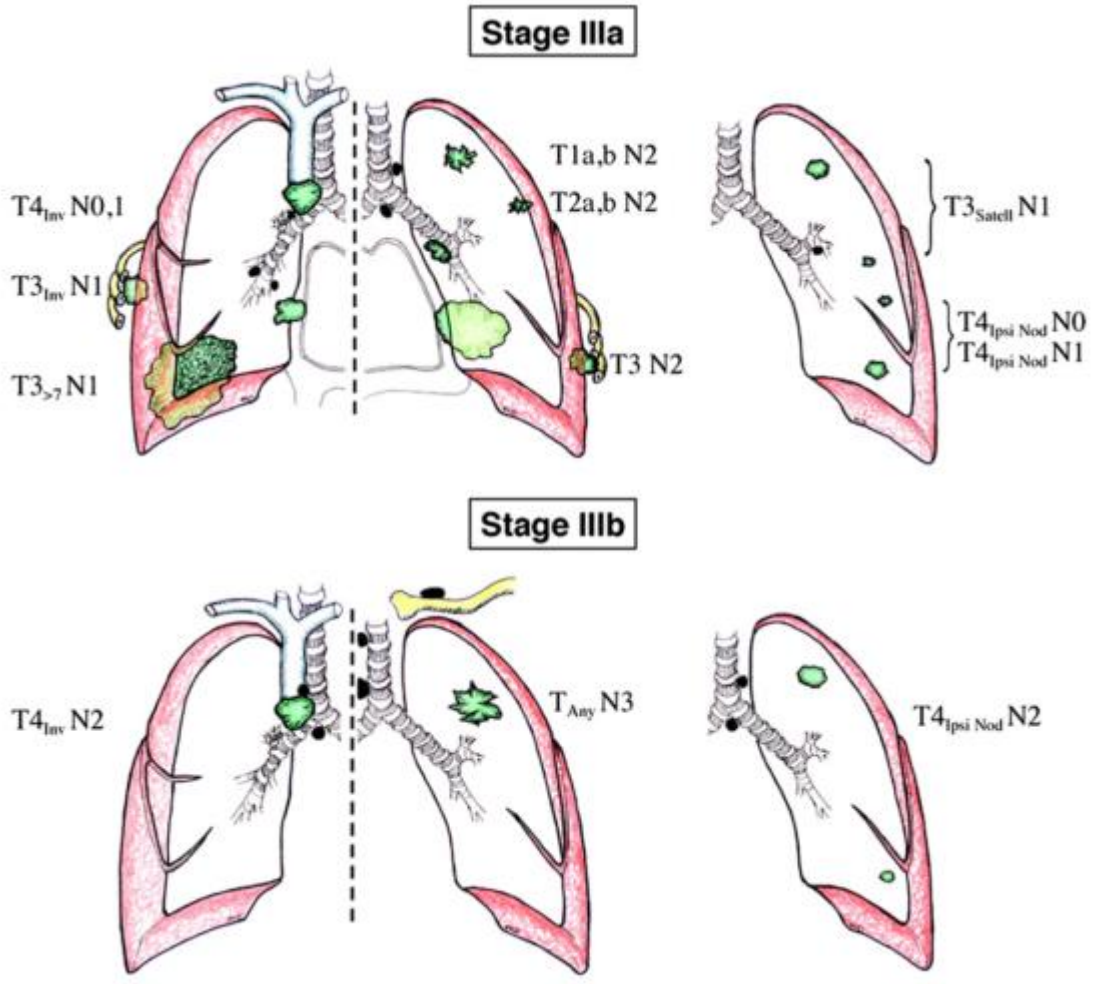


Figure 1.9: Illustration of locally advanced disease (stage III) according to the 7th edition of the TNM classification; Detterbeck, 2013.

Before the latest update, the TNM classification was only recommended for NSCLC, but according to the retrospective analysis performed using the new version, it can also be used to classify other intrathoracic malignancies such as small-cell lung cancer (SCLC) and carcinoid tumours (Rami Porta, 2009, Howington et al., 2013).

1.5 Screening and diagnosis for lung cancer

1.5.1 Screening for lung cancer

One of the main challenges in lung cancer is the difficulty in obtaining an early diagnosis. Individuals with lung cancer rarely experience any symptoms in the early stages of the disease,

which minimizes the chances of detecting the illness on time. As a matter of fact, the vast majority of the cases diagnosed with stages I and II are made incidentally during a workup for other purposes.

The primary purpose of a screening test is to reduce the chance of dying from one particular disease without causing any harm in the process (Detterbeck et al., 2013b). In the lung cancer context, this raises two main concerns: first, there is currently no definitive cure for lung cancer, and second, a systematic screening for lung cancer would involve some form of radiation, which is potentially harmful for the individual.

Several screening tests have been studied over the last few years in an attempt to improve the number of cases diagnosed with early stage. A chest X-ray (CXR) is usually the first step in the workup of lung cancer, although they provide little proof of the disease. Increasing the frequency of CXRs has been proposed as a plausible and economic strategy for enhancing an early diagnosis in individuals at high risk of lung cancer; however, this approach has shown no effectiveness in reducing the mortality and therefore is currently not recommended by the main guidelines (Detterbeck et al., 2013b). Sputum analysis is an inexpensive and harmless procedure that can be added to a conventional CXR during screening for lung cancer. Some studies have suggested that performing a sputum analysis every four months might help detect some forms of NSCLC, especially in heavy smokers (Detterbeck et al., 2013b). However, these results were not statistically significant and thus it was concluded that a sputum analysis did not provide any additional benefit to an annual CXR. Screening with low-dose computed tomography (LCTD) has shown the best results so far. A large meta-analysis conducted by the National Lung Screening Trial found a dramatic 20% reduction in lung cancer mortality with LCTD compared to those screened with a CXR (RR: 0.80; 95% CI, 0.73–0.93) (Aberle et al., 2011). The risk of radiation-induced cancer was estimated to be only one cancer death for every 2,500 screened participants, thus LCTD is

currently the only recommended screening test for patients at high risk of lung cancer (Detterbeck et al., 2013a, Detterbeck et al., 2013b).

1.5.2 Diagnosis of lung cancer

As reported previously, patients with lung cancer may not exhibit any symptom at the time of diagnosis. In those cases, the suspicion of lung cancer arises from an abnormal CXR or CT scan despite clinical evidence of the disease. A pulmonary nodule is defined as a single, well-circumscribed, radiographic opacity surrounded by aerated lung (Gould et al., 2013b) and constitutes the typical form of presentation of lung cancer. However, it is also frequently the result of an old inflammatory or infectious disease (such as tuberculosis or pneumonia); in this case, a review of an old CXR is recommended before proceeding with further analysis (Gould et al., 2013b). In the case that a nodule has shown no growth in the past two years, no more additional evaluation is recommended. The size of the nodule as well as the morphology are two basic features to look at before moving to the next step. Usually, nodules measuring less than 8 mm or showing smooth borders are more likely to be benign in nature than those bigger than 8 mm or with spiculated borders. In Figure 1.10 an algorithm of the recommended management of an individual with pulmonary nodule(s) is shown.

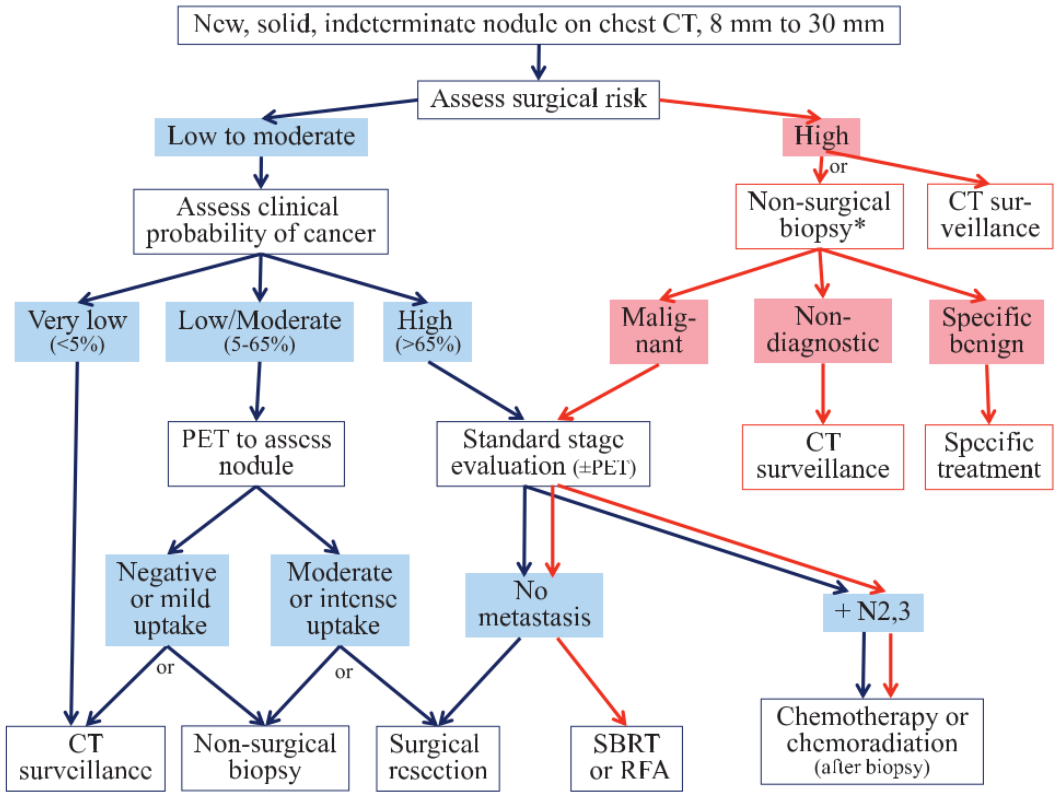


Figure 1.10: Algorithm in the management of individuals with pulmonary nodules; Gould, 2013.

Approximately 80–85 % of lung cancer cases corresponds to NSCLC (Rivera et al., 2013, de Cos Escuín et al., 2006, León-Atance et al., 2011, Jones et al., 2009a). In patients suspected of having NSCLC, the preferred diagnostic technique is usually based on the presumed stage of the disease (Rivera et al., 2013). Sputum cytology, bronchoscopy (including flexible bronchoscopy), endobronchial ultrasound (EBUS) and transthoracic needle aspiration are the most common methods besides surgical biopsy for diagnosing lung cancer. Sputum cytology is the least invasive and is more recommended for central tumours (SCLC and squamous-cell carcinoma), especially in high-risk patients (heavy smokers, low pulmonary function, etc.). Bronchoscopy and flexible bronchoscopy are also recommended for central tumours and constitute an excellent alternative to mediastinoscopy for the assessment of lymph nodes. Plus, the addition of an endobronchial needle aspiration to obtain cytology or histology samples substantially improves the sensitivity of the test (Rivera et al., 2013). In contrast, for peripheral tumours, bronchoscopy has proved to be less

effective and sensitivity is considerably lower (Rivera et al., 2013). Furthermore, bronchoscopy is also greatly affected by the size of the lesion (the larger the better). In those tumours, radial EBUS has shown more sensitivity and specificity than bronchoscopy (73% and 100%, respectively) (Rivera et al., 2013). Finally, transthoracic needle aspiration has also shown good sensitivity in the diagnosis of peripheral nodules (90%). Importantly, even if these tests come up negative, in the context of a clinical suspicion of lung cancer further investigations are warranted. The next step would involve a surgical biopsy of the tissue (usually by means of thoracoscopy) to provide final pathologic diagnosis or lung resection with exploratory/therapeutic intent (Rivera et al., 2013).

1.6 Treatment for stages I and II of NSCLC(Swanson et al., 2007)

1.6.1 Surgery

Surgery is the treatment of choice for early stages of lung cancer (I and II) since it presents the best chance of cure (Benzo et al., 2007, Jones et al., 2009a, Ilonen et al., 2011). Selected patients with locally advanced disease (stage IIIA) can also be potentially treated with surgery and adjuvant chemotherapy to achieve complete remission (Crandall et al., 2014, Wilson, 1997). Unfortunately, stages I and II of NSCLC only account for 20% to 40% of lung cancer diagnoses (Howington et al., 2013, Leiro-Fernández et al., 2014, Gullón et al., 2012, de Cos Escuín et al., 2006). In those few cases, the presence of co-morbid diseases, advanced age, low cardiorespiratory fitness and poor pulmonary function can prevent patients from undergoing surgery safely (Beckles et al., 2003, Sekine et al., 2002, Luchtenborg et al., 2012). As a result, surgical rates for lung cancer are strikingly low, ranging from 11% in the UK to 27% in the US (Jones et al., 2009a, Lim et al., 2010). In Spain, the EPIClip Study of 2003 found a surgical rate of 14.8%, similar to the rates reported in most European countries (de Cos Escuín et al., 2006, Sánchez De Cos Escuín, 2009).

Lobectomy plus systematic lymphadenectomy has been the gold standard for lung cancer surgery since 1995, when a randomized controlled study conducted by the Lung Cancer Study Group found less cancer recurrence after lobectomy than after smaller resections (Ginsberg and Rubinstein, 1995). However, for those patients considered unfit to tolerate a lobectomy, the international guidelines recommend that a sublobar resection (wedge resection or segmentectomy) is preferred over no surgical treatment (Howington et al., 2013), since similar overall and cancer-specific survival rates have been achieved after adjusting for age, stage and other influencing factors (Howington et al., 2013). At the other end, in the presence of large tumours (> 7 centimetres) or extensive lymph node invasion (N2), a pneumonectomy (removal of the whole lung) may be necessary. The decision to proceed with one or another should not only be justified in terms of oncological safety but also take into consideration the short- and long-term impairments associated with the procedure and the patient's baseline functional status (this topic will be discussed in more detail in chapter three).

The traditional approach to lung resection surgery consists of a posterolateral thoracotomy, which involves opening the ribcage and separating the adjacent muscles to access the lungs (Figure 1.11). However, over the past two decades, minimally invasive techniques have been steadily replacing the traditional approach and are now routinely performed around the world for the treatment of several respiratory diseases. Video-assisted thoracic surgery (VATS) has been inconstantly defined in the studies affecting the generalization of the results obtained. Today, VATS standard definition includes the use of *video screen for guidance, two to three ports, and the absence of a retractor or rib spreading* (Swanson et al., 2007). The technique, initially described for exploratory procedures, was used for the first time to perform a lobectomy in 1992 in Italy (Landreneau et al., 1992, Roviaro et al., 1992). Since then, the surgical approach has been gaining acceptance thanks to the results published by some of the largest series (McKenna Jr et al.,

2006, Gonzalez-Rivas et al., 2011, Loscertales et al., 2009) and is now the treatment of choice for early stages of lung cancer (Howington et al., 2013). Despite the initial misgiving among the cardiothoracic community, the technique has demonstrated identical oncological results when compared with open thoracotomy (Flores et al., 2011, Flores et al., 2009, Scott et al., 2010, Higuchi et al., 2014) and even less economic costs (Swanson et al., 2012).

Although there is no standardized technique for the VATS approach, most surgeons make an anterior incision measuring three to five centimetres and then add one or two more ports so they can have better access to the lung (Figure 1.11). In 2010, surgeons at the Thoracic Surgery Department at the hospital of A Coruña went a little further and performed the first lobectomy using a single-port VATS with overall good short-term results (Gonzalez-Rivas et al., 2013).

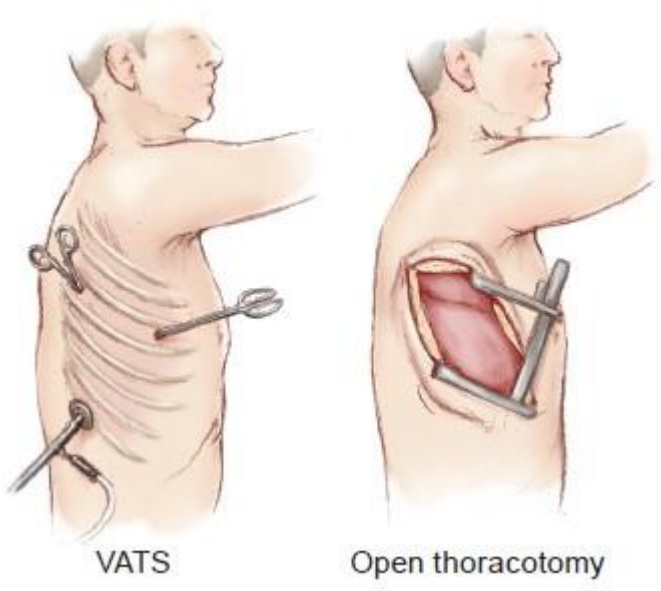


Figure 1.11: VATS incision vs. posterolateral thoracotomy; Harris, 2012.

The main advantage of the videothoracoscopic approach over a conventional thoracotomy is that the incision to the patient's chest is relatively minor, which leads to reductions in post-operative infection and wound dehiscence. This hastens post-operative recovery and allows the

patient to return to full activity in a shorter time (Fan et al., 2013). For this reason, VATS could be an alternative to open thoracotomy for patients at high risk of developing post-operative complications and/or those denied surgery based on their cardiorespiratory fitness, poor pulmonary function or general frailty (Table 1.6). The specific benefits of the VATS approach will be discussed in detail in chapter three.

Table 1.6: Special situations for which VATS may be preferable; Demmy, 2008

Special Population	Examples
Pulmonary compromise	Poor FEV_1/DLCO, heavy smoking, sleep apnea, recent pneumonia
Cardiac dysfunction	Congestive heart failure, severe coronary artery disease, recent myocardial infarction, valvular disease
Extrathoracic malignancy	Solitary brain metastasis from lung cancer, deep pulmonary metastases requiring lobectomy
Poor physical performance	Performance status 2 to 3, morbid obesity
Rheumatologic/orthopedic	Spinal disease, severe rheumatoid arthritis, severe kyphosis, lupus, osteomyelitis
Advanced age	Older than 70
Vascular problems	Aneurysm, severe peripheral vascular disease
Recent or impending major operations	Urgent abdominal operations, joint replacement requiring crutches, contralateral thoracotomy needed
Psychologic/neurologic	Substance abuse, poor command following, pain syndromes
Immunosuppression/ impaired wound healing	Recent transplant, diabetes

DLCO = lung diffusing capacity of carbon monoxide; FEV_1 = forced vital capacity in first second.

Despite the large body of evidence supporting the superiority of VATS over the traditional approach, the number of videothoracoscopic lobectomies performed worldwide is still very low, accounting for only 16 to 20 % in the US and most European countries (Boffa et al., 2008, Begum

et al., 2014). Denmark has the highest VATS resection rates across Europe with 55% of lobectomies being performed using this approach (Begum et al., 2014). Spain also has extensive experience with more than 2000 cases performed. Out of the 46 hospital units surveyed in our country, three did not perform VATS and 22 responded positively (Begum et al., 2014), including our centre, where the vast majority of lung cancer patients (≥80%) are operated on using this approach.

1.6.2 Radiation therapy

Although surgical resection is the treatment of choice for localized disease, there are other plausible non-surgical options for those not able or willing to undergo surgery. International guidelines recommend that for high-risk patients with stage I NSCLC, conventional radiotherapy is an appropriate treatment option with curative potential, but five-year regional and overall survival remains suboptimal (Donington et al., 2012). Stereotactic body radiotherapy (SBRT) has been proposed as an effective alternative to conventional radiotherapy for treating stages I and II in patients who are unfit to tolerate sublobar resection or refused operation. SBRT differs from conventional radiotherapy in that it delivers shorter, more convenient regimens that involve smaller fields and higher doses delivered to the field (Howington et al., 2013). There are some advantages to this approach over surgical resection, including no need for hospitalization, better preservation of lung function, shortened waiting times and a faster return to daily life activities (Howington et al., 2013, Aragón et al., 2015). In addition, SBRT appears to have similar long-term outcomes to surgical resection of the tumour. For instance, an observational study comparing propensity-matched patients with stage IA treated with surgical resection versus SBRT found no difference in local recurrence or overall three-year survival (Crabtree et al., 2010). Another recent study, however, found that after a median follow-up of 48 months, VATS offered better outcomes than SBRT in patients with pathologically proved stage I NSCLC (Hamaji et al., 2015). Plus, SBRT

cannot provide a pathologic confirmation of the tumour; given this, whenever possible sublobar resection is usually preferred over SBRT (Howington et al., 2013).

Hadron therapy is another alternative to conventional radiotherapy for treating early but otherwise inoperable NSCLC, although it is extremely costly (Molina et al., 2008). The five-year survival rate for this treatment appears to be very similar to the rates observed after lung resection (60 to 65 %), thus it can be regarded as a good option for patients with non-resectable disease.

Radiotherapy is also frequently administered in the form of post-operative radiotherapy (PORT), but the results found in the literature are quite controversial. Patients with resected stage I NSCLC appear to have worse survival after PORT, although the reasons for this are not completely clear (Howington et al., 2013). In contrast, a randomized controlled trial (RCT) published in 1996 found that in stage I NSCLC, PORT increased the five-year survival rate in 9% of patients in comparison to those who underwent surgery alone (p =0.048) (Trodella et al., 2002). Given the lack of consistent results, PORT is not currently recommended for stages I and II NSCLC unless there is a positive bronchial margin (Howington et al., 2013).

1.6.3 Chemotherapy

Lung cancer patients are at risk of developing local recurrence after lung resection surgery (Molina et al., 2008). Since the publication of a meta-analysis in 1995 showing a marginal increase in the five-year survival rates with adjuvant chemotherapy, several studies have been conducted comparing surgery alone with surgery plus chemotherapy (Molina et al., 2008). In an updated version of the meta-analysis, a 4% increase in the five-year survival rates was found (HR = 0.86; 95% CI: 0.81–0.92) with little variation regarding the type of chemotherapy used (Burdett et al., 2015). The problem with adjuvant chemotherapy lies in the difficulty of delivering the whole treatment, with some studies showing that only 70% of patients submitted to adjuvant chemotherapy finish their treatment (Howington et al., 2013). One alternative proposed to

overcome this issue is the delivery of the chemotherapy agents prior to lung resection. A Cochrane systematic review published in 2008 suggests that preoperative chemotherapy versus surgery alone can provide a slight increase in the five-year overall survival across all stages of NSCLC (Burdett SS, 2008). Another more recent meta-analysis found a significant benefit of preoperative chemotherapy on survival of 5% at five years (HR = 0.87; 95% CI: 0.78–0.96) and a 13% decrease in the relative risk of death (NSCLC Meta-analysis Collaborative Group, 2014). However, neoadjuvant therapy has also been identified as a risk factor for post-operative complications (Amar et al., 2010), hence the importance of conducting an exhaustive individual preoperative evaluation of surgical candidates to prevent potential mortality and morbidity. There is solid consensus in the literature not recommending chemotherapy for patients with stage IA since it doesn't provide any additional benefit (Howington et al., 2013). This seems less obvious when dealing with patients with stage IB and further investigation is needed to draw definitive conclusions. For patients with stage IIA onwards, post-operative chemotherapy is clearly advocated whenever there is N1 node involvement (Howington et al., 2013).

In summary, the current international recommendations for the treatment of resectable IA to IIIA NSCLC are the following:

- For stages I and II NSCLC and no medical contraindications, surgical resection (lobectomy) is the preferred treatment (Grade 1B).
- For patients with clinical stage I NSCLC, a minimally invasive approach is preferred over a thoracotomy (Grade 2C).
- For patients with stages I and II who may not tolerate a lobectomy, sub-lobar resection (segmentectomy or wedge resection) is preferred over no surgical treatment (Grade 1B).

- For patients with stage I and II who cannot tolerate a sub-lobar resection (segmentectomy), SBRT plus wedge resection is suggested (Grade 2C).
- Post-operative radiotherapy (PORT) is recommended to clear surgical margins after wedge resection (Grade 1C).
- For stage I NSCLC, adjuvant therapy is not recommended outside of a clinical trial (Grade 1B).
- For stages II to IIIA, adjuvant platinum-based chemotherapy is advocated (Grade 1A).

1.6.4 Complementary therapies in lung cancer: the role of exercise training

Complementary therapies in individuals with lung cancer refer to those evidence-based techniques that are related to an improvement in physical and emotional well-being, HRQoL and alleviation of cancer-related symptoms (Deng et al., 2013). Those therapies include, but are not limited to, yoga, meditation, acupuncture, nutritional support, physical activity and exercise (Deng et al., 2013).

Pulmonary rehabilitation (PR) is a comprehensive intervention designed to improve the physical and psychological condition of people with chronic respiratory diseases (Spruit et al., 2013). PR has been raised to the category of gold standard therapy in the management of patients with COPD, where it has been shown to improve exercise and functional capacity, dyspnoea, muscular fatigue and HRQoL and reduce exacerbations and hospital admissions (Nici and ZuWallack, 2014, Ries et al., 2007). However, evidence of the effectiveness of PR, and particularly exercise, in other respiratory diseases is still limited. In the early 2000s, the first studies looking at the effects of PR on lung cancer started to emerge. Given the rationale for PR in COPD patients, it seemed logical to assume that PR could also result in significant improvements in people with lung cancer (Venturelli, 2010). Indeed, preliminary studies have shown an increase in exercise tolerance

and functional capacity in individuals with lung cancer, but inconsistent results have been found in other relevant outcomes such as HRQoL and pulmonary function.

In patients with lung cancer, respiratory rehabilitation may play an important role across the whole continuum, from pre- to post-operative care (Bozonne, 2004) and in advanced disease. In the preoperative setting, exercise training could increase exercise capacity (peak oxygen consumption), which is associated with a lower incidence of post-operative complications and overall better surgical outcomes (Benzo et al., 2007). However, before implementing a preoperative PR programme in the context of lung cancer, the safety and feasibility of the intervention must be assessed. Throughout this thesis, we will examine the current literature on this topic and provide new evidence to support the implementation of such interventions in the lung cancer population.

CHAPTER TWO: CLINICAL AND SOCIO-ECONOMIC IMPACT OF LUNG CANCER

2.1 Economic and health-care burden

Lung cancer is a major public health issue. Economic costs incurred by lung cancer include those derived from its screening, diagnosis and therapeutic management but also those caused by the associated physical and psychosocial impairments (e.g. sick leave and labour incapacity) and early death. A recent study conducted among the 27 countries of the European Union estimated that in 2009 the costs originating from cancer were 126 billion euros, which accounted for 4% of the total health-care expenditure and 1% of gross domestic product (Luengo-Fernández et al., 2013). Interestingly, the majority of the costs (60%) were attributed to productivity losses caused by cancer morbidity and mortality (Table 2.1).

Table 2.1: Cost of cancer in the European Union in 2009 by country; Luengo-Fernández et al., 2013.

	Cancer-related health-care costs							Productivity losses		Informal care costs	Total costs	
	Primary care	Outpatient care	Accident and emergency	Inpatient care	Drugs	Total	Percentage of total health-care expenditure	Mortality	Morbidity		Total	Percentage of gross domestic product
Austria	33	53	22	750	343	1202	4%	750	136	550	2638	0·95%
Belgium	34	70	9	550	346	1010	3%	1047	604	553	3214	0·94%
Bulgaria	10	12	2	56	44	124	5%	119	26	31	300	0·86%
Cyprus	<1	1	1	12	22	36	4%	53	5	15	109	0·65%
Czech Republic	29	77	14	284	194	598	5%	446	166	122	1331	0·94%
Denmark	4	55	11	299	205	574	2%	1010	380	277	2241	1·00%
Estonia	8	10	7	27	10	61	6%	61	34	17	172	1·25%
Finland	21	145	20	460	157	804	5%	464	77	166	1511	0·88%
France	114	176	19	3716	3025	7051	3%	4990	2299	2543	16 883	0·90%
Germany	710	1689	29	9760	2705	14 893	5%	11 607	2213	6414	35 126	1·48%
Greece	57	126	25	584	453	1244	5%	917	86	348	2596	1·12%
Hungary	26	19	5	121	221	393	5%	416	48	122	980	1·07%
Ireland	32	30	13	417	127	619	4%	603	63	162	1447	0·89%
Italy	487	452	115	4136	1664	6854	5%	3966	143	5491	16 454	1·08%
Latvia	5	7	2	34	11	60	5%	88	20	23	191	1·03%
Lithuania	8	8	4	30	9	59	3%	100	40	29	228	0·85%
Luxembourg	4	7	1	53	26	91	3%	57	18	26	191	0·53%
Malta	1	1	<1	6	7	16	4%	12	1	9	38	0·63%
Netherlands	172	250	13	1351	356	2143	3%	2519	706	983	6350	1·11%
Poland	129	368	15	619	267	1399	6%	1306	386	550	3641	1·17%
Portugal	43	65	28	182	247	564	3%	1118	98	268	2048	1·22%
Romania	19	62	2	133	205	421	6%	643	81	112	1257	1·06%
Slovakia	28	71	3	92	112	306	5%	180	88	53	627	1·00%
Slovenia	3	7	5	82	47	145	4%	147	72	42	406	1·14%
Spain	776	340	208	1275	1515	4114	4%	2838	482	1581	9016	0·86%
Sweden	47	244	40	408	233	971	3%	323	478	337	2783	0·93%
UK	153	1072	44	2916	1054	5241	3%	6186	682	2334	14 442	0·91%
Total for European Union	2954	5419	659	28 357	13 604	50 994	4%	42 565	9431	23 216	126 205	1·07%

In Spain, the mean health-care cost per person was 90 euros, slightly under the European mean (102€) but higher than other close countries such as Portugal and the United Kingdom. Of all the cancer types included in the study, lung cancer had the highest economic impact in the whole of the European Union (18.8 billion, 15% of total cost). In sharp contrast, in Spain the cost per person for lung cancer was among the lowest across the 27 countries studied, representing only half of the money spent on other common cancer types (colorectal, breast and prostate) (Table 2.2) (Figure 2.1).

Table 2.2: Health-care cost of all cancers and selected cancers in the EU in 2009, by country; Luengo-Fernández et al., 2013.

	All cancers		Colorectal cancer		Lung cancer		Breast cancer		Prostate cancer	
	Cost per person (€)	Adjusted cost per person (€)*	Cost per person (€)	Adjusted cost per person (€)*	Cost per person (€)	Adjusted cost per person (€)*	Cost per person (€)	Adjusted cost per person (€)*	Cost per person (€)	Adjusted cost per person (€)*
Austria	144	119	16	13	13	11	19	16	14	12
Belgium	94	71	12	9	8	6	12	9	11	8
Bulgaria	16	54	1	5	1	2	2	8	1	5
Cyprus	45	47	4	4	2	2	7	7	4	4
Czech Republic	57	104	7	13	5	9	7	13	6	11
Denmark	104	69	12	8	10	6	13	8	12	8
Estonia	45	82	6	11	4	7	7	13	4	7
Finland	151	127	15	13	12	10	20	16	16	14
France	110	97	10	9	7	6	15	13	15	13
Germany	182	171	21	20	16	15	29	27	21	20
Greece	111	128	8	10	10	11	17	20	14	16
Hungary	39	80	4	8	4	8	6	12	5	11
Ireland	139	88	15	10	13	8	15	9	11	7
Italy	114	96	13	11	9	8	11	9	10	8
Latvia	26	53	3	6	2	4	4	8	2	4
Lithuania	18	33	2	4	1	3	2	4	2	4
Luxembourg	184	141	22	17	21	16	26	20	18	14
Malta	39	59	4	7	2	3	6	9	4	6
Netherlands	130	123	17	16	13	12	19	18	9	8
Poland	37	78	4	9	5	11	4	9	2	5
Portugal	53	61	5	6	3	4	7	8	6	7
Romania	20	52	2	5	1	4	3	8	2	6
Slovakia	57	103	6	11	5	9	7	14	6	10
Slovenia	72	90	7	9	6	7	8	10	8	10
Spain	90	96	9	10	5	5	11	12	10	11
Sweden	105	92	7	6	8	7	11	10	13	11
UK	85	92	10	10	7	8	9	10	7	7
Total for European Union	102	102	11	11	8	8	13	13	11	11

*Adjusted for price differentials with the purchasing power parity method.

Inpatient care was the major component of health-related costs in lung cancer (68%) followed by drugs expenses and primary care (Figure 2.1). The elevated cost derived from productivity losses in lung and other cancer types is partially caused by a delayed diagnosis; hence it is essential to

develop strategies to enhance physical and psychological functioning in cancer survivors to minimize the expenses derived from sick leave and early retirement.

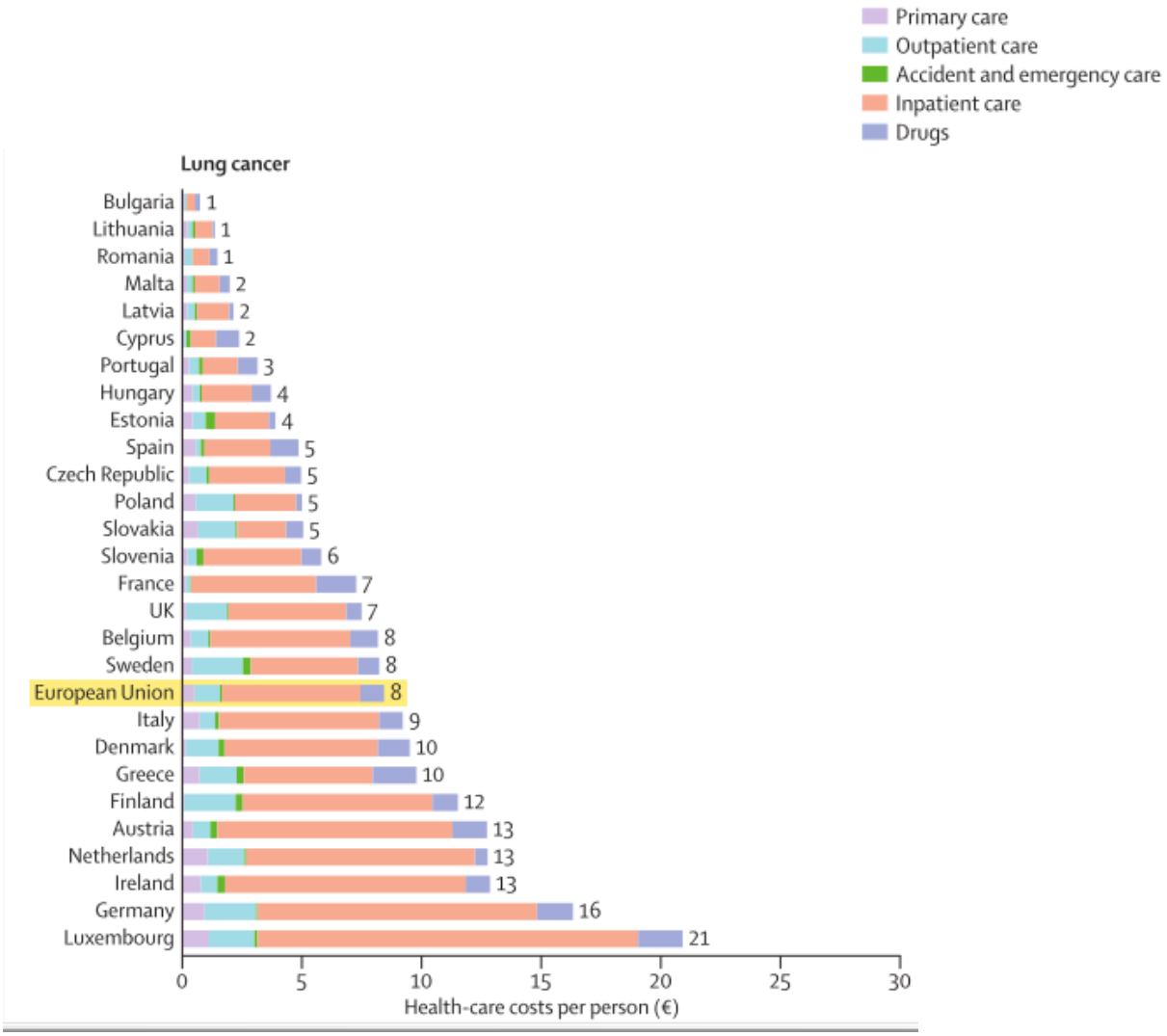


Figure 2.1: Health-care cost of lung cancer per person in 2009, by health-care service category; Luengo-Fernández et al, 2013.

2.2 Clinical manifestations

Lung cancer is often a silent disease, especially in the early stages. Thanks to the advances in screening tools and early detection, the number of patients who are asymptomatic at the time of diagnosis is slowly increasing (Sánchez De Cos Escuín, 2009, Leiro-Fernández et al., 2014). Data

extracted from the latest series published in Spain showed that around one-third of patients were asymptomatic at the time of diagnosis (Leiro-Fernández et al., 2014). Symptoms experienced by individuals with lung cancer can be linked to the primary site of the tumour, derived from metastatic disease, a result of the anti-cancer treatment or manifestations of underlying conditions (Simoff et al., 2013). Cancer-related symptoms are a burden to patients and a major detriment to their HRQoL (Martins et al., 2005). In particular, patients with lung cancer often complain of higher levels of fatigue, dyspnoea and worse HRQoL than those with other cancer types, which can persist for five or more years after the initial diagnosis (Walling et al., 2015, Shi et al., 2011, Walker et al., 2014).

The symptom experience is based on two different entities: symptom occurrence and symptom distress (Cooley et al., 2002). The first refers to the frequency and duration of the symptomatology while the second relates to the intensity and subjective perception of the symptoms. Both are affected by diverse factors stemming from the clinical status (type of cancer, stage, treatment received, number of co-morbidities) and socio-demographic and patient-related characteristics (age, gender, race, smoking history, education, marital status, dwelling status, employment) (Sarna et al., 2008, Shi et al., 2011, Cooley et al., 2002, Lowery et al., 2014, Hung et al., 2011). Typically, patients with advanced disease are at high risk of experiencing severe symptom distress, but even early-stage functional patients can suffer from disabling symptoms such as dyspnoea or cancer-related fatigue across the lung cancer continuum (Temel et al., 2006, Walling et al., 2015, Cooley et al., 2002). At the time of diagnosis, the symptoms most frequently reported by lung cancer patients are fatigue (37–80 %), cough (31.5–75 %), chest pain or chest discomfort (22–50 %), dyspnoea (33%), haemoptysis (19–35%) and anorexia/weight loss (23.8–45 %) (Koczywas et al., 2013, Sánchez De Cos Escuín, 2009, Leiro-Fernández et al., 2014, Yoder, 2006, Shim et al., 2014, Walling et al., 2015) (Figure 2.2).

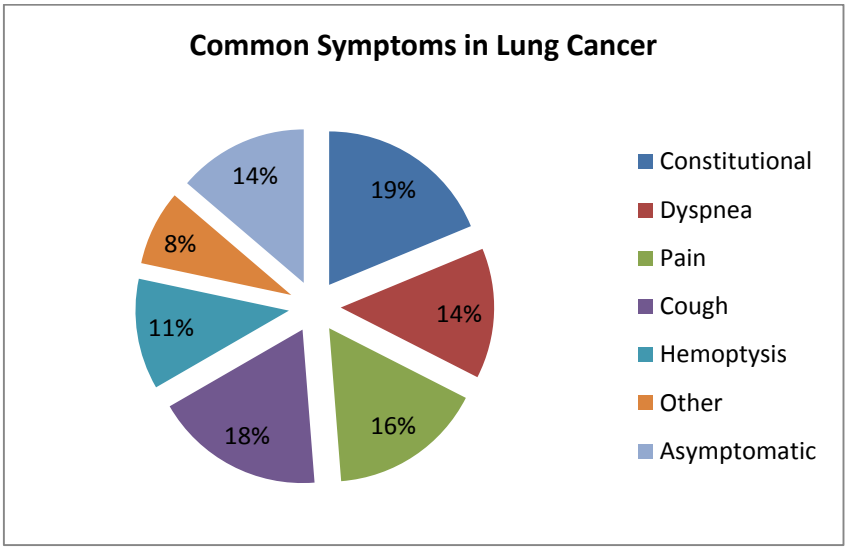


Figure 2.2: Common symptoms in lung cancer at the time of diagnosis; Leiro-Fernández et al, 2014.

Other less common manifestations include hoarseness, wheezing, nausea/vomiting, swelling, bone pain (from bone metastases), clubbing, headache and seizures (Yoder, 2006). The majority of the symptoms are quite unspecific and commonly found in other chronic respiratory diseases, thus they should be only regarded as a clinical suspicion for further testing. The only symptom that has actually proved to be a strong predictor of lung cancer is the presence of haemoptysis (Shim et al., 2014).

2.2.1 Fatigue

Fatigue is the most common symptom reported by cancer patients (Temel et al., 2006). The prevalence and severity of fatigue usually increase with the progression of the disease and the administration of anti-cancer therapies but it can also be found in early stages of the disease and in long-term cancer survivors. In a study conducted by Hung et al., 57% of stage I NSCLC survivors reported some degree of fatigue. Of those, almost 17% had moderate or severe fatigue, which led to significant functional impairment in one-quarter of them (Hung et al., 2011).

Cancer-related fatigue (CRF) is defined as a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and that interferes with usual functioning (Berger et al., 2015). In comparison to the typical fatigue reported by the healthy population, CRF is more distressing and less likely to be alleviated with rest (Berger et al., 2015). As a matter of fact, patients report CRF as the most distressing symptom associated with cancer and/or its treatment, greater even than pain or nausea/vomiting, which can generally be controlled with medication (Berger et al., 2015, Cykert et al., 2010). Despite its high prevalence and severity, oncologists usually neglect the clinical importance of fatigue and therefore it remains undertreated (Temel et al., 2006).

The mechanisms behind CRF are diverse and not entirely known. The possible pathophysiology includes a proliferation of pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, circadian rhythm desynchronization, skeletal muscle wasting and genetic dysregulation (Berger et al., 2015). There are also a number of potentially reversible causes of CRF including anaemia, metabolic abnormalities, sleep disorders, psychosocial stress and side effects of medications (Temel et al., 2006). In fact, most frequently CRF is a result of anti-cancer treatments. Any local or systemic therapy used in the management of lung cancer is associated with an increase in fatigue, but it appears to be especially frequent after radiotherapy. In a longitudinal study looking at the symptom prevalence and evolution pattern after treatment for NSCLC and SCLC, 73% of NSCLC patients treated with radiotherapy exhibited a $\geq$ 10% worsening of fatigue compared to only 44% after chemotherapy (Rolke et al., 2010). Besides the type of treatment, the prevalence and severity of fatigue in lung cancer patients are also affected by the presence of other psychological and clinical features. For instance, in two studies conducted in NSCLC survivors, they found that functional status, concurrent lung disease and clinical

symptoms of depression and anxiety were risk factors associated with increased fatigue one to five years after surgery (Hung et al., 2011, Huang et al., 2015b).

Patients with NSCLC are particularly at risk of developing physical deconditioning and functional impairment because of co-morbid cardiovascular and pulmonary disease secondary to tobacco abuse (Temel et al., 2006, Granger et al., 2014). Low levels of physical activity have been reported for patients with lung cancer at the time of diagnosis, which further deteriorated during and after treatment (Granger et al., 2014). Physical activity has been identified as a protective factor against functional decline and CRF in NSCLC survivors (Hung et al., 2011, Huang et al., 2015b). In this line of treatment, exercise has been proposed as a non-pharmacological intervention to ameliorate fatigue and increase physical functioning and HRQoL. A systematic review and meta-analysis looking at the effects of exercise in cancer patients undergoing or following treatment found a significant reduction in CRF (MD = 0.32; 95% CI: 0.21, 0.43 and 0.38; 95% CI: 0.21, 0.54, respectively) after an exercise-based intervention (Puetz and Herring, 2012). Among those studies conducted following treatment, there were greater improvements for trials with longer periods between treatment completion and exercise initiation, those with shorter exercise programme lengths and studies using waiting list comparison (Puetz and Herring, 2012). In another meta-analysis including cancer survivors, the authors found a significant reduction in fatigue, especially for older cancer survivors engaging in moderate to intense exercise (MD = 0.31 (95% CI = 0.22–0.40) (Brown et al., 2011). This finding is of particular interest given that most cancer patients (including those with lung cancer) are typically old. Globally, this data suggest that both physical activity and structured exercise interventions should be considered for patients with cancer to reduce CRF and improve functional and psychological well-being.

2.2.2 Dyspnoea

Respiratory symptoms are common among patients with lung cancer or metastatic disease to the lung (Temel et al., 2006). Dyspnoea and cough are the two respiratory symptoms most frequently reported at the time of diagnosis (Leiro-Fernández et al., 2014, Walling et al., 2015). Dyspnoea affects approximately 60% of patients with early disease and up to 87% of patients with advanced disease (Feinstein et al., 2010, Smith et al., 2001). Dyspnoea is clinically defined as an uncomfortable sensation or awareness of breathing (Temel et al., 2006) and is commonly reported by patients as being 'out of breath', 'suffocated' or as 'having trouble with breathing'. The pathophysiology of dyspnoea in lung cancer is not completely understood, and there are several potential mechanisms involved (Koczywas et al., 2013) (Figure 2.3). The most common causes of dyspnoea in lung cancer are tied to the location of the tumour, anti-cancer therapies or to the presence of underlying respiratory conditions (Temel et al., 2006) (Table 2.3).

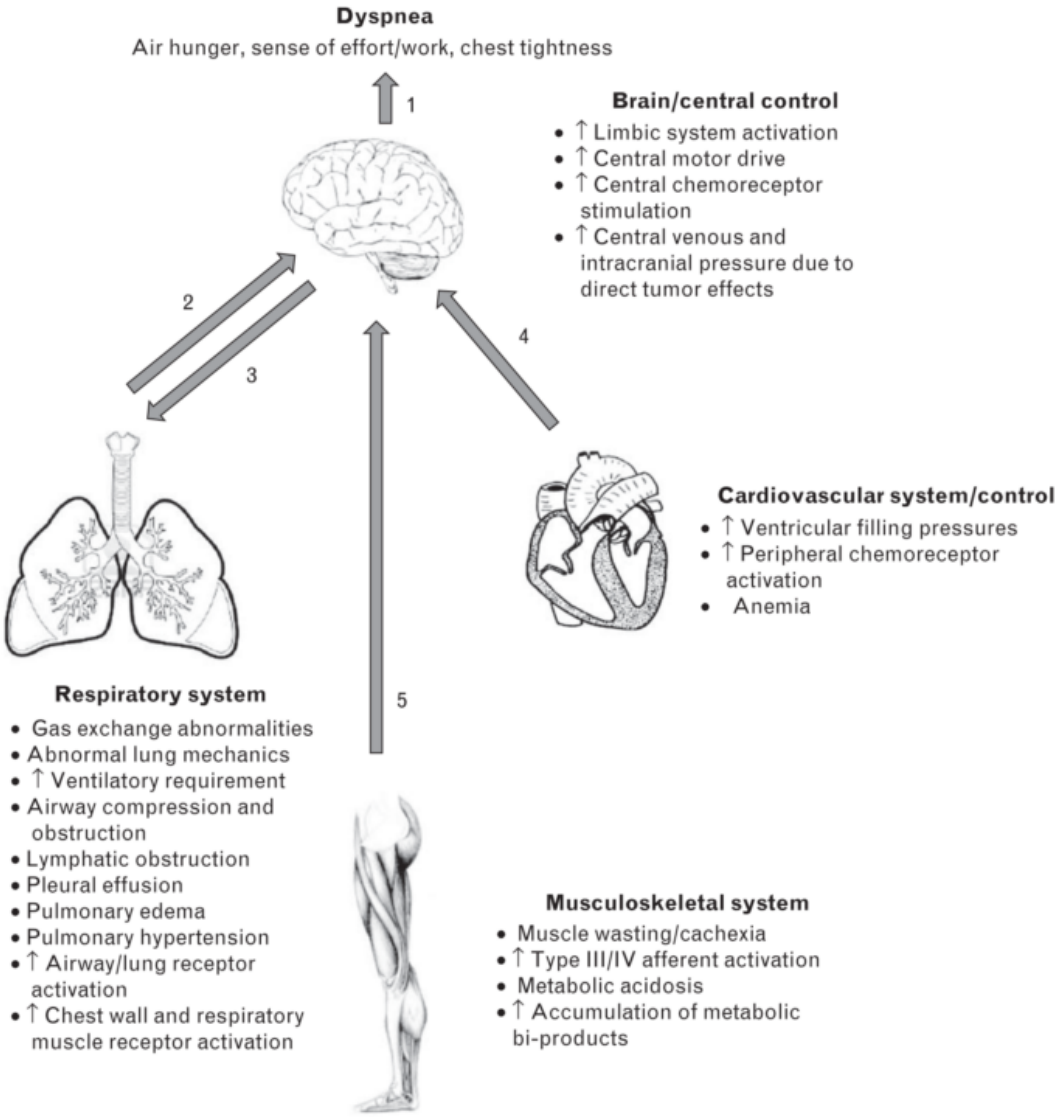


Figure 2.3: Potential mechanisms of dyspnoea in patients with cancer; Koelwyn et al., 2012.

In patients with early NSCLC, predictors of dyspnoea include impaired pulmonary diffusion capacity, clinical anxiety or depression symptoms and lack of moderate to strenuous physical activity (Feinstein et al., 2010). Males and older patients typically refer more severe dyspnoea than females or younger individuals (Smith et al., 2001) (Feinstein et al., 2010, Smith et al., 2001). Surgery is more intensely associated with an increase in dyspnoea in comparison to other systemic treatments, probably because of the loss in lung tissue and the disruption of the oxygen cascade (Rolke et al., 2010, Jones et al., 2009a).

Table 2.3: Common aetiologies of dyspnoea in lung cancer; adapted from Temel, 2006

Common Aetiologies of Dyspnoea in Lung Cancer
Related to Cancer Parenchymal lung involvement Lymphangitic spread of tumour Pleural Effusion Pericardial Effusion Airway Obstruction Superior vena cava syndrome
Not-related to Cancer Pulmonary Embolus Pneumonia Anaemia Paraneoplastic syndromes Underlying respiratory disease
Related to Cancer Therapy Lobectomy/Pneumonectomy Radiation pneumonitis Chemotherapy-related pneumonitis Pulmonary Fibrosis

Dyspnoea has a strong impact on HRQoL, particularly on physical functioning and social functioning. Patients complaining from dyspnoea often exhibit other concurrent physical symptoms, including weakness, suffocation, tightness, congestion and pain, which further aggravate the feeling of breathlessness (Smith et al., 2001). Patients with dyspnoea are also at higher risk of developing panic attacks and anxiety (Shin et al., 2014, Temel et al., 2006). A relationship between dyspnoea and anxiety is common among lung cancer patients and may exacerbate the intensity and severity of breathlessness (Temel et al., 2006). Furthermore, the clinical manifestations of the two entities are very close and most patients experience difficulties in distinguishing one from the other.

Adequate management of dyspnoea includes both pharmacological and non-pharmacological interventions. Opioids are the most effective pharmacologic agent for improving dyspnoea (Temel et al., 2006). On the other hand, non-pharmacological interventions include

oxygen, cognitive/behavioural therapies, breathing and relaxation techniques and exercise (Temel et al., 2006, Zhao and Yates, 2008). Like CRF, dyspnoea can be improved by increasing physical activity and structured exercise training programmes. Moderate to strenuous physical activity has been shown to be inversely correlated with the prevalence and severity of dyspnoea in lung cancer patients (Feinstein et al., 2010). Exercise training has been shown to significantly reduce dyspnoea in patients with COPD and other chronic respiratory diseases (McCarthy et al., 2015) but the results found in lung cancer patients are still controversial (Koczywas et al., 2013). An RCT conducted by Gattlik et al. found large improvements in exertional dyspnoea after a pulmonary rehabilitation programme conducted in lung cancer survivors (Glattki et al., 2012). Cesario et al. also observed an improvement in both exertional and baseline dyspnoea after a 4-week PR programme in post-surgical lung cancer patients (Cesario et al., 2007b). However, Spruit et al., in a single-arm study, found no difference in exertional dyspnoea or leg fatigue after a post-thoracotomy rehabilitation programme (Spruit et al., 2006). The type of exercise prescribed (endurance vs. resistance or both), the timing of the intervention and the measurement tools chosen can explain the variation found in the results.

2.2.3 Pain

Pain is another frequent symptom found in cancer patients across the trajectory of the disease. Up to 50% of individuals with lung cancer report pain to some degree at the time of diagnosis (Yoder, 2006, Walling et al., 2015) and this percentage rises to 75% in individuals with advanced disease (Di Maio et al., 2004). Pain in lung cancer can be due to peripheral growth of the tumour, nerve involvement or dissemination of the disease (Di Maio et al., 2004). The two most common sites for pain presentation in lung cancer are the chest and spine (from bone metastasis or spine compression) (Temel et al., 2006). In individuals with advanced disease, pain is regarded as among the most distressing symptoms affecting their ability to carry out most activities of daily

living (Di Maio et al., 2004, Wang et al., 1999). Surgery can also cause significant pain by damaging the muscles, nerves and ribs. Plus, in the immediate post-operative period, the thoracic cavity suffers major trauma because of the use of chest tubes and other drainage devices (Hopkins and Rosenzweig, 2012). Post-thoracotomy pain syndrome (PTPS) is a condition occurring in as many as 50% of post-surgical patients with lung cancer (Rolke et al., 2010, Hopkins and Rosenzweig, 2012). The potential causes of PTPS include: a) trauma and compression of the intercostal nerves during surgery; b) fractures and compressed ribs from the use of separators during surgery; c) inflammation of the chest muscles and adjacent structures; d) atrophy of the chest muscles; and e) scar tissue rubbing the pleural cavity (Hopkins and Rosenzweig, 2012). Even after less invasive techniques such as VATS, the removal of lung tissue can damage the nerves and ribs, causing PTPS. On top of that, PTPS can be aggravated by the presence of other symptoms including anxiety, depression, fatigue and dyspnoea.

There are other intrinsic factors that can affect the prevalence and perception of pain in lung cancer patients. In a cross-sectional study, Gonzalez et al. examined the prevalence and severity of pain in patients with lung and colorectal cancer according to their smoking status (current, former or non-smoker). They observed that among lung cancer patients, current smokers reported pain more often than former smokers (48.8% vs. 38.5%, respectively; p <.001) and that smoking was also associated with the intensity of pain, with former smokers and lifetime non-smokers reporting less pain severity than current smokers (Gonzalez et al., 2014) (Figure 2.4). Other features associated with pain severity in this study were depression, black or Hispanic race and female gender (Gonzalez et al., 2014).

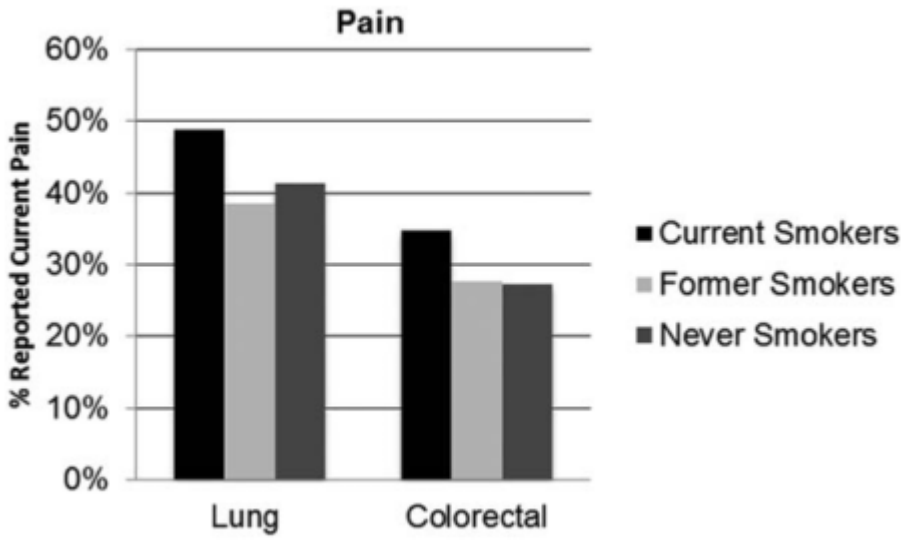


Figure 2.4: Prevalence of pain according to smoking history; Gonzalez et al., 2014.

Pain management is important in oncologic care for maximizing patient outcomes (Bao et al., 2014). The current body of literature suggests that unrelieved pain significantly affects HRQoL and survival (Bao et al., 2014). In the cancer setting, the assessment and management of chronic pain are performed according to the WHO pain ladder developed in the mid 1980s (Figure 2.5). This simple visual scale divides cancer pain into three categories (mild, moderate and severe) and establishes the most appropriate pharmacological treatment for each one according to the current evidence.

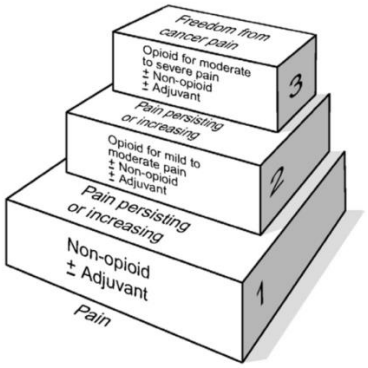


Figure 2.5: World Health Organization analgesic pain ladder.

Unfortunately, there are several side effects associated with long-lasting use of pain medication, which have driven physicians to investigate the effectiveness of non-pharmacological interventions for controlling cancer pain. Currently, there is some evidence claiming that acupuncture can be beneficial for patients with cancer pain, although the number of investigations is small and there are some methodological issues that prevent solid conclusions being drawn (Paley et al., 2011). A recent overview of all the systematic reviews examining the effects of complementary therapies in pain management concluded that although there might be some symptom alleviation related to these interventions, no formal recommendations could be extracted due to the lack of homogeneity and high risk of bias of the studies included (Bao et al., 2014).

2.2.4 Anorexia, weight loss and cancer-related cachexia

Cancer-related cachexia is a well-known issue in cancer patients and is strongly associated with a poor prognosis. Cancer cachexia is a multifactorial symptom characterized by the co-occurrence of anorexia and involuntary weight loss as a result of low calorie intake, muscle and adipose catabolism or both (Gould et al., 2013a). It is a progressive state of the body that cannot be fully reversed and that eventually leads to progressive functional impairment (Blum et al., 2011).

Although cachexia can be found in all types of cancer, it mostly affects those individuals with gastrointestinal tract and lung tumours (Gould et al., 2013a). Cancer cachexia is typically associated with progression of the disease and therefore it has been mostly studied in advanced patients. Nevertheless, anorexia and weight loss, which are initial manifestations of cachexia, are also common at the time of diagnosis in lung cancer patients (Leiro-Fernández et al., 2014, Sánchez De Cos Escuín, 2009, Muscaritoli et al., 2006).

As with CRF and dyspnoea, the pathophysiology of cachexia has not been entirely uncovered. It appears that different mechanisms are involved in the development of cancer

cachexia, including dysregulations in several hormones and appetite mediators (such as leptin, ghrelin and neuropeptide Y among others), the release of pro-inflammatory cytokines (TNF-α, IL-1, IL-6 and IFN-γ), insulin resistance, and certain side effects derived from medications and anti-cancer treatments (Suzuki et al., 2013, Muscaritoli et al., 2006) (Figure 2.6). The most common manifestations of cachexia are weight loss (due to depletion of lipid stores and muscle mass), malnutrition (due to loss of appetite, nausea and vomiting, and post-radiation dysphagia) and muscle dysfunction (due to muscle catabolism and atrophy) (Muscaritoli et al., 2006, Suzuki et al., 2013). The progressive loss of muscle mass is by far the most prominent phenotypic feature of cancer cachexia and is related to major functional impairment (Muscaritoli et al., 2006). In the absence of stimuli (i.e. exercise), muscle mass remains constant and protein synthesis (anabolism) and degradation (catabolism) are balanced (Suzuki et al., 2013). During cancer cachexia, however, this state of balance is disrupted and the amount of muscle catabolism outstrips muscle anabolism, causing weight loss, weakness and fatigue (Suzuki et al., 2013).

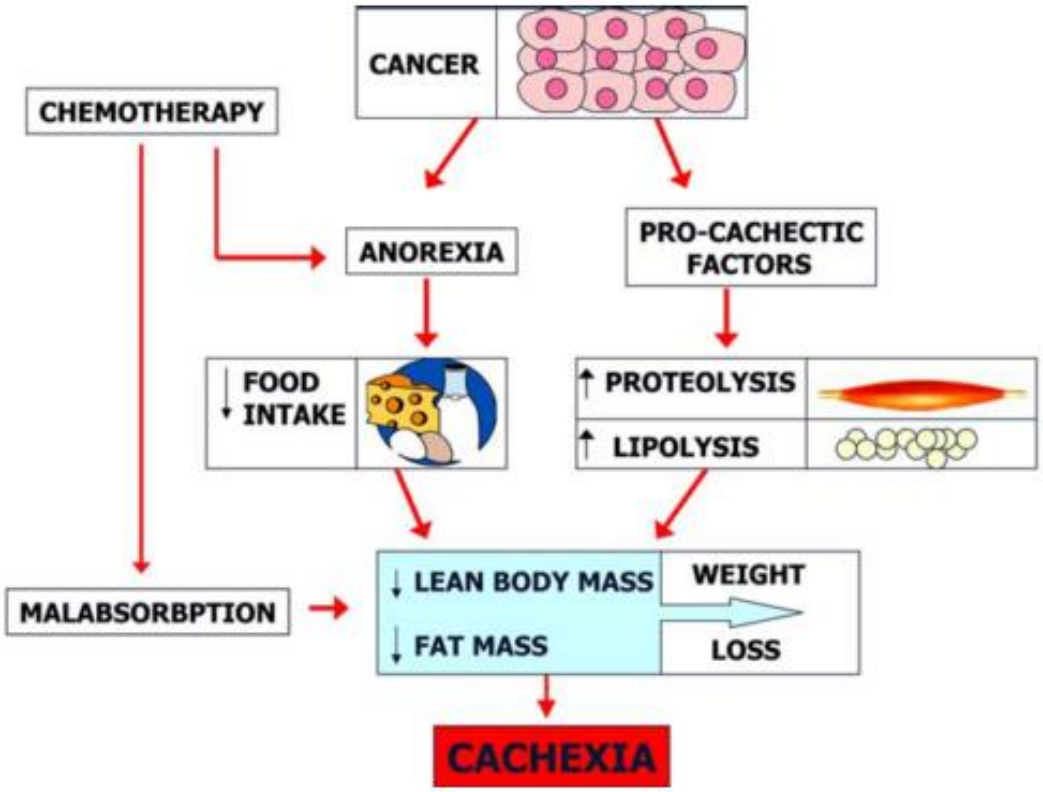


Figure 2.6: Pathogenesis of cancer cachexia; Muscaritoli, 2006.

The clinical consequences of cancer cachexia are severe. Weight loss at presentation is a well-known strong predictor of cancer outcomes. Both the amount of weight loss and the rate at which it occurs significantly affect prognosis and survival in the cancer population (Gould et al., 2013a). In patients with NSCLC and SCLC, weight loss significantly correlates with poor physical and cognitive functioning and results in shorter overall survival (Mohan et al., 2007, Temel et al., 2006). In particular, the progressive destruction of the muscle mass results in muscle dysfunction and atrophy, which eventually lead to reduced physical activity and physical functioning, increased fatigue and dyspnoea, and worsening of HRQoL (Muscaritoli et al., 2006, Gould et al., 2013a). Cancer cachexia also affects surgical risk as well as responsiveness and tolerability to first- and second-line chemotherapy/radiotherapy (Muscaritoli et al., 2006). Malnutrition, which can occur

as a result of untreated anorexia, is also associated with impaired wound healing, immune dysfunction, respiratory muscle fatigue and tissue wasting following surgery (Jones et al., 2013).

To reverse cancer cachexia, the ultimate goal would be to cure cancer, but since this is not a reasonable scenario for the vast majority of cases, health professionals must develop other strategies to at least maintain optimal weight and prevent further deterioration. A comprehensive treatment for cancer cachexia should start by identifying the potential causes and include specific measures for all mechanisms involved, from anorexia and a lack of appetite to loss of muscle mass and muscle dysfunction. An adequate nutritional support that ensures enough calorie intake as well as the prescription of appetite stimulants and medication to reduce nausea and vomiting should be the selected approach to treat anorexia and loss of appetite. Unfortunately, improving muscle mass and reversing muscle dysfunction seems more challenging to achieve due to all the pathophysiological mechanisms involved. Theoretically, there are two potential lines of action that can be used to reverse muscle wasting: a) preventing muscle catabolism and b) stimulating muscle protein anabolism. Numerous pharmacological agents and supplements have been tested to reach those goals, including the prescription of anti-inflammatory cytokines, proteasome inhibitors and anabolic steroids and other anabolic hormones (Muscaritoli et al., 2006). Interestingly, both could potentially be achieved by engaging in conventional exercise training, thanks to its role in reducing inflammation and its ability to grow muscle mass by stimulating protein synthesis (Gould et al., 2013a). The potential pathways involved in the effectiveness of exercise for reducing and preventing cancer cachexia are beyond the scope of this thesis, but briefly, repeated exercise training is associated with increased levels of anti-inflammatory IL-10 and other cytokine inhibitors, which contribute to fighting the pro-inflammatory status observed in patients with cachexia. Exercise is also known for generating an antioxidant effect, which can protect from the damage derived from reactive oxygen species. Finally, exercise has also been shown to increase

insulin sensitivity, which facilitates the transport and catchment of glucose and amino acid into the muscle cells (Gould et al., 2013a).

2.2.5 Mood and symptom distress

Patients' initial response to a cancer diagnosis is influenced by the type and stage of the disease but also by pre-existing psychological factors (Zabora et al., 2001, Sarna et al., 2008). Compared to other cancer types, patients with lung cancer have the highest level of emotional distress (Zabora et al., 2001). For instance, the prevalence of depression is higher in patients with lung cancer than in those with cancers in other primary sites (Walker et al., 2014), and it persists even after successful surgical resection of the tumour (Sarna et al., 2008). In one study investigating the changes in the prevalence of anxiety and depression before and after surgical treatment, researchers found that after surgery, depression was significantly higher than at baseline and 37.5% of patients needed supportive therapy and/or pharmacologic intervention (Park et al., 2015). The percentage of lung cancer patients suffering from major depression has been reported to be 5.8% three months after surgery, which although not high, is not too low either to be neglected (Uchitomi et al., 2000). Depression in patients with cancer is associated with worse anxiety, pain, fatigue and physical functioning (Walker et al., 2014). As previously mentioned, anxiety is also common in lung cancer patients. Epidemiological studies have shown that 15–40 % of individuals with NSCLC have clinically significant levels of anxiety (Dean et al., 2013). Risk factors associated with depression and anxiety in the lung cancer population include younger age, low income, female gender, having more co-morbidities, poor performance status and functional impairment (Hopwood and Stephens, 2000, Walker et al., 2014, Uchitomi et al., 2000, Shi et al., 2011).

Symptom severity and distress tend to be reduced over time. A study looking at the symptom burden in lung cancer patients over the first year after diagnosis found that a substantial increase was observed in most symptoms at six weeks (approximately at the beginning of the

planned treatment) but significant reductions were observed thereafter (Koczywas et al., 2013). In sharp contrast, in another longitudinal study involving individuals newly diagnosed with lung cancer, Cooley et al. observed that symptom distress was reduced three months after the diagnosis, but surprisingly it was intensified at six months (Cooley et al., 2002). This study also found significant differences in symptom distress according to the type of cancer treatment. Thereby, patients undergoing surgery reported less symptom distress both at three and six months in comparison to radio- and chemotherapy. It is worth noting, though, that patients undergoing surgery are mostly diagnosed with early stages of the disease and therefore are most likely to experience less symptom burden.

2.2.6 Symptom clusters and prognosis value

In the context of almost any illness, symptoms are rarely unique manifestations. Most of the time, the symptom burden experienced by patients results from the simultaneous occurrence of symptoms, also known as 'clustering' of symptoms (Fox and Lyon, 2006). The term 'symptom cluster' was first used by Dodd et al. in 2001 to refer to the coexistence of three or more symptoms together that may or may not share a common aetiology (Dodd et al., 2001). Since then, other authors have made minimal changes to this definition, including the consideration of only two or more symptoms together as a cluster as long as they have an impact on a major outcome. Because individual symptoms in lung cancer are associated with worsening HRQoL and poor performance, it seems reasonable to deduce that the combination of two or more symptoms may result in a more severe deterioration.

In consequence, there has been an escalating body of research conducted in cancer populations to identify potential clusters of symptoms and examine their prognosis value. As an example, nausea and vomiting have been described as a gastrointestinal symptom cluster in most cancer patients, including those with lung cancer (Wang et al., 2008). Dyspnoea, cough and fatigue

are another persistent cluster in lung cancer patients even up to 5 years after diagnosis (Cheville et al., 2011a). This particular cluster was found to be inversely associated with survival, especially when presenting during the first two years after diagnosis (Cheville et al., 2011b). The combination of dyspnoea and fatigue with mood disorders such as anxiety and depression has also been frequently acknowledged in the lung cancer population as a symptom cluster (Cheville et al., 2011a, Fox and Lyon, 2006). Pain, fatigue, disturbed sleep and distress shape another cluster reported in a study involving post-operative lung cancer patients, with three-quarters of the patients displaying the four symptoms at the same time (Lin et al., 2013). Other clusters associated with poor prognosis are depression, fatigue and pain (Shin et al., 2014) and anxiety, fatigue and dyspnoea (Cheville et al., 2011a).

Recognizing the presence of symptom clusters in specific populations is a big step in understanding a patient's symptom experiences (Chen et al., 2011a). Hopefully, this would help health professionals involved in cancer management to specifically address patients' issues, thereby improving their physical and psychological well-being.

2.3 Co-morbid diseases

Lung cancer patients often present with co-morbidities that can extensively affect the decision-making process regarding treatment options (Cykert et al., 2010, Blanco et al., 2008, Colinet et al., 2005). Individuals diagnosed with lung cancer are frequently old and carry a history of smoking, both intimately linked with the incidence of respiratory and cardiovascular disorders. In one study examining the prevalence and severity of co-morbidities in lung cancer, the authors found that almost 90% of the patients had at least one co-morbidity and 40% had three or more (Grose et al., 2014). The most frequent coexisting conditions were COPD (43%) and renal impairment (28%). In other epidemiological studies, the prevalence of cardiovascular and

respiratory diseases in a population with lung cancer ranged from 36 to 44 % (Colinet et al., 2005, Sánchez de Cos Escuin et al., 2013).

Aging is associated with a higher incidence and prevalence of several co-morbid diseases due to the metabolic changes taking place as a consequence of senescence. During the early 1970s, patients with lung cancer who were ≥ 70 years old were considered unfit to undergo surgery based solely on their age, as increased age was a risk factor for thoracic surgery. However, the number of patients with advanced age diagnosed with lung cancer has exponentially increased in recent decades with the current average surpassing 65 years (Schulte et al., 2010, de Cos Escuín et al., 2006, Sánchez De Cos Escuín, 2009). Thanks to the multiple advances in the perioperative management of patients with lung cancer, elderly people can now safely undergo surgical resection with similar post-operative and oncological outcomes to younger individuals. Yet the pre-existence of co-morbidities is a potential risk factor for post-operative complications and a torpid recovery. Therefore, although advanced age should not be regarded as an isolated factor for precluding surgery, older patients (especially ≥ 75 years old) should be evaluated and monitored closely to avoid potential complications and enhance surgical recovery (Agostini et al., 2010).

The presence of an underlying respiratory disease is a well-established risk factor for lung resection surgery. Severe airway obstruction (FEV_1 < 40%) has been traditionally viewed as a contraindication for anatomic surgical resection (Beckles, 2003). However, advances in perioperative management, and in particular the introduction of minimally invasive techniques that minimize chest trauma, have allowed patients with poor pulmonary function to undergo surgery, although significant morbidity is still reported (Wang et al., 2014). COPD is the fourth leading cause of death worldwide and is a major source of respiratory morbidity and mortality (Zhai et al., 2014). COPD is often found among patients diagnosed with lung cancer, especially men, affecting between 50 and 75 % of cases (Nakajima et al., 2009, Montero et al., 2003, Loganathan et al.,

2006). Several hypotheses have been proposed to explain the high prevalence of COPD encountered in lung cancer patients. Some epidemiological studies have shown a link between airway obstruction and the risk of lung cancer, particularly for squamous-cell carcinomas (Mayne et al., 1999). Chronic inflammation present in COPD and other obstructive diseases such as asthma could affect the mucociliary clearance efficacy for expelling the carcinogenic substances found in cigarette smoke (Raviv et al., 2011) (Figure 2.7). Conversely, other studies suggest that the relationship between COPD and lung cancer is mostly explained by the shared smoking history and is not related to the physiopathology of COPD (Powell et al., 2013). Irrespectively of the nature of the relationship, the presence of COPD in lung cancer has been identified as an independent predictor factor for both PPCs and disease-free and overall survival (Agostini et al., 2010, Sekine et al., 2002, Okami et al., 2009, Zhai et al., 2014, Nakajima et al., 2009).

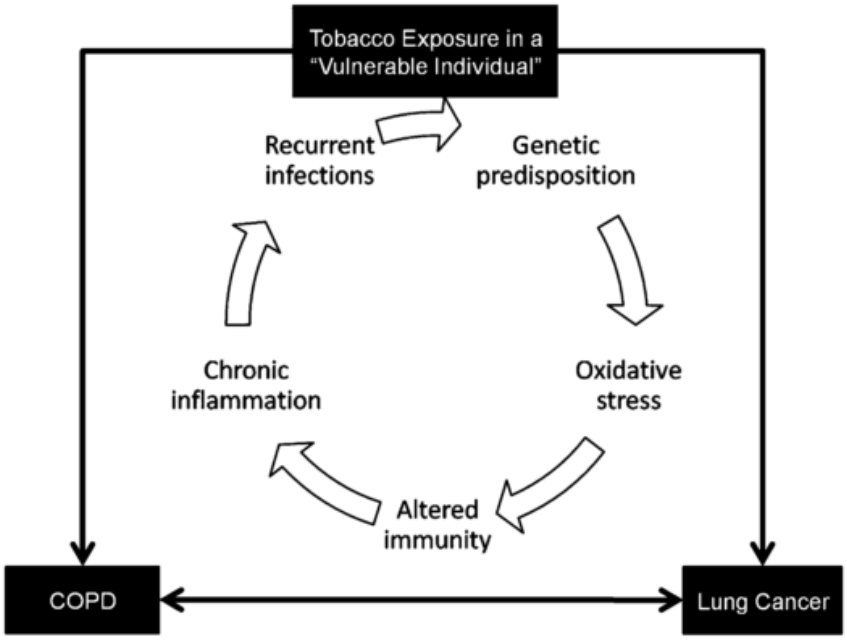


Figure 2.7: Postulated mechanisms for the link between COPD and lung cancer; Raviv et al., 2010.

Given the important role that co-morbidities play as a prognostic factor in the short- and long-term outcomes of lung cancer, several instruments have been developed to quantify the severity and hazard of each particular one. The most widely used clinical score for assessing co-morbidities is the Charlson Co-morbidity Index (CCI), which encompasses 19 medical and surgical conditions weighted according to their risk of death. The CCI has been used in lung cancer patients and it has been shown to predict post-operative mortality and morbidity (Moro-Sibilot et al., 2005, Strand et al., 2007, Asmis et al., 2008). However, due to the number of multiple conditions included, a simplified alternative was sought. In 2005, Colinet et al. designed a simplified co-morbidity score specifically for patients with NSCLC (Colinet et al., 2005). This score system was developed in a multicentre cohort of 735 patients with histologically proven untreated NSCLC and was then prospectively validated in another population of 136 patients. Co-morbidities were divided into seven categories and scored according to their contribution to the relative risk of death (Table 2.4).

Table 2.4: Summary of changes in physiological function and body composition with advancing age in healthy humans; adapted from Chodzko-Zajko et al., 2009

Variable	Typical Changes	Functional Significance
Muscle Strength	Isometric, concentric and eccentric strength decline from age 40 year, accelerate after age 65-70 years. Lower body strength declines at a faster rate than upper body strength.	Declines in strength and power predict disability in old age and mortality risk.
Cardiac function	HR_{max} stroke volume and cardiac output decline. Slowed HR response at exercise onset. Reduced left ventricular ejection fraction %.	Reduced exercise capacity with ageing
Vascular function	Aorta and its major branches stiffen. Vasodilator capacity and endothelium-dependent dilatation of most peripheral arteries (brachial, cutaneous) decrease	Arterial stiffening and endothelial dysfunction increase CVD risk
Maximal O_2 Uptake	Overall decline averages 0.4-0.5ml/kg^{-1}/min^{-1}/yr^{-1} (9% per decade) in healthy sedentary	Disease and mortality risk factor.

	adults. Decline accelerates with advancing age.	
FFM	FFM declines 2-3% per decade from 30 to 70 years of age. Losses of total body protein and potassium likely reflect the loss of metabolically active tissue (i.e: muscle).	FFM seems to be an important physiological regulator
MQ	Lipid and collagen content increase. Peak-specific force declines. Oxidative capacity per kg muscle declines.	Changes may be related to insulin resistance and muscle weakness.
Regional adiposity	Body fat increases during 30-50s with a preferential accumulation in the visceral (intra-abdominal) region, especially in men. After age 70 years, fat decreases	Accumulation of visceral fat is linked to CVD and metabolic disease.

*HR_{Max}= Maximal Heart Rate; HR = Heart rate; CVD = Cardiovascular Disease; O2 = Oxygen; FFM = Free Fat Mass.

The presence of an underlying respiratory disease is a well-stablish risk factor for lung resection surgery. Severe airway obstruction (FEV_1 < 40%) has been traditionally viewed as a contraindication for anatomic surgical resection (Beckles, 2003). However, advances in perioperative management and in particular, the introduction of minimally invasive techniques which minimizes chest trauma, has allowed patients with poor pulmonary function to undergo surgery, although significant morbidity is still reported (Wang et al., 2014). COPD is the fourth leading cause of death worldwide and is a major source of respiratory morbidity and mortality (Zhai et al., 2014). COPD is often found among patients diagnosed with lung cancer, especially men, affecting between 50 - 75% of the cases (Nakajima et al., 2009, Montero et al., 2003, Loganathan et al., 2006). Several hypotheses have been proposed to explain the high prevalence of COPD encountered in lung cancer patients. As presented in Chapter 1, some epidemiological studies have shown a link between airway obstruction and the risk of lung cancer, particularly for SCC (Mayne et al., 1999). In addition, chronic inflammation present in COPD and other obstructive diseases such as asthma, could affect the mucociliary clearance efficacy to expel the carcinogenic substances found in cigarette smoke (Raviv et al., 2011) (Figure 2.7). Conversely, other studies

claim that the relationship between COPD and lung cancer is basically due to the intimately link between smoking and the development of both diseases and not related to the physiopathology of COPD (Powell et al., 2013). Irrespectively of the nature of the relationship, the presence of COPD in lung cancer has been identified as an independent predictor factor for both PPCs and disease-free and overall survival (Agostini et al., 2010, Sekine et al., 2002, Okami et al., 2009, Zhai et al., 2014, Nakajima et al., 2009).

Several instruments have been developed to assess the prognosis role of a wide range of co-morbidities in the lung cancer setting. The most widely used in clinical practice and research is the Charlson Co-morbidity Index (CCI), which encompasses 19 medical and surgical conditions weighted according to their risk of death. The CCI has been used in lung cancer patients and it has demonstrated to predict post-operative mortality and morbidity (Moro-Sibilot et al., 2005, Strand et al., 2007, Asmis et al., 2008). However, due to the multiple conditions included, a shortened alternative was sought. In 2005, Colinet et al., designed a simplified co-morbidity score specifically for patients with NSCLC (Colinet et al., 2005). This score system was developed in a multicentre cohort of 735 patients with histologically proven untreated NSCLC and was then prospectively validated in another population of 136 patients. Co-morbidities were divided in seven categories and were scored according to their contribution to the relative risk of death (Table 2.5).

Table 2.5: Colinet Co-morbidity Score; Colinet et al, 2005

Co-morbidity	Weighting
Tobacco Consumption	7
Diabetes Mellitus	5
Renal insufficiency	4
Respiratory Co-morbidity	1
Cardiovascular Co-morbidity	1
Neoplastic Co-morbidity	1
Alcoholism	1

In this research, the Colinet Co-morbidity Score (CCS) was found to be an independent factor of poor prognosis and reduced five-year survival in patients with NSCLC, especially for those with a CCS ≥ 9. The authors also concluded that the CCS was more informative than the CCI in predicting patients' outcomes.

2.4 Cardiorespiratory fitness

Cardiorespiratory fitness (or exercise tolerance) reflects the integrative capacity of the components in the oxygen cascade to supply adequate oxygen for adenosine triphosphate (ATP) resynthesis (Jones, 2011). Peak oxygen consumption (VO_{2peak}) is the gold standard in the assessment of cardiopulmonary fitness (Jones, 2011). It has been acknowledged that patients with lung cancer exhibit low cardiopulmonary fitness across the whole lung cancer continuum in comparison to age- and sex-matched populations. In a study conducted among patients with lung cancer awaiting lung resection surgery, VO_{2peak} was found to be reduced by 25 to 44 % in comparison to normative data (Loewen et al., 2007). The reasons for this marked reduction in exercise tolerance are diverse and relate to cancer pathophysiology (tumours in the lungs directly affect the oxygen cascade), patients' baseline status (presence of co-morbidities, advanced age, low physical activity levels) and the effects of the anti-cancer therapies (Jones, 2011, Jones et al., 2009a) (Figure 2.8).

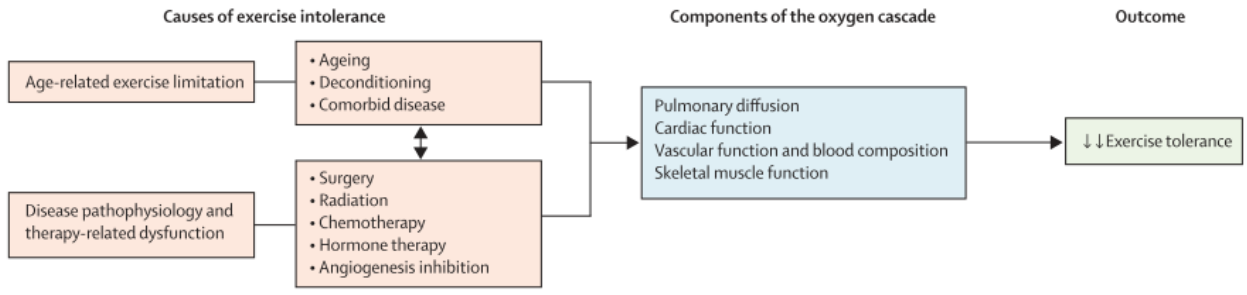


Figure 2.8: Proposed causes of reduced exercise tolerance in cancer patients; Jones, 2009.

In the lung cancer setting, the role of VO_{2peak} is critical as it provides valuable information regarding surgical tolerability and prognosis of the disease. The ability of the preoperative VO_{2peak} to predict post-operative complications has been extensively acknowledged in the literature (Jones et al., 2010, Loewen et al., 2007, Benzo et al., 2007, Brunelli et al., 2014). Postoperatively, reduced VO_{2peak} has also been associated with physical decline and worsening HRQoL (Jones et al., 2008). In advanced disease, Jones et al. found that VO_{2peak} was 33% below age- and sex-predicted values. In this population, functional exercise capacity has been shown to predict survival in addition to other well-established factors such as performance status (PS) (Jones et al., 2012).

Given the prognostic role of exercise tolerance in the perioperative setting of lung resection surgery, it's not surprising that VO_{2peak} has been proposed as an attractive modifiable therapeutic target to reduce surgical risk, hasten recovery, and improve symptom control and hopefully cancer-specific outcomes (Jones, 2011). Repeated exercise training is regarded as the most effective way to increase VO_{2peak} in healthy people (Jones, 2011) and has also been successfully prescribed in people with COPD and other chronic respiratory diseases. Therefore, it is reasonable to believe that exercise training could yield similar results in the cancer population and, more specifically, in lung cancer. Consequently, a systematic review and meta-analysis conducted in people with cancer found a statistically significant increase in VO_{2peak} after an exercise-based intervention (WMD = 2.90 $ml.kg^{-1}.min^{-1}$; 95% CI: 1.16; 4.64) (Jones et al., 2011). In lung cancer patients, preliminary pilot RCTs and cohort studies have also found significant improvements in VO_{2peak} after an exercise intervention (Stefanelli et al., 2013, Jones et al., 2009c, Jones et al., 2007). Altogether, this data constitutes proof or principle that exercise can improve cardiopulmonary fitness in lung cancer patients, which could be used as a means to improve physical functioning and enhance post-operative recovery.

2.5 Health-related quality of life

Quality of life is a subjective and multidimensional concept that refers to an individual's physical health, perception of symptom distress, functional status and ability to carry out activities of daily living (Anant et al., 2005). HRQoL is a serious concern for lung cancer patients. Although traditionally post-operative outcomes and long-term survival have been robust indicators of success after treatment for lung cancer, from the patient's point of view those statistics deal inadequately with important functional issues that may arise after cancer treatments (Balduyck et al., 2011). In particular, for patients undergoing lung surgery, reduction in self-care and limited physical function may be more worrisome issues than post-operative complications (Cykert et al., 2000).

There are multiple instruments designed to evaluate HRQoL in the context of health and illness. Several health profiles are used to assess HRQoL in people with cancer, which are further classified into generic and disease-specific. Among the latter, the European Organization for Research and Treatment of Cancer's (EORTC) QLQ-C30 questionnaire is one of the most widely administered for evaluating HRQoL in cancer populations. This questionnaire covers general aspects of quality of life as well as symptom prevalence and symptom distress in a variety of cancer patients. In 1994, a subscale of 13 items (the LC-13) was added to specifically evaluate lung cancer symptomatology and side effects derived from conventional chemo- and radiotherapy in this population (Bergman et al., 1994). The Functional Assessment of Cancer Therapy (FACT) is another disease-specific instrument for measuring HRQoL in patients with cancer, which also includes a lung cancer module (FACT-L). On the other hand, there are other generic instruments that were designed to evaluate HRQoL in a broader sample of individuals. The Short Form 36 Health Survey (SF-36), developed in 1992, is a self-administered questionnaire that includes 36 items evaluating eight major health domains, which are then further summarized into two major

categories (the Physical and Mental Component Summaries (PCS and MCS, respectively)) to provide a wider overview of physical and psychological status (Ware and Sherbourne, 1992).

Studies have shown that individuals with lung cancer exhibit low levels of HRQoL across the lung cancer continuum, from the time of diagnosis to active treatment and post-treatment. Several investigations have shown that self-reported quality of life for newly diagnosed lung cancer patients is below normative data (Granger et al., 2014, Coats V, 2013, Moller and Sartipy, 2010, Möller and Sartipy, 2012) and declines further during and after treatment (Dean et al., 2013, Paull et al., 2006, Koczywas et al., 2013), especially after major surgical resection (Kenny et al., 2008, Ilonen et al., 2010, Handy Jr et al., 2002).

Treatment efficacy in lung cancer should then be measured by its effects on quantity of life but also quality of life (Ediebah et al., 2014). Performance status and HRQoL have been identified as strong predictors of overall survival, both in patients undergoing surgery and chemotherapy/radiotherapy (Li et al., 2012, Ediebah et al., 2014, Pompili et al., 2013, Lemonnier et al., 2014). Several studies have found a correlation between preoperative PCS and overall survival in patients with NSCLC (Pompili et al., 2013, Brunelli et al., 2013b, Moller and Sartipy, 2010). In particular, Pompili et al. found that a preoperative PCS $\leq$ 50 was associated with a significant reduction in overall survival in patients with stage I NSCLC (HR = 2.3; 95% CI: 1.44–4.4; P=0.01). Also, Ediebah et al. found that for every 10-point improvement in physical function in the EORTC-CQC at baseline, there was a 7% reduction in the risk of lung cancer death (HR = 0.93; 95% CI: 0.88, 0.98). Post-operative PCS and MCS have also been found to predict long-term survival in patients with lung cancer (HR for a 10-point increment 0.649; 95% CI: 0.45, 0.937 and 0.701; 95% CI: 0.519, 0.946 for the PCS and MCS, respectively (Moller, 2012)). Furthermore, having an MCS below normative data six months after surgery was significantly associated with a higher risk of death (HR = 2.90; 95% CI: 1.18, 7.17). These findings are genuinely important since

mental and physical well-being are potentially modifiable factors to target in the perioperative period of lung cancer and could lead to significant improvements in overall and cancer-specific survival.

CHAPTER THREE: PERIOPERATIVE MANAGEMENT IN PATIENTS UNDERGOING LUNG RESECTION

3.1 Preoperative evaluation of the lung resection candidate

As previously mentioned, lung resection surgery provides the best chance of survival in individuals with NSCLC (Ilonen et al., 2011, Benzo et al., 2007, Toker et al., 2007). However, the side effects associated with lung surgery have been extensively acknowledged and may influence the decision-making process regarding the appropriate treatment. Patients considered at high risk of experiencing severe physical and psychological deconditioning after surgery might be considered unfit to undergo standard lobectomy and offered sublobar resection or even non-surgical treatment, which would reduce their long-term survival. The potential negative effects associated with lung resection may be triggered by the patient's clinical status, the surgical features (duration, blood loss, etc.) and/or the suitability of the perioperative measures adopted. Individuals with lung cancer are frequently old and with a long history of smoking, which predisposes them to severe chronic co-morbidities such as COPD and cardiovascular disorders that significantly increase the risk of post-operative complications. The chest trauma caused by the surgery along with the anaesthetic agents administered can lead to hypoventilation during the first 24 hours, reduce coughing and increase sputum retention, leading to respiratory complications (Escribano Martin et al., 2009). For these reasons, patients with confirmed or suspected early-stage lung cancer who are candidates to undergo surgery with curative intent should be submitted to a comprehensive evaluation of the potential risks associated with surgery and the results must be counterbalanced against the long-term survival if an oncological suboptimal treatment is chosen (Brunelli et al., 2013a).

There are three major pillars in the physiologic preoperative evaluation of the lung resection candidate: evaluation of the cardiac risk, assessment of the pulmonary function and measurement of the cardiorespiratory fitness.

3.1.1 Cardiovascular risk

The risk of major cardiovascular events after lung resection surgery has been estimated to be between 2 and 3 % (Brunelli et al., 2011). The main international associations recommend the use of the Recalibrated Thoracic Revised Cardiac Risk Index (ThRCRI) as the preferred risk-scoring tool for assessing cardiac risk in patients undergoing non-cardiac procedures (Brunelli et

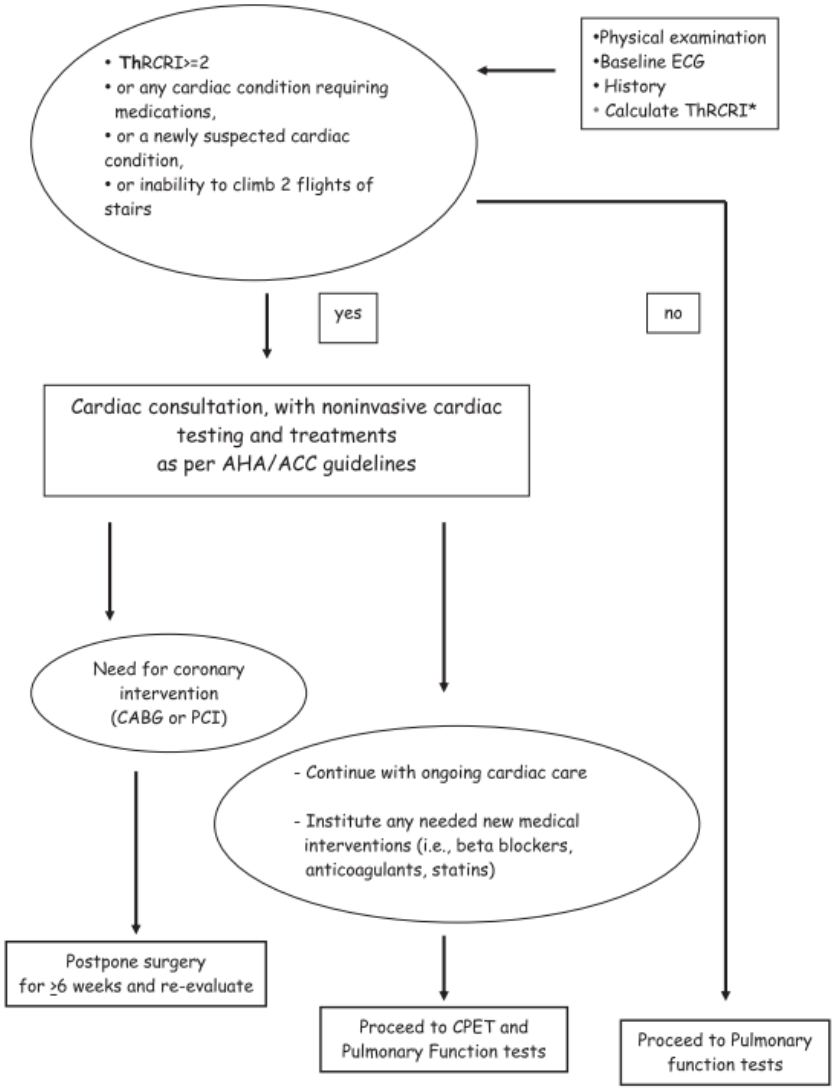


Figure 3.1: Thoracic Revised Cardiac Risk Index (ThRCRI); Brunelli et al., 2013a.

al., 2013a) (Figure 3.1). This assessment tool stratifies patients into four categories: 0 (A), 1–1.5 (B), 2–2.5 (C) and above (D) (Choi and Mazzone, 2015). A ThRCRI score of two or more should be derived in a cardiology consultation for further evaluation before lung resection surgery (Choi and Mazzone, 2015).

3.1.2 Pulmonary function

Spirometry, and particularly preoperative FEV_1, has traditionally represented the key test in the functional evaluation of the lung resection candidate (Brunelli et al., 2013a). Several cut-off values have been proposed in the literature but a preoperative $FEV_1 < 60\%$ was found to be the most accurate for predicting post-operative complications after lung resection surgery (Licker et al., 2006). Nevertheless, the ability of the FEV_1 to predict post-operative morbidity has been questioned in the literature after patients with $FEV_1 \leq 40\%$ of predicted have been operated on, with relatively low mortality and acceptable post-operative outcomes. In light of this, the post-operative predicted (PPO) FEV_1 has been proposed as a more precise alternative to preoperative FEV_1 for predicting post-operative outcomes after lung surgery and therefore it should be calculated in patients with $FEV_1 < 80\%$ according to the international guidelines (Brunelli et al., 2013a). In a retrospective study examining the role of PPO FEV_1 in predicting post-operative respiratory complications, Alam et al. demonstrated that the OR for developing PPCs increased as the PPO FEV_1 decreased (with a 10% increase in morbidity for every 5% decrease in PPO lung function) (Alam et al., 2007). Generally, a PPO $FEV_1 > 40\%$ is considered to be safe for performing lung resection surgery; however, what happens to patients under this threshold is not so clear. Multiple studies have suggested that individuals with poor pulmonary function could safely undergo lung surgery by means of a sublobar resection with similar short- and long-term outcomes (Brunelli et al., 2013a, Brunelli et al., 2009b, Solli et al., 2003). As a matter of fact, in those patients with a $FEV_1 < 70\%$, PPO FEV_1 is not even considered a reliable predictor of complications since

individuals with poor lung function experience only a mild deterioration in FEV_1 compared to non-obstructed patients due to the so-called 'lung volume reduction effect' (Brunelli et al., 2002, Brunelli et al., 2009b, Brunelli et al., 2007a). In contrast to patients with normal pulmonary function, those with severe airway obstruction can even experience an improvement in their FEV_1 after lung resection (Brunelli et al., 2007a). In addition, although PPO FEV_1 may be accurate for estimating the residual definitive FEV_1 three to six months after lung resection, it appears that it actually overestimates the FEV_1 during the first post-operative days, when most of the complications occur (Brunelli et al., 2007a, Varela et al., 2007). All these findings suggest that pulmonary function should not be used alone as a stratification tool to select patients for thoracic surgery.

The diffusing capacity of the lung for carbon monoxide (D_LCO) is a valuable measurement for alveolar oxygen exchange in the assessment of the lung resection candidate (Brunelli et al., 2009b). Calculation of PPO D_LCO is currently recommended by the main guidelines for patients with either preoperative FEV_1 or $D_LCO < 80\%$. A PPO D_LCO of less than 40% is consensually regarded as the cut-off to distinguish between normal- and higher-risk resection patients (Brunelli et al., 2009b). Both D_LCO and PPO D_LCO have shown a good correlation with pulmonary complications, better than PPO FEV_1. A preoperative $D_LCO < 60\%$ has been associated with a 25% risk of mortality and 40% risk of pulmonary morbidity (Ferguson et al., 1988). Similarly to PPO FEV_1, PPO D_LCO has also been shown to correlate significantly with the risk of pulmonary complications and mortality after lung resection, even in patients with otherwise normal pulmonary function ($FEV_1 > 80\%$) or without COPD (Ferguson and Vigneswaran, 2008). According to some observational studies, at least 40% of individuals may have an abnormal D_LCO with an otherwise normal FEV_1. Consequently, measurement of D_LCO has been systematically recommended in the

preoperative evaluation of the lung resection candidate regardless of the preoperative FEV_1 (Brunelli et al., 2013a).

3.1.3 Cardiorespiratory fitness

Patients at moderate to high risk of post-operative complications according to their pulmonary function should undergo further examinations before being submitted to lung resection surgery. The European Respiratory Society and the European Society of Thoracic Surgeons (ERS/ESTS) guidelines recommend that all patients with a preoperative FEV_1 or D_LCO <80% should undergo exercise testing to measure their VO_{2peak} (Figure 3.2) (Brunelli et al., 2009b). The American College of Chest Physicians (ACCP), however, advocates that for patients with a PPO

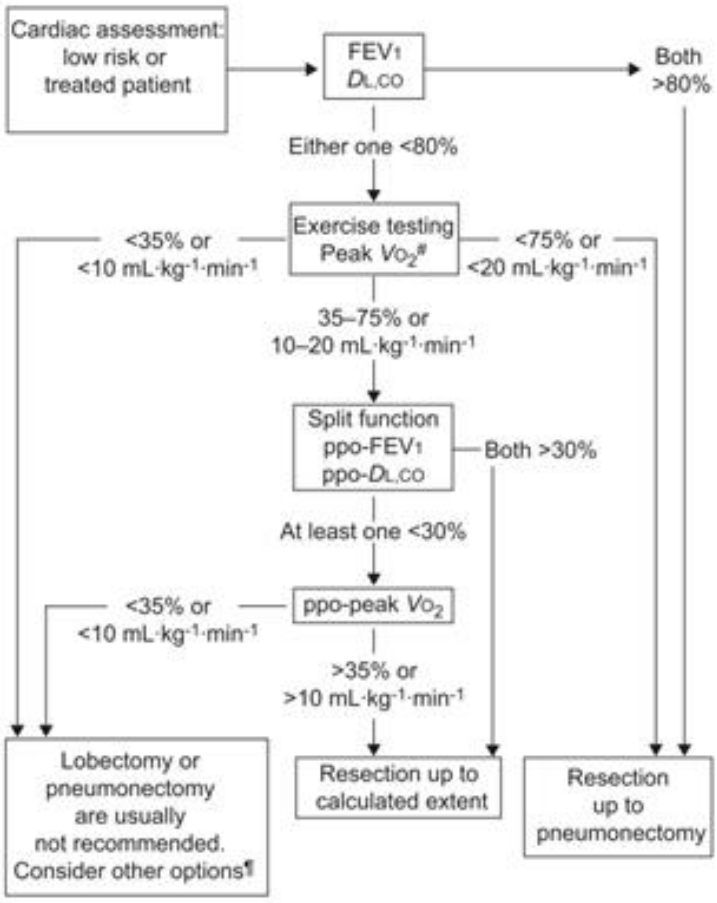


Figure 3.2: ERS/ESTS algorithm for assessment of cardiopulmonary reserve before lung resection in lung cancer patients; Brunelli et al., 2009.

FEV_1 or D_LCO of between 30 and 60 % a low-technology exercise testing is enough to estimate their cardiopulmonary fitness while those with a pulmonary function lower than 30% should perform a high-standardized cardiopulmonary exercise testing with direct VO_{2peak} measurement (Choi and Mazzone, 2015, Brunelli et al., 2013a) (Figure 3.3).

Cardiopulmonary exercise testing (CPET) is the gold standard for assessing exercise capacity both in healthy individuals and people with chronic diseases (Jones, 2011). CPET is a sophisticated physiologic testing technique that includes recording the exercise electrocardiogram, heart rate response to exercise, minute ventilation and oxygen uptake per minute among other physiological responses to strenuous exercise (Brunelli et al., 2013a). The aim of the test is to stress the whole cardiopulmonary/systemic oxygen delivery system and estimate the physiological reserve that may be available after surgery (Brunelli et al., 2009b).

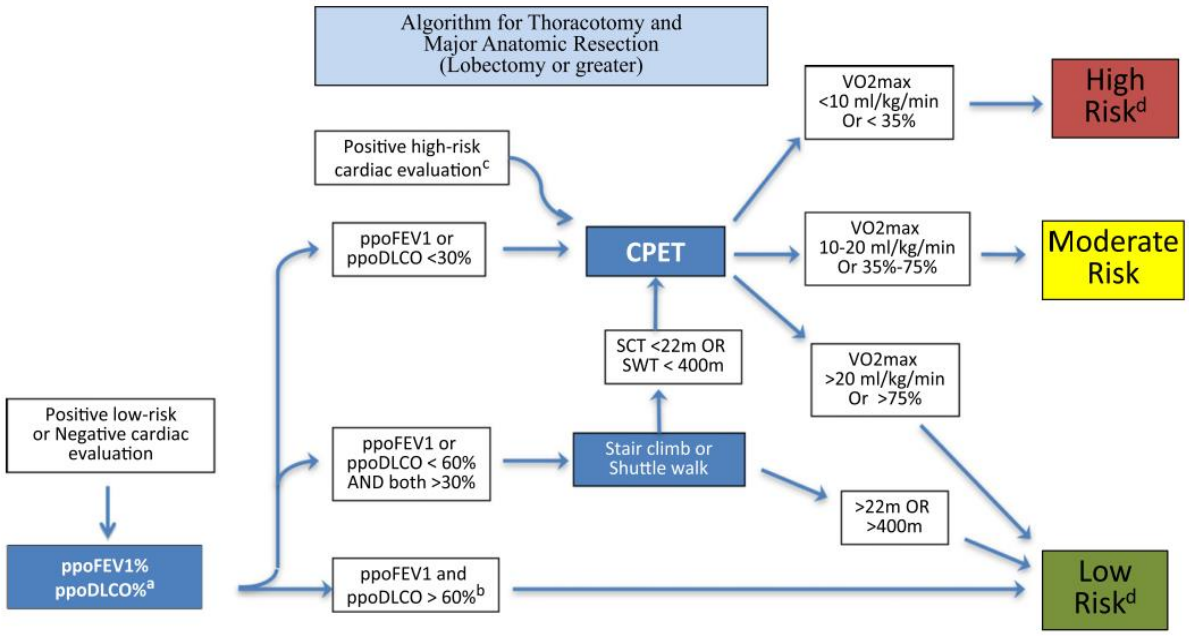


Figure 3.3: ACCP algorithm for thoracotomy and major anatomic resection (lobectomy or greater); Brunelli et al., 2013.

It is assumed that the test simulates the physiological stress experienced after surgery and therefore patients who are unable to perform adequately in the exercise test may respond similarly to surgical stress or adverse post-operative events (Brunelli et al., 2009b). A VO_{2peak} of 20 ml/kg^{-1}/min^{-1} (or 75% of predicted) has been established as safe for undergoing lung resection up to a pneumonectomy (Brunelli et al., 2009b, Brunelli et al., 2013a). Patients with a VO_{2peak} of between 35 and 75 % of predicted are considered to be at some risk of post-operative mortality and morbidity and those under 35% (or 10 ml/kg^{-1}/min^{-1}) should be offered alternative options to surgery due to the high risk of post-operative death and long-term disabilities. In a meta-analysis of the relationship between cardiopulmonary fitness and post-operative complications, Benzo et al. found that those who experienced post-operative complications after surgery had a lower mean preoperative VO_{2peak} than those without complications, both in ml/kg^{-1}/min^{-1} and percentage of predicted (MD = 3; 95% CI: 2–4.1 and MD = 8.1; 95% CI: 3.3–12.8, respectively) (Benzo et al., 2007). In an observational study conducted in 204 patients undergoing lung resection, Brunelli et al. found that the mortality rate in those patients with a VO_{2peak} < 12 ml/kg^{-1}/min^{-1} was tenfold higher than those with a peak VO_{2peak} > 12 ml/kg^{-1}/min^{-1}. Therefore, they concluded that the best cut-off value for pulmonary complications was 12 ml/kg^{-1}/min^{-1} or 40% of predicted (Brunelli et al., 2009a). In a recent propensity-matched comparison of patients undergoing thoracic surgery by VATS or open lobectomy, morbidity and mortality were also significantly higher in those patients with a VO_{2peak} < 15 mml/kg^{-1}/min^{-1} (morbidity: 35% vs 31% and mortality: 7.6% vs. 3.7%, respectively; p <.05) (Begum et al., 2015).

The main inconvenience with CPET is the difficulty in performing it in most centres due to the sophisticated equipment required and the need for experienced and trained personnel to conduct the test. In those cases, field tests have been proposed as an alternative to conventional CPET, and they have shown a good correlation with the measured VO_{2peak} in populations with chronic diseases

such as COPD. The Stair Climb Test (SCT) has been successfully used as a surrogate for CPET in the preoperative evaluation of the lung resection candidate (Brunelli et al., 2013a). This inexpensive and easy-to-administer test was first used in the preoperative setting of thoracic surgery in 1968 and has proven to effectively discriminate patients at risk of developing post-operative complications (Wilson, 1997). In a prospective cohort of 640 patients who underwent lung resection surgery, Brunelli et al. found that the altitude reach with the SCT was a strong independent predictor of post-operative morbidity and mortality and increased hospital costs (Brunelli et al., 2012). Furthermore, patients who were unable to climb more than 12 m (approximately two flights of stairs) had a 13-fold increase of mortality than those who climbed 14 m or more. Other factors that have proved to be associated with a higher rate of post-operative complications are the speed of the test, heart rate difference pre- to post-test and oxygen desaturation during the performance (Dong et al., 2014). A desaturation greater than 4% has been associated with an increased risk of perioperative complications, including respiratory failure, intensive care unit (ICU) admission, prolonged hospital stay, home oxygen requirement and mortality (Toker et al., 2007, Dong et al., 2014). Low preoperative oxygen saturation at rest has also been acknowledged as an independent predictor of post-operative morbidity (Toker et al., 2007). The main issue with the SCT is the lack of standardization. The height of the step, number of steps per flight and the speed in conducting the SCT can drastically influence the results obtained. In a study conducted by Bernasconi et al., the SCT was only significantly correlated with the measured VO_{2peak} in those patients who were able to climb the equivalent of 20 m with an average speed of $\geq$ 15 m/min (Bernasconi et al., 2012). Finally, heart rate recovery following the SCT has also been suggested as another factor to pay attention to when assessing cardiorespiratory fitness. Dong et al. found that post-operative complications were more common in those patients

who had a heart rate difference pre-post SCT of less than 55 beats per minute than in those with more than 55 (35.1% vs. 18.1%, respectively) (Dong et al., 2014).

Other common field tests have been suggested as an alternative to CPET in the preoperative evaluation of thoracic surgery. The Incremental Shuttle Walk Test (ISWT) is a standardized, external-pace test that has shown a good correlation with VO_{2peak} in people with chronic respiratory disorders (van Tilburg et al., 2009, Win et al., 2006). During the test, patients must complete as many shuttles as possible between two cones separated by 10 metres at an incrementally progressive speed. In a study comparing four common field tests, Granger et al. found that the ISWT has moderate criterion validity with the CPET VO_{2peak} and was the most promising field test for stratifying patients in the perioperative setting of lung cancer (Granger et al., 2015a). It has been reported that 25 shuttles are equivalent to a VO_{2peak} of approximately 10 $ml/kg^{-1}/min^{-1}$ and thus this has been established as the cut-off for a higher risk of post-operative mortality and morbidity (van Tilburg et al., 2009, Brunelli et al., 2012). On the other hand, a total distance of 450 metres is considered equivalent to a $VO_{2peak} > 15$ $ml/kg^{-1}/min^{-1}$ and therefore is considered as being safe for performing surgery. However, the role of the ISWT in predicting post-operative complications is limited and is not supported by the current evidence. Erdogan et al. found no statistically significant correlation between the risk of post-operative complications and the ISWT in 20 patients undergoing lung cancer surgery (Erdogan et al., 2013). Win et al. found no significant difference either in the endurance or Incremental Shuttle Walk Test between those patients with and without post-operative complications (Win et al., 2004).

The most widespread field test for assessing functional exercise capacity in individuals with chronic respiratory diseases including lung cancer is the 6MWT (Granger et al., 2013a). The test has shown good validity and reproducibility and a good correlation with VO_{2peak} (Nakagawa et al., 2014), being equivalent to approximately 15 $ml/kg^{-1}/min^{-1}$ when a distance of 450 metres is reached

(van Tilburg et al., 2009). Although the test has shown little validity with the CPET VO_{2peak} in patients with lung cancer (Granger et al., 2015a), it has demonstrated the ability to predict more accurately post-operative complications after lung resection surgery. For instance, one study found that those individuals who could not reach 500 metres in the preoperative assessment for a lobectomy were at higher risk of developing post-operative complications and a prolonged hospital stay (Marjanski et al., 2015). In another retrospective study conducted in Japan, the authors concluded that an oxygen saturation < 91% at baseline or a decrease in oxygen saturation of > 4% during the 6MWT were both correlated with a VO_{2peak} of < 15 $ml/kg^{-1}/min^{-1}$ and therefore could be used as a replacement for CPET in the absence of more sophisticated equipment. In a retrospective analysis, Ha et al. reported that an impaired heart rate recovery (defined as a reduction of less than 18 beats in one minute) after a 6MWT was associated with an increase in post-operative cardiopulmonary complications in patients who underwent lung cancer surgery (Ha et al., 2015). Altogether, these data suggest that field tests are a powerful alternative for selecting potentially operable lung cancer patients with borderline lung function. However, for those unable to reach the proposed cut-offs, formal CPET with VO_{2peak} assessment must be undertaken prior to making any final decision (Choi and Mazzone, 2015).

3.1.4 Development of aggregate scores to predict post-operative outcomes

None of the previous measurements are enough to predict the risk of post-operative complications alone (van Tilburg et al., 2009). As a result, researchers have developed aggregate scores to quantify more effectively the risk of post-operative complications. A predictive model can define a composite of complications or may focus on a particular complication due to its clinical relevance and/or frequency (for instance, pneumonia or respiratory failure). For example, Falcoz et al. developed a risk prediction model (the Thoracoscope) using data from 15,183 patients that include age, sex, dyspnoea score, ASA score, performance status, priority of surgery (elective or

urgent), diagnosis (malignant or benign), procedure class and co-morbid disease as predictive factors of post-operative mortality and morbidity (Falcoz et al., 2007). The model was found to be extremely reliable and accurate for predicting in-hospital mortality, showing an almost perfect correlation between the expected and the observed deaths, thus it is currently the most common assessment tool for predicting post-operative complications. In a retrospective analysis, Amar et al. found that PPO DLCO and the need for neoadjuvant chemotherapy could also predict post-operative complications with moderate accuracy (Amar et al., 2010). Finally, Agostini et al., in a cohort of 234 patients undergoing thoracic surgery, reported that advanced age (≥ 75 years old), BMI ≥ 30, American Society of Anesthesiologists (ASA) score ≥ 3, smoking history and COPD were independent risk factors for developing PPCs. Finally, Simonsen et al., in a retrospective analysis of 7,479 patients undergoing thoracic surgery for lung cancer, found that advanced age > 80 years, obesity, history of previous pneumonia, COPD, alcoholism and atrial fibrillation were risk factors for post-operative pneumonia (Simonsen et al., 2015).

In summary, although predicted models and algorithms are useful in assessing the perioperative risk of lung resection, an individualized, comprehensive evaluation should be provided for all patients being considered for lung resection surgery in order to guarantee the best possible outcomes. Finally, it is worthy noting that the recommendations described in this chapter have been made for patients undergoing open thoracotomies. It is unclear whether the same guidelines are encouraged in patients undergoing minimally invasive techniques such as VATS or robotic thoracic surgery. Preliminary studies have shown controversial results. Zhang et al., using a prospective cohort of patients undergoing lobectomy by VATS or open thoracotomy, demonstrated that in both procedures, PPO D_LCO and PPO FEV_1 were good predictors of post-operative complications (Zhang et al., 2015). However, in a retrospective study, neither a preoperative FEV_1 nor D_LCO < 60% were found to be good predictors of post-operative

complications in patients undergoing VATS (Berry et al., 2010). The role of cardiopulmonary fitness and VO_{2peak} is also not clear, but a recent study conducted using the ESTS database found that in patients undergoing VATS, low VO_{2peak} was not associated with an increased surgical risk (Begum et al., 2015). Further research is needed in this new surgical context to elucidate which factors could influence the post-operative trajectory in patients undergoing VATS.

3.2 Impact of lung resection surgery on patients' outcomes

3.2.1 Post-operative mortality and morbidity

The most common reported outcomes after thoracic surgery are hospital morbidity and mortality (Donington et al., 2012). Mortality following lung resection is affected by the type of operation performed, the presence of co-morbidities, the expertise of the surgeon, the volume of the institution and the stage of the disease (Shaw et al., 2008). Mortality after lung surgery has been steadily declining over the past decade (Shaw et al., 2008, Rosen et al., 2014) and is currently 3.7 to 11.5 % for pneumonectomy and 1–5 % for lobectomy (Rosen et al., 2014, Shaw et al., 2008, Otake et al., 2011). However, for patients with co-morbid disease, advanced age or poor cardiopulmonary fitness, mortality has been reported to be as high as 60% (Brunelli et al., 2013a). Respiratory failure is the leading cause of mortality after lung resection surgery (Donington et al., 2012). The current established factors associated with increased in-hospital mortality are male gender, older age, co-morbidities, surgery on the right side of the lung and a more extensive procedure (Strand et al., 2007). In a large series of patients operated on for lung cancer in the USA, a higher mortality rate was found among right-side pneumonectomies without neoadjuvant therapy (12.1%) (Rosen et al., 2014). Mortality also seems to be slightly higher in those patients undergoing sublobar resections compared to standard lobectomy, probably due to pre-existing co-morbidities and/or low cardiopulmonary reserve (Rosen et al., 2014, Shaw et al., 2008). In addition, highly experienced thoracic surgeons, high hospital case volume and teaching status are also associated

with lower 30-day mortality rates (Shaw et al., 2008, Rosen et al., 2014). However, perioperative mortality might not be an adequate quality indicator for lung cancer resection after all. In a study comparing 30-day mortality with 90-day mortality, authors found that whereas the former was fairly low (3.69%), the latter was almost double (Hu et al., 2014). In most cases, death was due to the primary cancer, but coexistent COPD, cardiovascular diseases, renal failure and infection were also common causes of mortality in this period. In the multivariate analysis, a preoperative diagnosis of congestive heart failure was the most statistically significant predictor of 90-day mortality (Hu et al., 2014). These results are consistent with another similar study comparing the 30- and 90-day mortality according to hospital volume, where the authors also reported that the latter was almost double the former (Pezzi et al., 2014). This data confirms that the current measures of in-hospital or 30-day mortality rates underestimate the actual mortality risk after lung resection surgery.

Despite the reduction in in-hospital and 30-day mortality rates, morbidity is still very frequent after thoracic surgery (Donington et al., 2012). In particular, post-operative pulmonary complications (PPCs) are the leading cause of death and increased hospital cost in cardiothoracic and non-cardiothoracic surgery (Cassidy et al., 2013, Sabate et al., 2014). According to the National Surgical Quality Improvement Programme, the attributable cost of PPCs was more than 52,000 US dollars per patient (Dimick et al., 2004). The incidence of PPCs ranges from 2 to 40 % depending on the type of procedure, the extent of resection, the surgical approach and the patient baseline status (Sabate et al., 2014, Cassidy et al., 2013, Begum et al., 2015). Furthermore, the lack of standardization in the definition highlights the disparities found across studies in the PPC rates. In theory, the term 'post-operative pulmonary complication' encompasses any pulmonary abnormality occurring during the post-operative period producing an identifiable disease or dysfunction that is clinically significant (Agostini et al., 2011). Under the umbrella of PPCs are

included events of different severity and management such as respiratory failure, reintubation, weaning failure, pneumonia, atelectasis, bronchospasm, pneumothorax, pleural effusion and various forms of upper-airway obstruction (Sabate et al., 2014). Several evaluation tools have been proposed for accurately assessing the frequency and severity of post-operative complications after thoracic surgery. In 2008, Reeve et al. developed the Melbourne Group Scale (MGS), which was primarily designed to identify those pulmonary complications more likely to be prevented by a physiotherapy intervention. A positive score of four points out of eight was considered to be a positive diagnosis of PPC (Reeve et al., 2008). Other common scales used to assess PPCs are the Brooks-Brunn Score and the Gosselink Score (Table 3.1). In a prospective study comparing the three scoring systems, the incidence of PPC according to the MGS, the Gosselink Score and the Brooks-Brunn score was 13, six and 39 %, respectively. The clinical incidence of PPC as described in the cohort was 12%, thus the MGS was shown to have the strongest correlation and the highest specificity and sensitivity (99 and 100 %, respectively), demonstrating large superiority (Agostini et al., 2011). Finally, the ESTS has published a special report in an attempt to standardize the definition of the most common PPCs after thoracic surgery (Fernandez et al., 2015). However, unlike the previous instruments, this statement only provides a list of definitions and therefore cannot be used to assess severity and frequency of PPCs.

Table 3.1: Post-operative pulmonary complications criteria according to three common scales; Reeve et al., 2011

Melbourne Group Scale	Gosselink Score	Brooks-Brunn Score
Temperature >38 °C	Temperature >38 °C	Temperature ≥38 °C
White cell count >11.2 or respiratory antibiotics	White cell count >12 (or positive microbiology)	
Physician diagnosis of pneumonia or chest infection		Physician documentation of atelectasis or pneumonia
Chest X-ray report of atelectasis/consolidation	Chest X-ray score 0: No abnormality	Chest X-ray documentation of atelectasis/new infiltration
Production of purulent (yellow/green) sputum differing from preoperative	1: Minor unilateral atelectasis 2: Minor bilateral atelectasis	New cough/sputum
Positive signs on sputum microbiology	3: Major unilateral atelectasis or infiltration	
SpO_2 <90% on room air	4: Major bilateral atelectasis or infiltration	
Re-admission to or prolonged stay (over 36 hours) on the intensive care unit/high dependency unit for respiratory problems		
		Abnormal breath sounds compared with baseline
PPC = four or more positive variables	PPC = Chest X-ray score of 3 or 4 and positive in other two variables	PPC = two variables positive for 2 consecutive days

SpO_2 = percutaneous % of haemoglobin oxygen saturation.

Brooks-Brunn JA. Chest 1997;111:564–71.
Gosselink R *et al.* Crit Care Med 2000;28:679–83.
Reeve JC *et al.* J Cardiothorac Surg 2008;3:48.

PPCs are a major concern both for the patient and for the health system. In the immediate post-operative period, PPCs are responsible for a prolonged hospital stay and increased health-care costs, delaying the patient's recovery to full activity (Stephan et al., 2000, Varela et al., 2006, Branson, 2013). In the long term, they can also affect physical functioning and HRQoL. In a cross-sectional study investigating the correlates of physical activity among long-term lung cancer survivors, Coups et al. found that those patients who had had post-operative complications were less likely to engage in leisure physical activity (Coups et al., 2009). Furthermore, post-operative complications can also impact on overall and disease-free survival. In a retrospective analysis performed in 2010 by Rueth et al., the authors found that among those patients who had at least one post-operative complication, the five-year cancer-specific and overall survival was lower than in patients with no complications (p <.001) (Rueth et al., 2011). The same tendency was found when comparing patients with and without pulmonary complications alone (overall survival 52.7% vs. 68.9%, respectively, p <.001). These findings were maintained even after adjusting for confounding variables, thereby highlighting the important role of assessing perioperative risk in surgical lung cancer patients. Similar results have been reported for some particular complications; for instance, Simonsen et al. found that those patients diagnosed with post-operative pneumonia after lung cancer surgery had decreased disease-free survival compared with those without a clinical diagnosis of pneumonia (Simonsen et al., 2015).

3.2.2 Pulmonary function

Alterations in pulmonary function and respiratory mechanics are frequent after lung resection surgery and can substantially impact on a patient's immediate recovery and/or quality of life (Choi and Mazzone, 2015). Pulmonary function decreases dramatically by around 30–50 % during the first post-operative days compared to baseline (Donington et al., 2012). The loss of pulmonary function is influenced by several factors, but the most significant is the extent of the

resection. For instance, a pneumonectomy can decrease the FEV_1 by 34–36 %, a lobectomy by 9–17 % and a segmentectomy by 5% (Choi and Mazzone, 2015). The surgical approach also influences changes in pulmonary function after surgery, with minimal-access techniques proving superior to traditional approaches for preserving pulmonary function and hastening recovery (Che et al., 2013, Ueda et al., 2006, Endoh et al., 2010).

The vast majority of the literature suggests that it takes approximately three to six months for the pulmonary function to return to baseline values but some discrepancies have been found. Early studies found a persistent reduction in FEV_1 beyond this time frame (Bolliger et al., 1996, Nezu et al., 1998, Miyazawa et al., 1999, Nomori et al., 2003, Wang et al., 2006, Kushibe et al., 2008a), which could last up to two years after lobectomy (Miyazawa et al., 1999) and beyond five after pneumonectomy (Deslauriers et al., 2011, Vainshelboim et al., 2015). Conversely, more recent investigations have found a return to baseline ($\geq$ 80% predicted) within the first three months (Brunelli et al., 2007b, Win et al., 2007, Saito et al., 2014), particularly after VATS (Che et al., 2013, Ueda et al., 2006). Along with FEV_1 and FVC, D_LCO and respiratory muscle strength could also be significantly impaired immediately after surgery and persist beyond the first post-operative month (Laurent et al., 2013). The long-term implications of pulmonary function loss have not been examined in the literature but it is likely that they can affect a patient's HRQoL and functional capacity.

Table 3.2: Long-term effects of surgical resection on pulmonary mechanics

Study	Participants	Extent of resection	Outcomes	Time of evaluation	Results
Pelletier, 1990	47 NSCLC[i]	Lobectomy (L) and pneumonectomy (P)	FEV_1 MIP MEP	2 months post-surgery	L: FEV_1 ↓ from baseline to post-surgery 89±22 to 74±10 P: FEV_1 decreased from 79±22 to 53±11 No changes in MIP and MEP
Bollinger, 1996	68 patients after lung resection	Lobectomy (L) and pneumonectomy (P)	FVC FEV_1	3 and 6 months post-surgery	L: FVC ↓ 7.3% and FEV_1 ↓ 8.8% at 6 months P: FVC ↓36.2% and 34% at 6 months
Nezu, 1998	82 lung cancer patients	Lobectomy (L) and pneumonectomy (P)	FEV_1 VC	3 and 6 months post-surgery	L: FEV1 ↓ 11.2% and VC ↓ 11.6% at 6 months P: FEV1 ↓ 36.1% and VC 40.7% at 6 months
Nugent, 1999	106 lung cancer patients	Thoracotomy alone, wedge resection, lobectomy (L) and pneumonectomy (P)	FEV_1 FVC	3 and 6 months post-surgery	L: FVC ↓ 11.4% but no changes in FEV1 P: FEV_1 and FVC significantly decrease by 26.1% and 32.2% respectively
Miyazawa, 1999	8 lung cancer patients	Lobectomy or bilobectomy	FEV_1 FVC VC D_LCO	6 months and up to 4 years	VC ↓ from 3.47±0.5 to 2.41±0.34 at 6 months and 2.67±0.46 at 4 years FVC ↓ from 3.26±0.63 to 2.31±0.3 and 2.62±0.41 respectively FEV_1 ↓ from 2.19±0.56 to 1.8±0.47 and 1.88±0.48 at 4 years D_LCO ↓ from 85.46.9% to 79.5% at 3 months but increased to 106.9±14.7 in the late postop
Nomori, 2003	112 lung cancer patients	Lobectomy	FEV_1 VC	1, 2, 4, 12 and 24 weeks post-surgery	VC values at 6 months ranged from 88.3±10.6% of baseline after VATS to 74.1±14.1% after standard thoracotomy
Bobbio, 2005	11 NSCLC	Lobectomy and bilobectomy	FEV_1 TLC D_LCO	3 months	FVC, FEV_1 and D_LCO did not decrease after surgery (p >.05); TLC ↓ from 120% of predicted to 99%

Wang, 2006	28 undergoing LRS	Lobectomy, pneumonectomy and wedge resection	FEV_1	12 months post-surgery	After 1 year, FEV_1 ↓ from 86±18 of predicted value to 74±15% (p <.001)
Brunelli, 2007	200 patients with lung cancer	Lobectomy (L) and pneumonectomy (P)	FEV_1 DLCO	Discharge, 1 and 3 months post-surgery	L: FEV_1 79.5% and 84% of the preoperative values at 1 and 3 months respectively; D_LCO was 81.5% and 88.5% of baseline at 1 and 3 months respectively P: FEV_1 was 65% and 66% of baseline 1 and 3 months respectively; DLCO was 75% at 1 month and 80% at 3 months.
Win, 2007	110 patients with lung cancer	Lobectomy (L) and pneumonectomy (P)	FEV_1 FVC	1, 3 and 6 months	L: FEV_1 was 75% and 85% of baseline at 1 and 6 months while FVC was 69% and 81% respectively P: FEV_1 was 61% and 65% of baseline at 1 and 6 months respectively while FVC was 56% and 61% respectively.
Nagamatsu, 2007	18 NSCLC	Lobectomy	FEV_1 FVC VC	1, 3, 6 and 6 months post-surgery	FVC was 78.5%, 81.6% and 82.7% of baseline at 3, 6 and 12 months respectively; VC was 82.6% of baseline at 12 months FEV_1 was 83.6% and 82.4% at 6 and 12 months respectively
Kushibe, 2008	106 NSCLC	Lobectomy	FEV_1 FVC	6 – 12 months	FEV_1 ↓ 9.2±16.7 to 14.9±9.8 depending on the lobe resected; FVC ↓ between 8.9±9.9 and 17.3±12.1
Kushibe, 2008	100 individuals with and without COPD	Lobectomy	FEV_1 FVC	6 – 12 months	FVC ↓ 14.6±10.5 in the non-COPD group and between 8.6±16.3 to 11.1 in the severe and moderate COPD groups respectively FEV_1 ↓ 14.7±11.5 in the non-COPD group and 11.6±10.7 in the moderate COPD group but ↑ 4.7±15.8 in the severe COPD group

Deslauriers, 2011	100 lung cancer patients	Pneumonectomy	FEV_1 FVC DLCO	>5 years after surgery	FEV_1 ↓ 44±16% from baseline and FVC ↓ 38±21%. D_LCO was 34±11% reduced comparing to baseline
Saito, 2014	178 I NSCLC	Lobectomy (L) and segmentectomy (S)	FEV_1 VC	1 and 6 months post-surgery	L: at 1 month VC was ↓ 17.5% and FEV_1 15.5%; at 6 months value had reached 80% of baseline S: at 1 month VC was ↓ 11.2% and FEV_1 7%: at 6 month, value had reached 90% of baseline
Kim, 2015	300 NSCLC	Lobectomy and sublobar resection	FEV_1 FVC D_LCO	3 and 12 months post-surgery	L: at 3 months, ↓ in FVC, FEV_1 and D_LCO were 13.9±10.3%, 13.4±9.6% and 14.9±14.2. At 12 months, ↓ were 6.8±10.1, 9.4±10.1 and 9.8±13.4 respectively S: at 3 months, ↓ in FVC, FEV_1 and D_LCO were 4.45±7.3, 4.8±8.7 and 3.4±11.5 respectively. At 12 months, ↓ were 2±8.3, 2.7±8.1 and 0.38±22.1 respectively

[i]NSCLC = Non-Small Cell Lung Cancer; FEV_1 = Forced Expiratory Volume 1 second; MIP = Maximal Inspiratory Pressure; MEP = Maximal Expiratory Pressure; FVC = Forced Vital Capacity; VC = Vital Capacity; D_LCO = Diffusion Capacity of Carbon Monoxide; TLC = Total Lung Capacity; VATS= Video-Assisted Thoracic Surgery.

3.2.3 Exercise and functional capacity

Exercise capacity (cardiorespiratory fitness) refers to the ability to perform a determinate task before reaching the level of exhaustion and is an excellent indicator of an individual's general health. Patients with lung cancer have been shown to exhibit low cardiorespiratory fitness at the time of diagnosis, most likely associated with a long history of smoking, a sedentary lifestyle, advanced age and/or concurrence of cardiovascular and respiratory co-morbidities. Surgery is associated with a decrease in VO_{2peak} during the early post-operative period, but this reduction is especially pronounced after resection of the lung parenchyma, because of the direct disruption of the oxygen cascade (Jones et al., 2009a, Jones, 2011). The pattern of decline in VO_{2peak} after lung resection surgery has been documented in several longitudinal studies, showing a significant decrease during the first weeks followed by a progressive recovery thereafter (Brunelli et al., 2007b, Nugent et al., 1999, Nagamatsu et al., 2007). However, other studies have shown a permanent reduction of up to 25% of VO_{2peak} after lobectomy in NSCLC (Nezu et al., 1998, Win et al., 2007, Kushibe et al., 2008b). Changes in VO_{2peak} after surgery may be influenced by several confounding factors including the extent of the resection and the surgical approach; similarly to what is seen in pulmonary function, individuals who undergo pneumonectomy experience more severe and persistent declines in exercise performance than those undergoing lobectomy or sublobar resection (Vainshelboim et al., 2015).

Functional capacity determined with a field test has the advantages of being easier and cheaper to obtain and reflecting more accurately the patient's ability to perform daily tasks than formal CPET. Functional exercise capacity is compromised after lung resection surgery and therefore can affect a patient's self-care and HRQoL. Several studies have shown a decrease in 6MWT immediately after surgery (Arbane et al., 2011, Nomori et al., 2003, Nomori et al., 2004) that can persist for up to six months (Granger et al., 2014). Again, this decline in physical

performance seems less severe after VATS and consequently performance returns faster to preoperative values (Nomori et al., 2003, Che et al., 2013, Ueda et al., 2006). A few studies have assessed the long-term impact of lung resection on functional capacity and found that somehow lung cancer survivors manage to maintain good levels of physical performance even in the presence of significant impaired pulmonary function, suggesting the development of several adaptive changes (Deslauriers et al., 2011, Vainshelboim et al., 2015).

Table 3.3: Long-term impact of lung resection on (functional) exercise capacity

Study	Participants	Extent of resection	Outcomes	Time of evaluation	Results
Pelletier, 1990	47 NSCLC[i]	Lobectomy (L) and pneumonectomy (P)	W_{max}	2 months post-surgery	L: Mean W_{max} ↓ 12% comparing to baseline P: Mean W_{max} ↓ 26% comparing to baseline
Bollinger, 1996	68 patients after lung resection	Lobectomy (L) and pneumonectomy (P)	VO_{2max}	3 and 6 months post-surgery	L: VO_{2max} ↓ from 18.6±4.8 to 16.9±4.9 (p <.05) at 3 months and increased to 18.8±5.4 at 6 months (p <.05) P: VO_{2max} ↓ from 18.9±5.6 to 14.2±2.5 at 3 months and to 15.1±2.7 at 6 months
Nezu, 1998	82 lung cancer patients	Lobectomy (L) and pneumonectomy (P)	VO_{2max}	3 and 6 months post-surgery	L: VO_{2peak} was ↓ 13.3% at 6 months P: VO_{2peak} was ↓ 28.1 at 6 months
Nuggent, 1999	106 lung cancer patients	Thoracotomy alone, wedge resection, lobectomy (L) and pneumonectomy (P)	VO_{2peak}	6 months post-surgery	L: VO_{2peak} ↓ 1.91 $ml/kg^{-1}/min^{-1}$ (p >.05) P: V_{O2peak} ↓ 6.72 $ml/kg^{-1}/min^{-1}$ (p <.01)
Miyazawa, 1999	8 lung cancer patients	Lobectomy and bilobectomy	W_{max}	6 months and up to 4 years	W_{max} ↓ from 62.5±13.7 to 45.8±10.2 at 6 months and didn't improve thereafter
Bobbio, 2005	11 NSCLC	Lobectomy and bilobectomy	VO_{2max}	3 months	VO_{2max} ↓ from 17.8±3.2 $ml/kg^{-1}/min^{-1}$ to 14.1±3 (p =.003)
Wang, 2006	28 undergoing LRS	Lobectomy, pneumonectomy and wedge resection	VO_{2max} W_{max}	12 months post-surgery	After 1 year, VO_{2max} ↓ from 18.5±4 to 16.3±4.8 (p <.001) and W_{max} from 111±31 Watts to 99.36 (p <.001)
Brunelli, 2007	200 patients with lung cancer	Lobectomy (L) and pneumonectomy (P)	VO_{2peak}	Discharge, 1 and 3 months post-surgery	L: VO_2Peak was 96% and 97% of baseline at 1 and 3 months respectively

					P: VO_{2peak} was 82% and 89% at 1 and 3 months respectively
Win, 2007	110 patients with lung cancer	Lobectomy (L) and pneumonectomy (P)	SWT (%)	1, 3 and 6 months	L: SWT was 70%, 83% and 84% at 1, 3 and 6 months respectively P: SWT was 60%, 71% and 77% respectively.
Nagamatsu, 2007	18 NSCLC	Lobectomy	VO_{2peak}	1, 3, 6 and 12 months	VO_{2peak} was 90% and 97% at 6 and 12 months respectively
Kushibe, 2008	106 NSCLC	Lobectomy	VO_{2peak}	6 – 12 months	VO_{2peak} was reduced between 9.4±12.7% and 18.1±12.3% according to the resected lobe
Kushibe, 2008	100 individuals with and without COPD	Lobectomy	VO_{2peak} W_{max}	6 – 12 months	VO_{2peak} ↓ 9.2±12.1% in the non-COPD group and from 9.7±18.3 to 12.2±10.4 in the severe and moderate COPD groups respectively W_{max} also ↓ 9.4±15.3% in the non-COPD and from 6±34.5 to 9.2±13.3 in the severe and moderate COPD group respectively

[i] NSCLC = Non-small Cell Lung Cancer; W_{max} = Maximal Workload; VO_{2max} = Maximal oxygen consumption; VO_{2Peak} = Peak of oxygen consumption; 6MWT = 6 Minute Walk Test; SWT = Shuttle Walk Test; COPD = Chronic Obstructive Pulmonary Disease; VATS = Video-Assisted Thoracic Surgery.

3.2.4 Muscle strength

There is a relative paucity of literature regarding the potential consequences of pulmonary resection on muscle strength and it is mostly limited to patients in the perioperative period of lung transplantation or lung volume resection surgery (LVRS). Although pulmonary resection does not directly cause muscle deconditioning, reduction in physical functioning and functional capacity after surgery can lead to a decrease in physical activity, muscle atrophy and increased dyspnoea, which further decrease physical functioning, leading to a vicious circle of functional decline. In a longitudinal study conducted by Granger et al., lung cancer patients showed a decrease in muscle strength (quadriceps, rotator cuff and tibialis anterior) both during active treatment and four months post-treatment in comparison to baseline (Granger et al., 2014). In a randomized controlled trial investigating the effects of an early post-operative pulmonary rehabilitation programme on muscle strength after lung cancer surgery, Salhi et al. observed that three months after radical therapy, there were significant reductions in muscle mass and quadriceps muscle force (p <.01) and that at six months, only those patients randomized to the training group had recovered their preoperative values (Salhi et al., 2014). Arbane et al. studied the effects of an early resistance and mobility intervention (starting on post-operative day 1) in post-surgical NSCLC in comparison to the standard care and found that there was a significant group effect (i.e, a decrease in muscle strength in the control group but an increase in the active group at post-operative day five; p <.05) (Arbane et al., 2011). On the other hand, Maruyama et al., in an observational study, looked at the effects of lung resection performed via mini-thoracotomy on respiratory muscle strength, quadriceps force and 6MWT during the first two weeks after surgery and found that only quadriceps force was significantly decreased by post-operative day (POD) 7 but recovered to baseline at POD 14 (Maruyama et al., 2011). These data suggest that there is most likely a negative effect of lung resection surgery on muscle strength and muscle mass; however, more studies are needed to

corroborate the potential effects of resistance training on preventing and/or restoring this deterioration.

3.2.5 Health-related quality of life

Health-related functional status and quality of life assessment are important and under-reported in the treatment of patients with early stages of NSCLC and should be incorporated into clinical decisions (Donington et al., 2012). Deterioration of physical functioning has been identified as one of the main concerns for patients undergoing lung resection surgery and thus should be specifically addressed before and after the surgery (Cykert et al., 2010). HRQoL is worse in patients who have undergone pulmonary resection than in age- and sex-matched subjects (Handy Jr et al., 2002) and is also significantly impaired comparing to baseline for the majority of dimensions (Kenny et al., 2008). In a systematic review published in 2013, Poghosyan et al. reported that six out of seven studies examining HRQoL six months after lung resection surgery found a significant decline in the PCS (Poghosyan et al., 2013) (Table 3.4). Only one study reported no change in the six-month follow-up, and this included only women undergoing thoracotomy (Sarna et al., 2010). Granger et al., in a longitudinal follow-up study, found that at the time of diagnosis, individuals with lung cancer had an HRQoL below normative data, which further deteriorated during and after treatment (Granger et al., 2014). In long-term lung cancer survivors (one to six years post-surgery), Ostroff et al. reported that HRQoL was also inferior to that among a cohort of matched smokers (Ostroff et al., 2011). Clinical and socio-demographic factors associated with significant declines in the PCS after surgery include age, extent of resection and post-operative adjuvant therapy (Möller and Sartipy, 2012). More strikingly, Pompili et al. found that patients with better preoperative physical functioning and bodily pain scores were at higher risk of a relevant physical deterioration after surgery, while those with lower PPO FEV_1, higher preoperative social functioning and better mental health were at higher risk of a significant emotional deterioration

(Pompili, 2011). In lung cancer survivors (one to six years post-surgery), being non-employed, the presence of dyspnoea, symptoms of depression and the number of co-morbid conditions were associated with poor PCS scores in the SF-36 (Ostroff et al., 2011). Other well-known factors that have been associated with changes in HRQoL after surgery are age (Schulte et al., 2010), the extent of lung parenchyma resected (lobectomy or bilobectomy versus pneumonectomy) (Schulte et al., 2009) and the surgical approach (VATS versus open) (Demmy and Nwogu, 2008), which will be covered in detail in the next section.

Table 3.4: Effects of lung resection surgery on HRQoL

Study	Population	Outcome	Time of evaluation	Results
Handy, 2002	139 NSCLC[i]	SF-36	6 months postop	Significant ↓ pre to post-surgery in PF, RP, SF, BP and MH
Sartipy, 2009	117 NSCLC (lobectomy vs. pneumonectomy)	SF-36	6 months postop	L: the PCS↓ from 46.6±11 at baseline to 38.1 post-surgery and the MCS from 39.5±13 to 43.4±13 P: the PCS ↓ from 47.8±9 to 33±10 and the MCS ↑ from 36.5±13 to 37.8±13 (p <.05)
Sartipy, 2010	198 NSCLC (men vs. women)	SF-36	6 months postop	M: the PCS ↓ from 45.2±11 to 40.5±11 and the MCS ↑ from 42.3±13 to 44.8±12 (p <.001) W: the PCS ↓ from 46.1±11 to 39.5±11 and the MCS ↑ from 36.4±14 to 42.3±14 (p <.001)
Pompili, 2010	100 NSCLC	SF-36	3 months postop	COPD: the PCS ↓ from 50.9±7.1 to 49.3±7.2 and the MCS ↑ from 45.4±11.7 to 46±12.5 Non-COPD: the PCS ↓ from 51.9±5 to 49.4±7.7 and the MCS ↑ from 45.7±11.1 to 47.8±10.6
Moller, 2010	198 NSCLC (Young vs. old patients)	SF-36	6 months postop	Y: the PCS ↓ from 46.4±10.9 to 41±11.1 and the MCS ↑ from 38.3±14.1 to 43.4±13.5 (p <.001) O: the PCS ↓ from 43.9±11.6 to 38±9.7 (P<.001) and the MCS ↑ from 41.8±12.8 to 43.8±12 (p =NS)
Pompili, 2011	172 NSCLC	SF-36	3 months postop	The PCS ↓ from 52.4 to 46.6 and the MCS ↑ from 46.6 to 48.2. 48 patients (27.9%) experienced a decline in PCS pre to post-surgery.
Moller, 2012a	170 NSCLC	SF-36	6 months postop	The PCS ↓ 9 points pre to post-surgery and the MCS ↑ 4 points
Moller, 2012b	213 NSCLC	SF-36	6 months postop	60% of the patients reported a ↓ in PCS and 33% in MCS pre to post-surgery
Granger, 2014	50 NSCLC	SF-36	10 weeks and 6 months postop	The PCS ↓ from 42.7±1.7 to 38.1±1.4 (P<.01) and 39.7±2 at 10 and 6 months respectively (p =NS); the MCS ↓ from 45±1.9 to 41.5±2.2 and 42.7±2.1 at 10 weeks and 6 months respectively (p =NS)

[i]NSCLC=Non-small Cell Lung Cancer; SF-36=Short-From 36 Health Survey; PF= Physical Functioning, RP=Role Physical; SF=Social Functioning; BP=Bodily Pain; COPD=Chronic Obstructive Pulmonary Disease; PCS=Physical Component Summary; MCS=Mental Component Summary; M=Men; W=Women; Y=Young patients (<70 years); O=Old patients (>70 years); NS=Non-significant.

3.3 Post-operative outcomes and surgical approach: VATS versus open thoracotomy

Since the first successful VATS lobectomy in the early 90s, the number of thoracoscopic procedures performed for lung cancer has been progressively increasing and it is now recognized as the preferable approach for stage I NSCLC, especially in those patients with a high risk of post-operative morbidity and mortality (Ceppa et al., 2012, Howington et al., 2013). Despite the outstanding results of this minimally invasive approach, acceptance has been slow and frustrating (Begum et al., 2014). Most cardiothoracic surgeons refuse to embrace the technique, alluding to its great complexity and being sceptical about its oncological safety and equivalence to the traditional approach. Consequently, numerous studies have been conducted addressing these and other important outcomes comparing both surgical methods to demonstrate the safety and effectiveness of the minimally invasive approach, although, given the ethical implications, very few randomized controlled trials have been undertaken and they are not expected in the future (Begum et al., 2014). In one of those RCTs, Kirby et al. allocated 55 patients with early-stage NSCLC to undergo either video-assisted or conventional lobectomy. The authors found a significant decrease in the number of post-operative complications but no difference in hospital stay, operation time, intraoperative complications or blood loss (Kirby et al., 1995). In 2000, Sugiura et al. conducted a pseudo-RCT involving 44 patients (22 per arm), examining the short- and long-term outcomes of the two approaches (Sugiura et al., 1999). They reported no significant difference in hospital mortality, morbidity or post-operative length of hospital stay but less post-operative pain and a shorter time to return to the preoperative level of activity. They also found less recurrence and overall better survival at maximal follow-up. Since these early and controversial studies, the majority of the research has consistently demonstrated a significant reduction in length of hospital stay and post-operative complications with VATS versus open thoracotomy. In the long-term outcomes, some studies have shown less recurrence after VATS than after open surgery (Higuchi et al., 2014, Flores

et al., 2011, Luo et al., 2014) and better overall survival (Fan et al., 2013), but the results are not consistent or disappear after propensity-matched scoring (Berry et al., 2014). The latest studies published in 2015 confirmed the superiority of VATS for reducing hospital stay, but conflicting results are still found in post-operative complications, recurrence, and cancer-specific and overall survival (Kuritzky et al., 2015, Murakawa et al., 2015, Cai et al., 2015, Begum et al., 2015). Altogether, this data seems to indicate that VATS may be superior to the traditional approach in the short-term outcomes (including length of hospital stay and most likely pulmonary complications) but provides no additional benefit in the long term. Nonetheless, it is important to acknowledge here that the VATS approach requires a long learning curve and some of the comparisons may be biased because of surgeon inexperience in performing the technique. This is reflected somehow in the studies reporting fewer dissected nodes with the VATS approach, longer operation times or higher rates of intraoperative complications and conversions to thoracotomies (Kawachi et al., 2009, Pan et al., 2012).

With regard to the functional outcomes, the majority of the research agrees that the minimally invasive access technique is superior to the conventional approach in terms of the incidence and severity of post-operative and chronic pain, the need for pain medication, functional capacity, exercise capacity and HRQoL. In a meta-analysis published by Cheng et al., the number of patients who were dependent at discharge was significantly reduced by VATS compared to open thoracotomy, as well as the time to return to full activity and the functional capacity (Cheng et al., 2007). Another study comparing early recovery of pulmonary function and cardiorespiratory fitness between VATS and open thoracotomy found that there were significant differences in the 6MWT between groups one week and one month post-surgery and pulmonary function was also better preserved in patients operated on by VATS (Che et al., 2013). Similar results were reported by Ueda et al., who found that following a fast-track rehabilitation protocol, patients undergoing

VATS return to preoperative values (≥ 80%) only three days after surgery (Ueda et al., 2006). In terms of quality of life, Handy et al. found that patients after VATS reported higher levels of HRQoL six months post-surgery than those undergoing the conventional approach (Handy, 2010). These differences have also been reported in the long term but the results are inconsistent (Li et al., 2002, Aoki et al., 2007). In light of these findings, it seems that VATS provides better functional outcomes, especially in the short term, but the evidence on this topic is less extensive and has received comparatively less attention than the other outcomes, thus larger propensity-matched cohort studies are required to further assess the influence of the surgical approach on the short- and long-term functional recovery after lung cancer surgery.

Table 3.5: Post-operative and functional outcomes in VATS vs open thoracotomy

Author, year	Design	Participants	Mortality	Complications	Length of stay	Recurrence	Survival	Functional outcomes
Kirby, 1995	RCT[i]	55 Stage I-IIIA NSCLC (25 VATS)	-	↓ in VATS	NS	-	-	-
Sugiura, 2000	Cohort	44 stage I NSCLC (22 VATS)	NS	NS	NS	↓ in VATS	-	VATS patients experienced less post-operative pain. Time to return to preoperative activity was also shorter in VATS
Li, 2002	Cross-sectional	51 (27 VATS)	-	-	-	-	-	Overall, NS in any HRQoL domain except for less constipation in VATS group
Park, 2007	RMC	244 stage I NSCLC (122 VATS)	-	↓ VATS	↓ VATS	-	-	-
Whitson, 2007	RC	147 stage I NSCLC (59 VATS)	NS	↓ pneumonia in VATS	NS	-	NS in 5-year survival	-
Sakuraba, 2007	PC	140 stage IA NSCLC (84 VATS)	NS	-	-	NS	NS in 5-year survival	-
Watanabe, 2008	RC	69 I-IIIA NSCLC (37 VATS)	-	-	-	NS	NS in 5-year survival	-

Cattaneo, 2008	RMC	164 Stage I NSCLC > 70 years (82 VATS)	NS	↓VATS	↓ VATS	-	-	-
Kawachi, 2009	RC	249 stage I NSCLC (VATS 73)	NS	NS	-	-	-	-
Handy, 2009	RC	241 NSCLC (49 VATS)	NS	NS	↓ VATS	-	-	Better HRQoL in VATS. No difference in 6MWT
Flores, 2009	PC	741 stage IA NSCLC (398 VATS)	NS	↓ VATS	↓VATS	-	NS in 5-year survival	-
Yang, 2009	RC	621 NSCLC (113 VATS)	NS	-	NS	↓	-	-
Gopaldas, 2010	RC	13619 lung resection (759 VATS)	NS	NS	NS	-	-	-
Scott, 2010	PMC	752 Stage I-II NSCLC (66 VATS)	NS	↓ VATS	↓VATS	-	-	-
Flores, 2011	PC	1172 Stage IA NSCLC (520 VATS)	-	-	-	↓ VATS	-	-
Ilonen, 2011	RMC	328 stage I NSCLC (116 VATS)	NS	↓VATS	↓VATS	-	NS 2-year survival	-
Swanson, 2012	RC	3961 (1054 VATS)	-	↓ VATS	-	-	-	-

Pan, 2012	RC	180 stage I-IIIA(83 VATS)	-	-	↓VATS	↓ VATS	-	-
Papiashvilli, 2012	RC	389 NSCLC (63 VATS)	NS	↓ AF in VATS	↓VATS	-	-	-
Papiashvilli, 2013	RC	103 early stage NSCLC (63 VATS)	NS	↓ VATS	NS	-	-	-
Fan, 2013	PC	148 stage I-II NSCLC (71 VATS)		↓ Chest tube duration, AF and chylothorax	↓VATS		↑ survival rate at the end of follow-up in VATS	
Lee, 2013	RMC	416 (208 VATS)	-	↓ VATS	-	-	NS in 5-year survival	-
Subroto, 2013	RMC	68350 lobectomies (10554 VATS)	NS	↓ VATS	↓VATS	-	-	-
Che, 2013	PC	138 lung cancer (68 VATS)	-	-	-	-	-	↓ Pulmonary function loss and 6MWT in VATS
Cao, 2013	PMC	2916 stage I-IIIA (1458 VATS)	-	-	-	-	NS in 5-year survival	-
Higuchi, 2014	PC	160 Stage IA NSCLC (114 VATS)	NS	↓ VATS	↓VATS	↓	NS in 5-year survival	-
Subroto, 2014	RMC	6008 NSCLC (1293 VATS)	-	-	-	-	NS in 5-year survival	-

Luo, 2014	RC	240 NSCLC (120 VATS)	-	NS	NS	↓ systemic recurrence for VATS	NS in 1 and 3-year survival	-
Jeon, 2014	RMC	182 stage I NSCLC and COPD (91 VATS)	NS	↓ PPCs in VATS	↓ VATS	-	-	-
Berry, 2014	RMC	1087 NSCLC (610 VATS)	↓ VATS	↓ VATS	-	-	↑VATS; NS after matching	-
Murakawa, 2015	RMC	285 Stage I-II NSCLC (101 VATS)	-	↓ VATS	NS	-	NS after matching	-
Kuritzky, 2015	PMC	298 Stage I NSCLC (74 VATS)	NS	↓ VATS	NS	-	NS in 5-year survival	-
Cai, 2015	RC	138 stage I-II NSCLC (71 VATS)	NS	↓ VATS	↓ VATS	NS	-	↓ Post-operative pain in VATS

[i]RCT=Randomized Controlled Trial; VATS=Video-Assisted Thoracic Surgery; NSCLC=Non-small Cell Lung Cancer; NS=Non significant; HRQoL=Health Related Quality of Life; RMC=Retrospective Matched Cohort; RCH=Retrospective Cohort; PCH=Prospective Cohort; PMC=Prospective Matched Cohort; 6MWT=6-Minute Walk Test; AF=Atrial Fibrillation; PPCs=Post-operative Pulmonary Complications.

CHAPTER 4: Prehabilitation vs. Rehabilitation. The role of preoperative exercise training on functional capacity, pulmonary function, HRQoL and post-operative outcomes in lung cancer patients: systematic review and meta-analysis

1.1 INTRODUCTION AND RATIONALE

There is growing evidence suggesting that individuals with lung cancer would greatly benefit from engaging in exercise training across the disease spectrum, from diagnosis to active treatment and also in palliative care (Jones, 2011). Cancer treatments add a significant burden to patients who are already exposed to the debilitating effects of the disease, leading to physical and psychological declines and affecting self-care and self-management. Patients undergoing lung resection surgery are particularly prone to physical deconditioning during the first few weeks. If this situation is not properly tackled, it can lead to permanent disabilities and HRQoL deterioration. Post-operative rehabilitation programmes have been recently proposed as a mean to restore functional fitness after surgery. Indeed, preliminary studies have shown an improvement in exercise tolerance, functional capacity, muscle strength and HRQoL in postthoracotomy patients after a comprehensive rehabilitation programme (Spruit et al., 2006, Stigt et al., 2013, Glattki et al., 2012, Salhi et al., 2014, Arbane et al., 2011). However, after lung resection surgery, patients often complain of significant dyspnoea and fatigue as well as experience high levels of anxiety and depression regarding their prognosis. Furthermore, a considerable percentage of them would be referred to neoadjuvant chemo- radiotherapy which could decrease adherence to the intervention and minimize the results obtained. In light of this, the preoperative period has been suggested as a more appropriate time to implement an exercise intervention given that patients have not seen compromised yet their physical functioning (Gillis et al., 2014). In addition, active engagement of the individual in the preparation process is likely to alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process (Carli et al., 2010). Finally, a

combination of pre and post-rehabilitation could lead to greater improvements in functional capacity than post-operative rehabilitation alone (Gillis et al., 2014).

Prehabilitation is defined as the process of enhancing functional capacity of an individual to enable him or her to withstand a stressful event (Ditmyer et al., 2002). In the preoperative phase, prehabilitation refers to the implementation of measures of diverse nature with the aim of reducing post-operative complications and improving the post-operative course (Debes et al., 2014). A generic prehabilitation programme may incorporate a warm-up, an endurance or resistance training, flexibility exercises and practicing functional task (Ditmyer et al., 2002). The rationale behind preoperative rehabilitation lies on the fact that surgery is a stressful event which usually involves bed rest for several days (Valkenet et al., 2011). Because bed rest is correlated with loss of muscle mass, physical deconditioning, longer hospitalization and a torpid post-operative course, optimizing physical functioning at baseline may contribute to improve post-operative outcomes and hasten recovery (Valkenet et al., 2011).

The effectiveness of preoperative exercise training in a wide range of patients has been extensively acknowledged in the literature. For instance, in abdominal and cardiac surgery, prehabilitation has shown to decrease 50% the incidence of PPCs and reduce hospital length of stay in one day (Valkenet et al., 2011). In patients undergoing Coronary Artery Bypass Graft (CABG) surgery, adding a preoperative exercise-based intervention twice weekly for ten weeks significantly reduced total hospital stay and days in the ICU. Plus, after the intervention, patients showed an increase in the PCS which was maintained at least six months after the surgery (Arthur et al., 2000). In a systematic review and meta-analysis involving cardiac surgical patients, participants in the prehabilitation groups showed a significant reduction in PPCs and time to extubation. In addition, older patients significantly reduced their hospital length of stay (MD = -1.32; 95% CI: -2.36 to -0.28) (Snowdon et al., 2014). Alone with preoperative exercise training, inspiratory muscle training

(IMT) has been suggested as another form of prehabilitation given the potential role of the respiratory muscles in preventing PPCs. In a meta-analysis including patients undergoing cardiothoracic and upper abdominal surgery, preoperative IMT effectively improved maximal inspiratory pressure (MD = 15 cmH2O; 95% CI: 9 – 21) and reduced PPCs (OR = 0.48; 95% CI: 0.26 – 0.89) although no significant difference was observed in length of hospital stay (Mans et al., 2015). On the contrary, in the meta-analysis conducted by Snowdon et al., IMT significantly reduced both PPCs and length of hospital stay in patients undergoing cardiac surgery (Snowdon et al., 2014).

Unfortunately, evidence of the effectiveness of prehabilitation in thoracic surgery has received comparatively less attention. In one longitudinal study, Nomori et al. examined the effects of IMT on maximal inspiratory and expiratory pressures (MIP and MEP respectively) in patients undergoing thoracic surgery. They found that patients who had a positive diagnosis of PPCs were those with lower MIP and MEP at baseline and furthermore, they didn't show any improvement after the training (Nomori et al., 1994). In a RCT evaluating the effects of IMT and incentive spirometry for two weeks in patients with COPD undergoing lung cancer surgery, Weiner et al. reported an increase in FEV_1 and inspiratory muscle strength prior to surgery but no differences in PPCs (Weiner, 1997). Some systematic reviews have also been published in the topic but most were conducted in a mix cohort of cancer patients or included pre and post-operative interventions (Rodriguez-Larrad et al., 2014, Granger et al., 2011, Crandall et al., 2014, Singh et al., 2013). Only one systematic review focused on the effects of preoperative exercise training in patients undergoing lung cancer surgery. After examining the studies included, the authors concluded that preoperative training might have a positive effect on post-operative complications, mortality, length of hospital stay, physical fitness and quality of life but no definitive conclusions could be drawn due to the heterogeneity of the programmes (Pouwels et al., 2015). Therefore, in this

systematic review and meta-analysis we aim to study the effectiveness of preoperative exercise training in lung cancer patients undergoing surgery and to quantify the effect of the intervention on each of the selected outcomes.

4.2 OBJECTIVES

The specific aims of this study were:

1) To examine the effectiveness of a preoperative exercise-based intervention in patients awaiting lung cancer surgery on the following outcomes: exercise capacity, functional capacity, pulmonary function and HRQoL.

2) To determine the impact of the intervention on the post-operative outcomes (post-operative complications and hospital length of stay) in comparison to the standard care (no prehabilitation).

3) To perform a meta-analysis and pool results to measure the effects of the intervention on each of the outcomes examined.

4.3 MATERIALS AND METHODS

4.3.1 Protocol

A protocol for this systematic review was registered in the PROSPERO database (registration number CRD42015024283). The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement guidelines were applied (Liberati et al., 2009).

4.3.2 Eligibility criteria

Articles were deemed eligible if they were 1) randomized or non-randomized controlled trials (RCTs and nRCTs), cohort studies or case – control studies including individuals with suspected or confirmed NSCLC; 2) described a pre-operative exercise based intervention, focused on endurance and/or resistance training and 3) reported results on at least one of the following

outcomes: exercise capacity, functional capacity, health-related quality of life (HRQoL), pulmonary function, post-operative complications or length of hospital stay. Systematic or narrative reviews, abstracts and conference papers were excluded as well as non-preoperative interventions and studies involving other cancer patients. Only articles published in English, Spanish or French were included.

4.3.3 Type of interventions

Studies must evaluate an exercise-based intervention focused on endurance or resistance training or a combination of both. Additionally, studies could include other components such as breathing exercises with or without incentive spirometry, inspiratory muscle training, stretching, relaxation and education regarding exercise and physical activity.

4.3.4 Outcomes

Studies must report results from at least one of the following outcomes 1) exercise capacity or functional exercise capacity; 2) pulmonary function; 3) health-related quality of life or 4) post-operative outcomes.

4.3.5 Information sources and search strategy

Prior to conduct this systematic review, the Cochrane Library, PROSPERO and PEDro were searched to ensure that no other similar meta-analysis was published or being undertaken at the moment. The following databases were searched to identify potentially eligible records: CINAHL (1982 – 2014), EMBASE (1974 – 2014), MEDLINE (1950 – 2014), PEDro (1990 – 2014), PUBMED (1974 – 2014) and SCOPUS (1975 – 2014). A manual crossed search was also conducted among the previous identified records. No restrictions were applied. The following terms were combined in the database search: “Exercise Therapy” OR ‘Exercise Training” OR “Pulmonary Rehabilitation” AND “Lung Neoplasms” OR “Lung Cancer”. The full description of

the search terms can be found in the Table 4.1. The last search was conducted on 17th September, 2015.

Table 4.1: Search Strategy

DATABASE	Search Fields	DESCRIPTORS
MEDLINE PUBMED	MESH and subject headings	1. Exercise Therapy 2. Pulmonary Rehabilitation 3. Lung Neoplasms 4. (#1 OR #2) AND #3
CINHAL	MESH and subject headings	1. Therapeutic, Exercise 2. Pulmonary Rehabilitation 3. Lung Neoplasms 4. (#1 OR #2) AND #3
EMBASE	All fields	1. Exercise Training 2. Rehabilitation, Pulmonary 3. Lung Cancer 4. (#1 OR #2) AND #3
SCOPUS	Title, Abstract, Key Words	1. Exercise Training 2. Pulmonary Rehabilitation 3. Lung Cancer 4. (#1 OR #2) AND #3
PEDro	All fields	1. "Lung Cancer "

4.3.6 Study selection

One reviewer (RS) performed the search and initial eligibility assessment based on title and/or abstract against the inclusion criteria. After removing for duplicates and not relevant records, two independent reviewers (RS and MY) assessed all abstracts and identified the potentially eligible records. Full-text analyses of those deemed eligible were conducted by two independent reviewers (RS and MY). In the presence of a disagreement, this was settled by a third reviewer (EG). All references were stored in Endnote X7 (Thomson Reuters, Thomson Corporation, USA) during the study period.

4.3.7 Data collection process

Data from each article were extracted by one reviewer (RS). Another review author checked the extracted data to ensure that all the key points were included (MY). Disagreements were resolved by discussion between the two authors. If no agreement was achieved, it was planned for a third author to decide (CG). Data extracted were stored in a Microsoft Office Excel 2010 (Microsoft Corporation®, Redmond, Washington, USA) spreadsheet.

4.3.8 Data items

Relevant information from each study was collected in the following aspects: 1) design, 2) participants, 3) intervention and 4) outcomes. A complete list of the items included can be found in Table 4.2. Authors were contacted by e-mail when any of the listed items was missing or was insufficiently described. Sixteen authors were reached and after two attempts, six (37.5%) responded.

Table 4.2: Study Data Collection

- **Design**
  - Location (country)
- **Participants**
  - Number of participants
  - Mean Age
  - Cancer type, stage and anti-cancer treatment
  - Type of surgery and extent of resection
- **Intervention**
  - Setting
  - Timing (preoperative alone or preoperative + post-operative)
  - Type of intervention (endurance, resistance, both)
  - Intensity and duration
  - Frequency and length of intervention
  - Adherence
  - Adverse events
- **Outcomes**
  - Primary and secondary outcomes
  - Measurement Tools
  - Results
  - Limitations

4.3.9 Risk of bias in individual studies

Assessment of risk of bias was conducted using the PEDro Scale for randomized controlled trials and the Newcastle – Ottawa Quality Assessment Scale (NOS) for cohort studies. The evaluation was conducted independently by two reviewers for each article (RS and EG). In case of a disagreement, this was settled by a third reviewer (MY).

4.3.10 Summary measures

The principal summary measures of this systematic review were mean change of exercise capacity (VO_{2peak}) and functional capacity (in meters) before and after a preoperative rehabilitation programme. Secondary summary measures include mean differences in pulmonary function (pre – post intervention) and inter-group differences in hospital LOS and Risk Ratio (RR) of post-operative complications. Two articles (Bradley et al., 2013, Morano et al., 2013) reported data as median and range (or interquartile range (IQR)) and thus estimations of the mean and standard deviation (SD) were made according to the available formulas (Wan et al., 2014).

4.3.11 Synthesis of results and statistical analysis

For each outcome of interest, the standardized (SMD) or mean difference (MD) for continuous variables and RR for dichotomous variables was calculated and 95% Confident Intervals (CI) were computed for statistical significance. Forest plots were generated to illustrate the study-specific effect size. Meta-analyses and pooled estimated effect sizes were undertaken when considered appropriate according to the number of studies included, measurements properties and between-studies variability. Heterogeneity was assessed using the X^2 and the I^2. A p value of $\leq$ 0.1 for the X^2 or $I^2 \geq 50\%$ was considered as substantial heterogeneity and a subgroup analysis was run to explore possible causes. All analyses were performed using the Review Manager (RevMan)

version 5.3 for Windows (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) based on a random-effects model.

4.4 RESULTS

4.4.1 Study selection

A flow diagram of the study selection is shown in Figure 4.1. Six databases were screened yielding a total of 1.656 studies. Additionally, 12 studies were identified from cross-manual search and personal records, accounting for a total of 1.668 references. After removing from duplicates and non-relevant records, 234 articles were assessed by title and abstract and 51 were selected for full-text analysis. Finally, 21 articles involving 17 participant samples fulfilled the inclusion criteria and were included in the review.

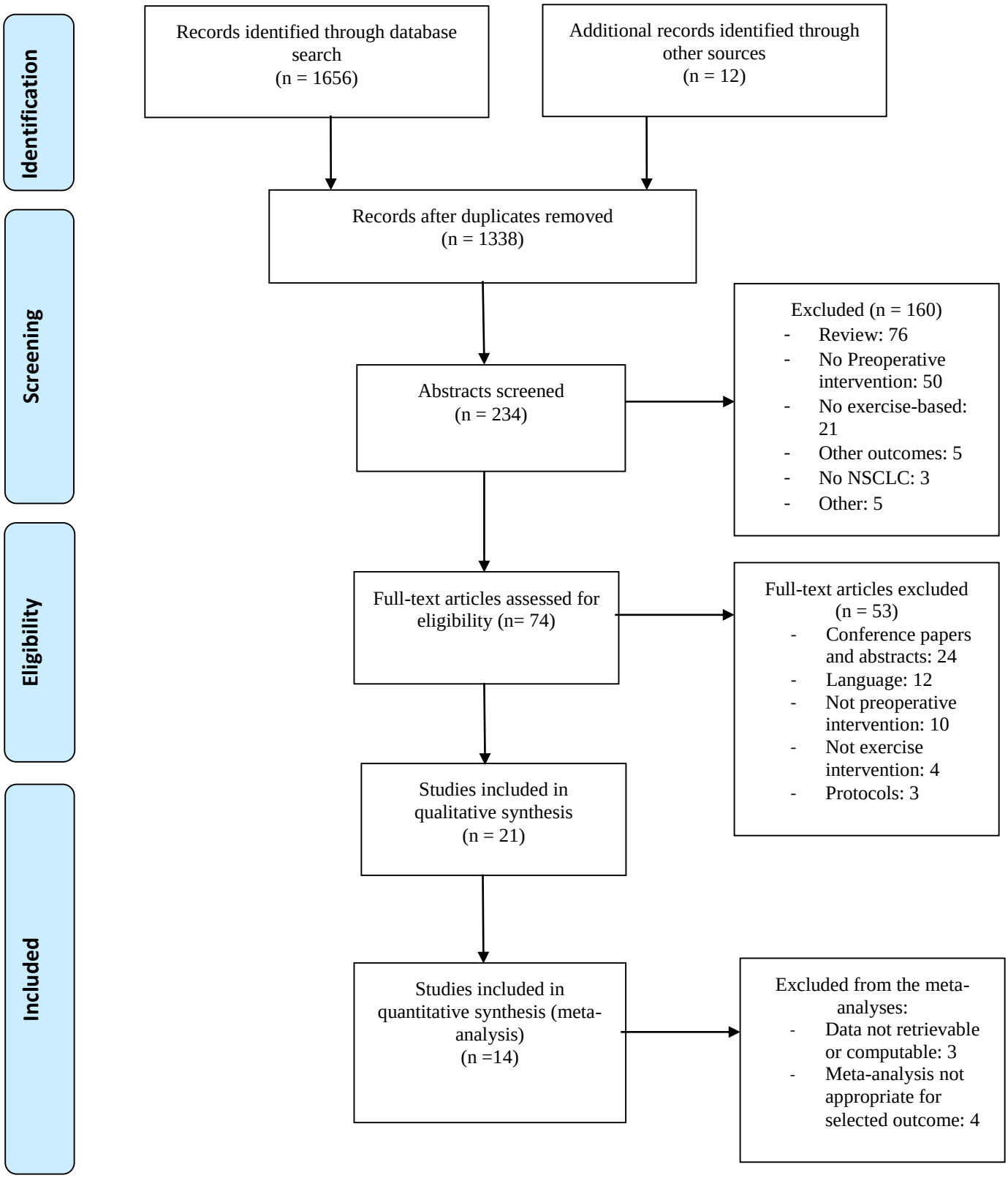


Figure 4.1: Flow diagram of the studies included in the systematic review and meta-analysis.

4.4.2 Study characteristics

The main characteristics of each study included are summarized in Table 4.3.

Design

This systematic review included five RCTs (Pehlivan et al., 2011, Benzo et al., 2011, Stefanelli et al., 2013, Morano et al., 2013, Morano et al., 2014), three non-RCTs or pseudo-RCTs (Fang et al., 2013, Li et al., 2013, Gao et al., 2014), three retrospective cohort studies (Sekine et al., 2005, Harada et al., 2013, Tarumi et al., 2015), one prospective cohort study (Bradley et al., 2011) and nine prospective case-series (Jones et al., 2009c, Jones et al., 2007, Peddle et al., 2009a, Cesario et al., 2007a, Bobbio et al., 2008, Bagan et al., 2013, Divisi et al., 2013, Coats V, 2013, Mujovic et al., 2014). Eight studies compared a rehabilitation programme vs. no intervention (control group) (Benzo et al., 2011, Bradley et al., 2013, Pehlivan et al., 2011, Stefanelli et al., 2013, Li et al., 2013, Gao et al., 2014, Fang et al., 2013, Sekine et al., 2005) while three studies compared two different interventions (Morano et al., 2013, Morano et al., 2014, Harada et al., 2013). One study evaluated two randomized controlled trials at the same time but only one of them was finally included (study #2) because data from the first study was missing (Benzo et al., 2011).

Participants

A total of 1,189 patients participated in the studies including 595 subjects engaging in the rehabilitation programmes and 594 acting as controls. Mean age was 64.8±5.28 in the experimental groups and 64.3±6.3 in the controls, and almost 62% were men in both groups. All studies included patients with NSCLC or a mixed cohort of lung cancer types (Jones et al., 2009c, Jones et al., 2007, Peddle et al., 2009a). Most patients were diagnosed with early stage of the disease (I – IIIA) and three studies included individuals who had underwent or were undergoing neoadjuvant therapy (Li et al., 2013, Tarumi et al., 2015, Coats V, 2013). Lung resection was mostly performed by an open thoracotomy (Bobbio et al., 2008, Bradley et al., 2013, Stefanelli et al., 2013, Fang et al., 2013, Li

et al., 2013, Sekine et al., 2005, Divisi et al., 2013, Mujovic et al., 2014) while other studies also included a small percentage of patients operated by VATS (Benzo et al., 2011, Morano et al., 2013, Gao et al., 2014, Harada et al., 2013). Only in one study patients were operated by means of VATS alone (data provided by the authors) (Coats V, 2013). The extent of parenchyma resected varied across studies with lobectomy being the most common procedure according to the international guidelines (Molina et al., 2008, Howington et al., 2013).

Table 4.3: Characteristics of the studies included in the systematic review

	Study	Design	Participants	Type of Cancer	Stage	Surgical Approach	Extent of resection	Neo-adjuvant Therapy
1	Sekine et al., 2005	Retrospective Cohort Study	22 (rehab) + 60 (historical controls)	NSCLC	I – IV	Open	Lobectomy	NR
2	Jones et al., 2007	Prospective case series	20	Lung Cancer and lung metastases	I – IIIA	NR	All types	NO
3	Cesario et al., 2007	Prospective case series	12	NSCLC + severe COPD	IA - IIB	NR	Lobectomy	NR
4	Bobbio et al., 2008	Prospective case series	12	NSCLC	I – IIIA	Open	Lobectomy	NO
5	Peddle et al., 2009	Prospective case series	9	Lung Cancer and lung metastases	I – IV	NR	All types	NO
6	Jones et al., 2009	Prospective case series	20	Lung Cancer and lung metastases	I – IIIA	NR	All types	NO
7	Pehlivan et al., 2011	RCT	60	NSCLC	IA-IIIB	NR	Lobectomy/ pneumonectomy	NR
8	Benzo et al., 2011 (Study #2)	RCT	19 (rehab 10 + 9 controls)	NSCLC + COPD	NR	VATS/Open	All types	NR
9	Harada et al., 2013	retrospective cohort study	50 (CVPR 29 + CHPR 21)	NSCLC + impaired PF	IA – IV	VATS/Open	Lobectomy	NR
10	Bagan et al., 2013	Prospective case series	20	NSCLC	IA – IIB	VATS/Open	Lobectomy/ bilobectomy/ pneumonectomy	NO
11	Stefanelli et al., 2013	RCT	40 (20 rehab. + 20 controls)	NSCLC + COPD	I – II	Open	Lobectomy	NR
12	Fang et al., 2013	pseudo-RCT	61 (39 rehab + 22 controls)	NSCLC + COPD	NR	Open	Lobectomy/ bilobectomy	NO

13	Divisi et al., 2013	Prospective case series	27	NSCLC + COPD	IA – IIB	Mini-thoracotomy	Lobectomy	NR
14	Morano et al., 2013	RCT	24 (12 PR + 12 CPT)	NSCLC + impaired PF	IA – IIIA	VATS/Open	NR	NR
15	Bradley et al., 2013	Prospective cohort study	363 (58 rehab. + 305 controls)	NSCLC	NR	Open	NR	NR
16	Coats et al., 2013	Prospective case series	16	NSCLC	IA – IV	VATS	Lobectomy/wedge resection	YES
17	Xu-Hong Li et al., 2013	nRCT	48 (24 rehab. + 24 controls)	NSCLC	IIA – IIIB	Open	All types	YES
18	Morano et al., 2014	RCT	24 (12 PR + 12 CPT)	NSCLC + Impaired PF	IA – IIIA	NR	NR	NR
19	Mujovic et al., 2014	Prospective case series	83	NSCLC + COPD	NR	Open	All types	NR
20	Gao et al., 2014	nRCT	142 (71 rehab + 71 controls)	NSCLC + High Surgical Risk	IA– IV	VATS/Open	NR	NR
21	Tarumi et al., 2015	Restrospective Cohort Study	82	NSCLC + chemo-radiotherapy	IIB – IV	Open	Lobectomy/Pneumonectomy	YES

NSCLC: Non-Small Cell Lung Cancer; RCT=Randomized Controlled Trial; nRCT=Non-randomized Controlled Trial; NR=Non Reported; COPD=Chronic Obstructive Pulmonary Disease; VATS=Video-Assisted Thoracic Surgery; PF=Pulmonary Function; CVPR=Conventional Pulmonary Rehabilitation; CHPR=Comprehensive Pulmonary Rehabilitation; PR=Pulmonary Rehabilitation; CPT=Chest Physical Therapy.

Type of interventions

A detailed description of the interventions is shown in Table 4.4.

Studies were undertaken in Europe (Cesario et al., 2007a, Bobbio et al., 2008, Pehlivan et al., 2011, Bagan et al., 2013, Stefanelli et al., 2013, Divisi et al., 2013, Bradley et al., 2013, Mujovic et al., 2014), Asia (Sekine et al., 2005, Fang et al., 2013, Li et al., 2013, Gao et al., 2014, Tarumi et al., 2015) and north and south America (Jones et al., 2009c, Jones et al., 2007, Peddle et al., 2009a, Benzo et al., 2011, Morano et al., 2013, Morano et al., 2014, Coats V, 2013). The majority of them were conducted as an out-patient intervention at a hospital or training facility. Only one investigation delivered a home-based programme (Coats V, 2013). Four studies resumed the rehabilitation programme after surgery (Bradley et al., 2013, Pehlivan et al., 2011, Li et al., 2013, Sekine et al., 2005) and three studies provided standard post-operative physiotherapy care until hospital discharge (Tarumi et al., 2015, Bagan et al., 2013, Mujovic et al., 2014).

The modality of exercise prescribed was predominantly endurance training for lower and/or upper limbs (Stefanelli et al., 2013, Fang et al., 2013, Sekine et al., 2005, Harada et al., 2013, Tarumi et al., 2015, Jones et al., 2009c, Jones et al., 2007, Peddle et al., 2009a, Cesario et al., 2007a, Bagan et al., 2013, Divisi et al., 2013) or a combination of endurance plus resistance training (Bobbio et al., 2008, Benzo et al., 2011, Bradley et al., 2013, Coats V, 2013). Only two studies focused on resistance training alone (Li et al., 2013, Mujovic et al., 2014). Breathing exercises with or without incentive spirometry were performed in 15 of the 21 studies (Benzo et al., 2011, Bobbio et al., 2008, Bradley et al., 2013, Pehlivan et al., 2011, Stefanelli et al., 2013, Fang et al., 2013, Li et al., 2013, Sekine et al., 2005, Harada et al., 2013, Tarumi et al., 2015, Cesario et al., 2007a, Bagan et al., 2013, Divisi et al., 2013, Mujovic et al., 2014).

Table 4.4: Description of interventions included in the studies

Study	Setting	Timing	Type of intervention					Intensity	Duration of session (duration RT)	Frequency	Length of intervention	Adherence
			ET[i]	RT	BE	IMT	Other[ii]					
Sekine et al., 2005	Supervised + unsupervised	Pre + post – op	*	-	*	-	-	NR	45' (30')	Everyday	2 weeks	NR
Jones et al., 2007, Peddle et al., 2009; Jones et al.2009	Supervised	Preoperative	*	-	-	-	-	Continuous and interval: 60 - 100% of VO_2peak[i]	20 – 30'	5/week	4 – 10 weeks	72, 88 and 78% respective.
Cesario et al., 2007	Supervised	Preoperative	*	-	*	-	*	80% W_{max}	3 hours (NR)	5/week	4 weeks	NR
Bobbio et al., 2008	Supervised + Unsupervised	Preoperative	*	*	*	-	*	50 – 80% of W_{max}	90' (40')	5/week	4 weeks	80%
Pehlivan et al., 2011	Supervised (in-patient)	Pre + post – op	*	-	*	-	-	%HR_{max} (Karvonen Formula)	NR	3/day	1 week	NR
Benzo et al., 2011 (Study #2)	Supervised + unsupervised	Preoperative	*	*	*	*	-	Borg Scale	NR (20')	5/week	2 weeks (10 sessions)	100%
Harada et al., 2013	Supervised	Preoperative	*	-	*	-	*	Borg Scale	NR	CHPR: 2/week CVPR: 1/week	2 – 5 weeks	NR
Bagan et al., 2013	Supervised	Pre + postop	*	-	*	-	*	Continuous: 20 – 30 W	NR (30')	Daily	2 weeks	MR
Stefanelli et al., 2013	Supervised	Preoperative	*	-	*	-	-	Continuous; at least 70%WMax	3 hours (30)	5/week	3 weeks	NR
Fang et al., 2013	Supervised	Preoperative	*	-	*	-	-	Interval; 60 – 80%WMax	NR (40')	5/week	2 weeks	NR
Divisi et al., 2013	Supervised	Preoperative	*	-	*	*	-	Incremental up to 100% of Wmax	90' (40')	6/week	4 – 6 weeks	NR

Morano et al., 2013 & Morano et al., 2014	Supervised	Preoperative	*	*	-	*	*	80% W_{max}	NR (30')	5/week	4 weeks	NR
Bradley et al., 2013	Supervised	Pre and post – op	*	*	*	-	-	Up to 60% Wmax	60' (NR)	2/week	Variable	NR
Coats et al., 2013	Home – based	Preoperative	*	*	-	-	-	Continuous (60 – 80% W_{max})	NR (30')	3 to 5/week	4 weeks	75%
Xu – Hong Li et al., 2013	Supervised	Preoperative	-	*	*	-	*	NR	NR	NR	NR	NR
Mujovic et al., 2014	Supervised	Preoperative	-	*	*	-	*	NR	45'(NA)	3/day; 5/week	2 – 4 weeks	NR
Gao et al., 2014	Supervised	Preoperative	*	-	*	-	-	Borg Scale (5 – 7)	1.5 – 2 hours (30-40')	2/day	3 – 7 days	NR
Tarumi et al., 2015	Supervised (in-patient)	Pre and post-op	*	-	*	-	*	?	NR (45')	5 times per week	10 weeks	NR

[i] ET = Endurance Training; RT=Resistance Training; BE=Breathing Exercises; NR=Not Reported; CHPR=Comprehensive preoperative pulmonary rehabilitation; CVPR=Conventional preoperative pulmonary rehabilitation; VO_2Peak=Oxygen Consumption Peak; W_{max}=Maximal Workload; HR_{max}=Maximal Heart Rate; IMT=Inspiratory Muscle Training.

[ii] Education, Relaxation, Stretching and/or nutritional support

IMT was also performed in four studies (Benzo et al., 2011, Morano et al., 2013, Morano et al., 2014, Divisi et al., 2013). Other minority interventions included educational sessions (Bradley et al., 2013, Cesario et al., 2007a, Bagan et al., 2013, Mujovic et al., 2014), relaxation techniques (Li et al., 2013, Tarumi et al., 2015, Bagan et al., 2013), stretching (Bobbio et al., 2008, Morano et al., 2013, Morano et al., 2014), Non-Invasive Ventilation (NIV) (Bagan et al., 2013) and Functional Electrical Stimulation (FES) of the abdominal muscles (Cesario et al., 2007a).

The total duration of the interventions ranged from one to ten weeks (median four) with a median frequency of five sessions per week (range two – 14). Intensity was described in the studies as moderate to high and was mostly individually tailored according to the patient's tolerance. Adherence was poorly assessed (Jones et al., 2009c, Jones et al., 2007, Peddle et al., 2009a, Coats V, 2013) and only two adverse events were recorded (abnormal decline in systolic blood pressure in both cases) which were solved after exercise was discontinued (Jones et al., 2007).

4.4.3 Outcomes

Primary outcomes

Cardiopulmonary fitness (measurement of VO_{2peak}) was the main (Bobbio et al., 2008, Stefanelli et al., 2013, Jones et al., 2007, Coats V, 2013) or the secondary (Fang et al., 2013, Jones et al., 2009c, Peddle et al., 2009a, Bagan et al., 2013, Divisi et al., 2013) outcome in nine studies. Functional capacity was also assessed in 11 studies (Benzo et al., 2011, Bradley et al., 2013, Morano et al., 2013, Morano et al., 2014, Pehlivan et al., 2011, Jones et al., 2009c, Jones et al., 2007, Cesario et al., 2007a, Divisi et al., 2013, Coats V, 2013, Mujovic et al., 2014).

Pulmonary function was measured in 13 studies as the primary (Morano et al., 2013, Fang et al., 2013, Tarumi et al., 2015, Cesario et al., 2007a, Bagan et al., 2013, Divisi et al., 2013, Mujovic et al., 2014) or secondary study endpoint (Bobbio et al., 2008, Bradley et al., 2013,

Stefanelli et al., 2013, Sekine et al., 2005, Harada et al., 2013, Jones et al., 2007). FVC, FEV_1 and D_LCO were the most frequently reported respiratory parameters. MIP and MEP were also examined in one study (Morano et al., 2013).

Only four articles assessed the impact of the preoperative rehabilitation programme on HRQoL as the primary (Li et al., 2013, Peddle et al., 2009a) or the secondary outcome (Morano et al., 2014, Coats V, 2013), using a lung cancer specific questionnaire or a generic instrument respectively.

Nine studies reported the post-operative outcomes as the primary (Benzo et al., 2011, Pehlivan et al., 2011, Gao et al., 2014, Sekine et al., 2005, Harada et al., 2013) or the secondary study endpoint (Bradley et al., 2013, Morano et al., 2013, Fang et al., 2013, Mujovic et al., 2014). Post-operative morbidity (frequency of post-operative complications) and post-operative length of stay (LOS) were recorded.

Secondary outcomes

Other additional outcomes assessed in the studies were the feasibility (Coats V, 2013) and cost-effectiveness of the intervention (Bradley et al., 2013, Gao et al., 2014), muscle strength (Coats V, 2013), fatigue (Peddle et al., 2009a), inflammatory markers (Jones et al., 2009c) and fibrinogen and albumin levels (Morano et al., 2014).

4.4.4 Risk of bias within studies

Risk of bias for individual studies was assessed by two independent reviewers (RS and EG) achieving a total agreement of 69.8% according to the Kappa Index, with the largest difference between raters being two points. The results are shown in Tables 4.5 and 4.6. The first displays the quality evaluation of the RCTs and pseudo-RCTs using the PEDro scale, while the latter depicts the results of the NOS for the quasi-experimental and cohort studies. The median score for the

RCTs and non-RCTs was five (range two – eight). This falls just below the published score in PEDro for moderate to high quality studies (6/10 points) but it is similar to the mean reported in the cardiothoracic research field (Geha et al., 2013). On the other hand, the median score for the observational studies according to the NOS was six (range four - eight) which is classified according to the literature as high risk of bias (Lo et al., 2014).

Table 4.5: Quality assessment of RCTs and nRCTs according to the PEDro scale

Study	Eligibility criteria	Random Allocation	Concealed Allocation	Baseline Comparability	Blind Subjects	Blind Therapist	Blind Assessors	Adequate follow-up	Intention-to-treat analysis	Between-group comparisons	Point estimate and variability	TOTAL SCORE
Benzo, 2011 (Study 2)	YES	YES	NO	YES	NO	NO	YES	YES	NO	YES	YES	6/10
Pehlivan, 2011	NO	YES	NO	YES	NO	NO	NO	YES	NO	YES	YES	5/10
Stefanelli, 2013	NO	YES	NO	YES	NO	NO	NO	NO	NO	YES	YES	4/10
Fang, 2013	NO	NO	NO	NO	NO	NO	YES	YES	NO	YES	YES	4/10
Morano, 2013	YES	YES	YES	YES	NO	NO	YES	YES	YES	YES	YES	8/10
Morano, 2014	YES	YES	YES	YES	NO	NO	NO	YES	YES	YES	YES	7/10
Gao, 2014	NO	NO	NO	NO	NO	NO	NO	YES	NO	YES	YES	3/10
GLOBAL SCORE (Median)												5/10

*Eligibility Criteria item des not contribute to total score

Table 4.6: Quality assessment of cohort studies and case series studies according to the Newcastle-Ottawa Scale for cohort studies

Study	Selection	Comparability	Outcome	Total Score
Sekine, 2005	XXXX	XX	XX	8/9
Cesario, 2007	XX	NA	XXX	5/9
Jones, 2007	XXX	NA	XXX	6/9
Bobbio, 2008	XXX	NA	XXX	6/9
Peddle, 2009	XXX	NA	XXX	6/9
Harada, 2013	XXXX	XX	X	7/9
Bagan, 2013	XXX	NA	X	4/9
Divisi, 2013	XXX	NA	XXX	6/9
Bradley, 2013	XXX	XX	XX	7/9
Coats, 2013	XXX	NA	XXX	6/9
Mujovic, 2014	XXX	NA	XXX	6/9
Tarumi, 2015	XXX	NA	XXX	6/9
GLOBAL SCORE (Median)				6/9

4.4.5 Results from individual studies

A summary of the main results of this systematic review can be found in Table 4.7.

Seven out of eight studies reported a statistically significant mean change in VO_{2peak} pre to post-interventions (Jones et al., 2009c, Jones et al., 2007, Peddle et al., 2009a, Bagan et al., 2013, Fang et al., 2013, Stefanelli et al., 2013, Divisi et al., 2013). The study from Coats et al., (Coats V, 2013) found no difference in VO_{2peak} but they reported a significant and clinically meaningful improvement in the Constant-load Endurance Test (CCET) after four weeks of a home-based endurance and strength training. Two studies also registered an increase in the maximal workload (W_{max}) achieved during the CPET (Bobbio et al., 2008, Fang et al., 2013).

Changes in functional capacity measured with the 6MWT demonstrated an improvement from baseline to post-intervention (Jones et al., 2007, Peddle et al., 2009a, Cesario et al., 2007a, Divisi et al., 2013, Morano et al., 2013, Bradley et al., 2013, Coats V, 2013). The study from Benzo et al., (Benzo et al., 2011) failed to find any significant difference after the training using an ISWT but data from this study was not retrievable and therefore it was not possible to calculate the mean difference and 95% C.I. The study from Pehlivan et al. (Pehlivan et al., 2011) found a significant improvement in exercise performance but since they used a non-standardized test the results were not incorporated into the analysis.

Both FVC and FEV_1 were significantly enhanced after the intervention comparing to baseline (Cesario et al., 2007a, Pehlivan et al., 2011, Harada et al., 2013, Bagan et al., 2013, Fang et al., 2013, Divisi et al., 2013, Morano et al., 2013, Bradley et al., 2013, Mujovic et al., 2014, Tarumi et al., 2015). The study from Jones et al., (Jones et al., 2007) found no differences in any of the pulmonary function parameters after eight weeks of intense aerobic exercise training. Only two studies compared the pulmonary function between groups after the surgery. Sekine et al., (Sekine et al., 2005) using an historical control group found that patients who had completed the

prehabilitation programme experienced a smaller reduction in FEV_1 one month after surgery (p =.023). On the contrary, Stefanelli et al. (Stefanelli et al., 2013) compared both groups 60 days postoperatively and found no significant differences.

Assessment of HRQoL after the training yielded no significant improvement in any of the health domains (Peddle et al., 2009a, Coats V, 2013, Morano et al., 2014). However, in comparison to a control group, Xu-Hong Li et al., (Li et al., 2013) found that patients engaging in the rehabilitation programme reported better scores in several domains of the EORTC QLQ-LC30 both at three and six months after the surgery. Due to the small number of studies and uniqueness measurement properties of the questionnaires, mean differences and 95% CI were not calculated for this outcome.

Finally, in terms of post-operative outcomes, post-operative hospital LOS was significantly reduced in comparison to the standard care with the exception of the study conducted by Benzo et al., (Benzo et al., 2011) where the authors were only able to find a trend towards a reduction which was almost statistically significant (p =.058). Post-operative morbidity was also significantly reduced, although studies showed significant heterogeneity (Benzo et al., 2011, Pehlivan et al., 2011, Harada et al., 2013, Fang et al., 2013, Morano et al., 2013, Bradley et al., 2013, Gao et al., 2014, Sekine et al., 2005). Again, the study conducted by Benzo et al., reported only a significant difference in the chest tube duration and the incidence of prolonged air leak while the study by Harada et al., found that the differences were only significant among patients with several co-morbidities (CCI $\geq$ 3).

Table 4.7: Results from individual studies

Study	Outcomes	Results	Limitations
Sekine et al., 2005 (retrospective cohort study)	LOS[i] PPC Pulmonary Function (post-operative FEV_1)	↓ LOS between groups (p =.003) Less change in FEV_1 after surgery (p =.023) No differences in PPCs	Historical control group. Intervention was not fully described. Study limited to patients with poor lung function.
Jones et al., 2007 (prospective case series)	Exercise Capacity (VO_{2Peak}) Functional Capacity (6MWT) Pulmonary function (FEV1, FVC, DLCO)	↑VO_{2peak} (ml/kg^{-1}/min^{-1} and % predicted); p =.002 and p <.001 ↑6MWT (m and % predicted) pre – post intervention (p =.003) No difference in lung function	No control group. Small sample size. Mix of cancer types.
Cesario et al., 2007 (prospective case series)	Pulmonary Function Functional capacity (6MWT)	↑FVC (L, % of predicted); p <.01 FEV_1 (% predicted); p<.05 ↑ 6MWT (m) pre – post intervention (p<.05)	No control group. Small sample size. Protocol was not fully described.
Bobbio et al., 2008 (prospective case series)	Exercise capacity (VO_{2Max}, W_{max}) Pulmonary Function (FEV_1, FVC, DLCO)	↑ VO_{2max} (ml/kg^{-1}/min^{-1}) and L; p =.001 ↑VO_{2max}@AT (ml/kg^{-1}/min^{-1}) and L; p <0.02 ↑W_{max}; p =.001	No control group. Small sample size. Study limited to patients with poor lung function.
Peddle et al., 2009 (prospective case series)	HRQoL (FACT-L; TOI; LCS) Exercise capacity (VO_{2Peak})	No changes in HRQoL pre – post intervention Correlation between changes in VO_{2peak} and ↑fatigue ↓HRQoL pre – post surgery	No control group. Small sample size. Mix of cancer types. Inadequate Follow-up
Jones et al., 2009 (prospective case series)	Exercise Capacity (VO_{2Peak}) Functional Capacity (6MWT) Inflammatory markers	↓ inflammatory markers ↑ VO_{2Peak} (mean change +0.13 L.min^{-1}; p=.002 ↑6MWT (mean +62m; p =.004)	No control group. Small sample size. Mix of cancer types.
Pehlivan et al., 2011 (RCT)	LOS PPC	↓ LOS and PPC (p <.001 and <.05 respectively) ↑ FEV_1 (L), FVC (L), PaO_2, $PaCO_2$ and D_LCO (p <.01) ↑ Exercise performance (P<.001)	Patients in the rehab group were significantly worse in lung function comparing to the control group. There is no description of how exercise capacity was measured (non-standardized test).

	Pulmonary Function (FEV_1, FVC, PaO_2, $PaCO_2$, SaO_2, DLCO) Exercise performance (non-standardized test)		
Benzo et al., 2011 (RCT)	PPC LOS Functional Capacity (SWT)	↓ of chest tube duration in the rehab group and ↓ PAL (p =.03) ↓ in LOS (p =.058) No difference in SWT (p >.05)	Sample size. Low intensity training; duration per session not specified.
Harada et al., 2013 (retrospective cohort study)	Post-operative complications Pulmonary Function (VC, FEV_1)	↓ of post-operative complications only in patients with CCI ≥ 2; p =.0362 ↑FEV_1 and VC pre – post intervention (p <.01)	Historical control group. There were no differences in the preoperative exercise programme between groups except in frequency. The programme was not fully described.
Bagan et al., 2013 (prospective case series)	Exercise Capacity (VO_{2Max}) Pulmonary Function (FEV1)	↑ VO_{2max} (3.5 $ml/kg^{-1}/min^{-1}$); ↑ $PPOVO_{2max}$ (p <.0001) ↑ FEV_1 (12%); ↑ $PPOFEV_1$ (p<.0001)	No control group. Patients shown poor cardiopulmonary fitness at the beginning. Intensity of the endurance training was not individually tailored.
Stefanelli et al., 2013 (RCT)	Exercise Capacity (VO_{2peak}) Pulmonary Function (FEV_1, FVC, FEV_1/FVC, D_LCO)	↑ VO_{2peak} ($ml/kg^{-1}/min^{-1}$) pre-post intervention and in comparison to the control group (p <0.001) both pre – post training and 60 days after surgery; No changes in Pulmonary Function at any point (intra-group or inter-group)	Patients were younger than other series (age <75) and had no severe co-morbidities. Quality assessment was poor.
Fang et al., 2013 (pseudo-RCT)	Pulmonary Function (FVC, FEV_1, FEV_1/FVC, D_LCO, MVV) Exercise Capacity (VO_{2peak}) Post-operative complications LOS HRQoL (results not reported)	↑ FVC (L), FEV_1/FVC, MVV, DLCO and DLCO/VA pre – post intervention (p <.05); No change in FEV_1 ↑ W_{max} (Watts), VO_{2max} (L) and SaO_2 pre - post intervention (p <.01) ↓ LOS in the rehabilitation group (p =.021) No difference in cardiopulmonary complications	Randomization was done among patients who were fit for surgery, while training was performed both in surgical and non-surgical candidates.

		59% patients of the non-operation group fulfilled operation criteria	
Divisi et al., 2013 (prospective case series)	Pulmonary Function (FVC, FEV_1, FEV_1/FVC, PEF, D_LCO) Exercise Capacity (VO_{2peak}) Functional Capacity (6MWT)	↑ FEV_1 (L and % predicted), FVC (% predicted), FEV_1/FVC, PEF (l/s; % predicted) and D_LCO (p <.05); ↑ VO_{2max} (l and $l/kg^{-1}/min^{-1}$), (p <.01) ↑ 6MWT (m) pre – post intervention (p < .00001)	No control group. Patients exhibited very low cardiopulmonary fitness and lung function at the beginning.
Morano et al., 2013 (RCT)	Lung Function (FVC, FEV_1, MIP, MEP, PaO_2, $PaCO_2$, SaO_2, MIP, MEP) Functional Capacity (6MWT) PPC LOS	↑ FVC (L and % predicted); (p <.01), and ↑ MIP and MEP (pre – post intervention); (p <.001) ↑ 6MWT (m) pre – post intervention (p <.001) ↓ LOS and PPCs (p <.05)	
Bradley et al., 2013 (prospective cohort study)	Functional Capacity (6MWT) Pulmonary Function (FEV_1) PPC LOS	↑ 6MWT pre – post intervention (p <0.001) ↑ FEV_1 pre-post intervention (p =.009 ↓ LOS in the rehab group (p =.05) No difference in PPCs	Non-randomized study. Protocol was barely described. High rate of dropouts. Low frequency and total duration of the training.
Coats et al., 2013 (prospective case series)	Exercise Capacity (VO_{2peak}, endurance time) Functional Capacity (6MWT) Muscle Strength HRQoL (SF-36)	No change in VO_{2peak} ↑ CET (s) (p <.05) ↑ Muscle strength (p <.05) ↑ 6MWT (m) (p <.05) No change in HRQoL	No control group. Small sample size.
Xu-Hong Li et al., 2013 (non-RCT)	HRQoL (EORTC QLQ-C30)	At 3 months there were significant differences in global health, physical function and emotional role between groups (p <.05) and fatigue (p =.006) At 6 months HRQoL there was also a significant difference in other symptoms (pain, dyspnoea, constipation, insomnia and appetite loss); p <.0001	The rehabilitation programme was not described. Only measured HRQoL.

Morano et al., 2014 (RCT)	Levels of fibrinogen and albumin HRQoL HADS	↑ fibrinogen levels intra and inter-group (p <.0001) but no changes in albumin levels ↓ Anxiety and Depression (p <.05) No differences in HRQoL	
Mujovic et al., 2014 (prospective case series)	Pulmonary Function (FVC, FEV_1, $FEF_{25,50\%}$, SaO_2) Functional Capacity (6MWT) PPC LOS	↑ FEV_1 (ml), VC (ml) and $FEF_{50\%}$ (p <.001 and p =.006 respectively) ↑ 6MWT (m); p <.01	No control group. Intervention was not properly described (intensity, length of intervention).
Gao et al., 2014 (non-RCT)	Post-operative Complications LOS Average hospital cost	↓ post-operative complications; p <.05 ↓ LOS; p =.00 No difference in hospital cost	Patients were not randomized and only included high-risk patients. Intervention was very short (3 – 7 days) and intensity of the training was low. Complications were of minor severity and include several types.
Tarumi et al., 2015 (prospective cohort study)	Pulmonary Function	↑ FVC and FEV_1 after the training (p <.001 and p <.0001 respectively) both in litres and % of predicted in patients with impaired pulmonary function only	Retrospective study. No analysis of functional capacity or exercise performance.

LOS = Length of Hospital Stay; PPC = Post-operative Pulmonary Complications; FEV_1 = Forced Expiratory Volume in 1 second; VO_{2peak} = Peak Oxygen Consumption; 6MWT = Six Minute Walk Test; FVC = Forced Vital Capacity; DLCO = Diffusion of Carbon Monoxide; W_{max} = Maximal Workload; HRQoL = Health-Related Quality of Life; FACT – L: Functional Assessment of Cancer Therapy – Lung Cancer; TOI = trial outcome index; LCS = lung cancer subscale; SWT = Shuttle Walk Test; VC = Vital Capacity; CCI = Charlson Co-morbidity Index; $PPOVO_{2peak}$ = predicted post-operative VO_{2Peak}; $PPOFEV_1$ = predicted post-operative FEV1; MVV = Maximal Voluntary Ventilation; SaO_2 = Oxygen Saturation; PaO_2 = Partial Oxygen Pressure; $PaCO_2$ = Partial Pressure of Carbon Dioxide; MIP = Maximal Inspiratory Pressure; MEP = Maximal Expiratory Pressure; CET = Constant Cycle-ergometry Test; SF-36 = Short Form 36 Health Survey; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; HADS = Hospital and Anxiety Distress Scale; $FEF_{25,50\%}$ = Forced Expiratory Flow at 25% and 50%.

4.4.6 Synthesis of results

For the primary outcomes (exercise and functional capacity) a large between-study heterogeneity was found and therefore it was consider not appropriate to conduct a meta-analysis and pooled results; to illustrate the results of each study, a forest plot with the standardized mean difference and 95% CI was generated (Figures 4.2 and 4.3). Due to the small number of studies included and the unique properties of the measurement tools, no forest plot was generated for the results on HRQoL.

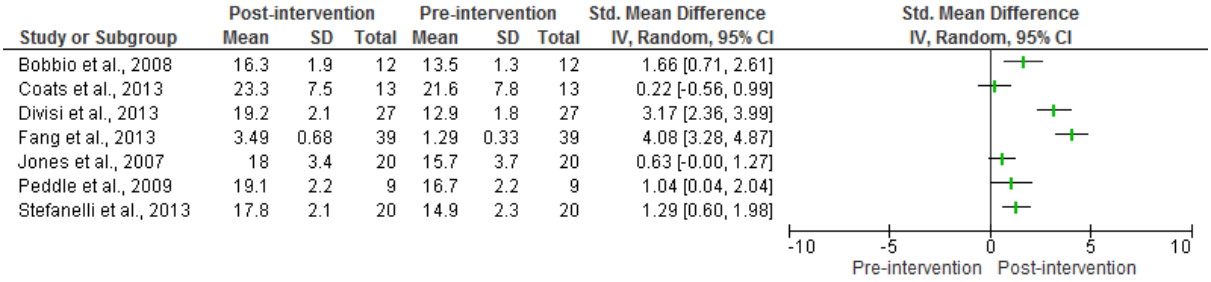


Figure 4.2: Forest plot with SMD and 95% C.I for the studies which examined VO_{2peak} changes pre- to post-intervention.

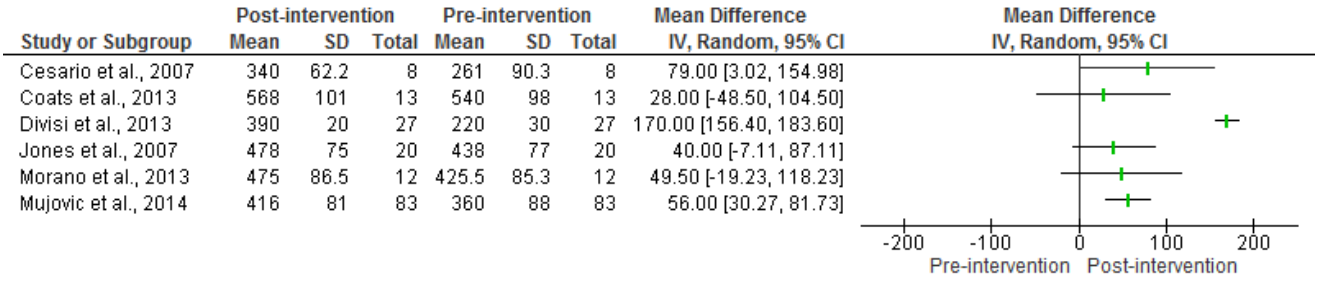
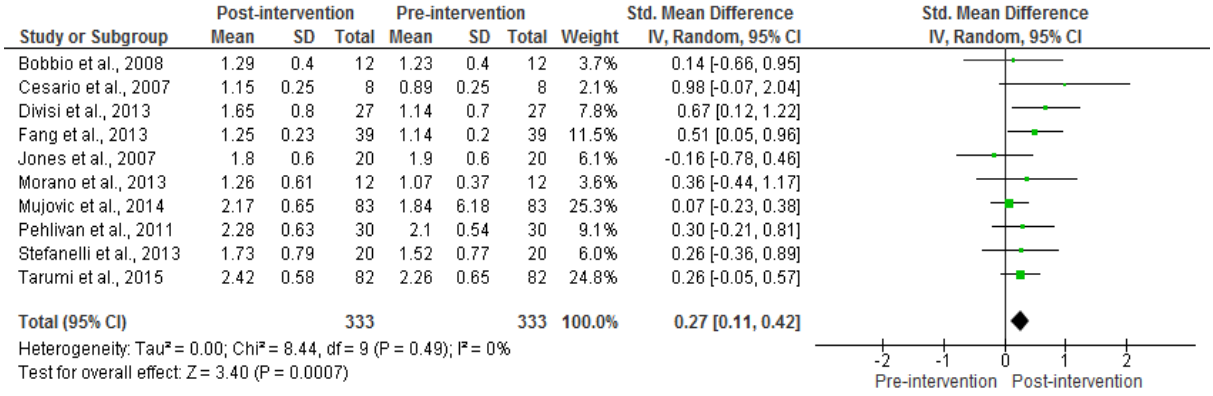


Figure 4.3: Forest plot with SMD and 95% C.I for the studies which examined 6MWT changes pre- to post-intervention.

For each of the other outcomes of interest (FVC, FEV_1, LOS and post-operative complications) a random-effect meta-analysis was performed to estimate the pooled effect size of the interventions. A significant increase for both FEV_1 (SMD = 0.27, 95% CI: 0.11, 0.42) and FVC (SMD = 0.38, 95% CI: 0.14, 0.63) pre to post-intervention was found (Figure 4.4A and 4.4B). In the post-operative outcomes, a significant reduction both in hospital LOS (MD = -4.83, 95% CI: -

5.90, -3.76) and post-operative complications (RR = 0.45, 95% CI: 0.28, 0.73) was obtained (Figures 4.5 and 4.6), although the latter showed substantial heterogeneity (X^2=20.08, p =.005; I^2=65%) (Figure 4.6A). To elucidate the possible reasons, we conducted a subgroup analysis according to the type of complications included (pulmonary alone vs. others) and found that when pulmonary complications were analysed separately, heterogeneity was significantly reduced without reducing the effect size (OR = 0.55; 95% CI: 0.34 - 0.89; p = .24 I^2 = 27%) (Figure 4.6B).

A



B

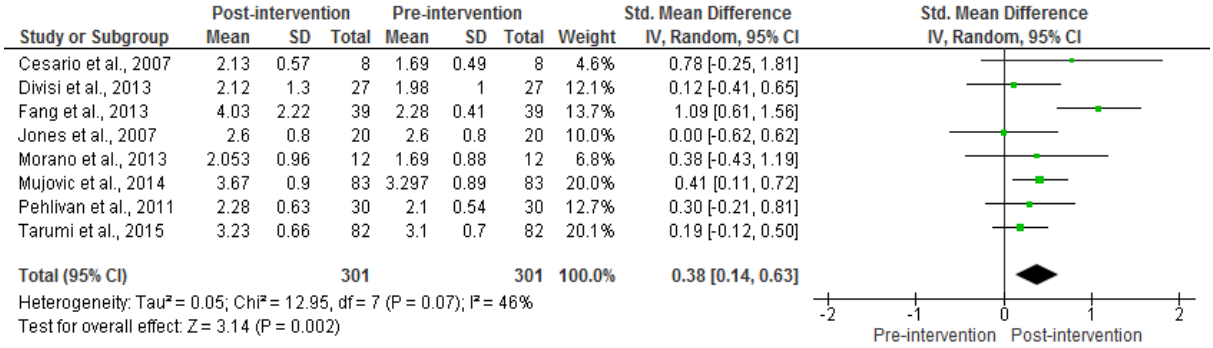


Figure 4.4: Forest plot and pooled estimated effect size of the interventions on FVC (A) and FEV1 (B) .

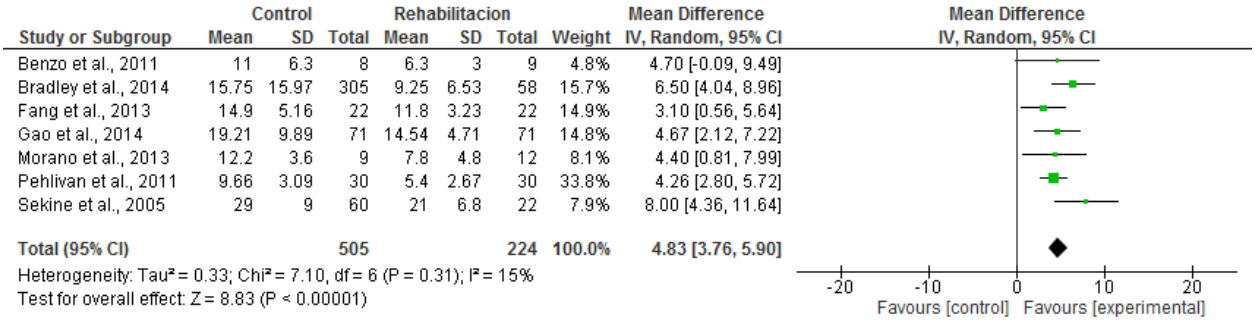
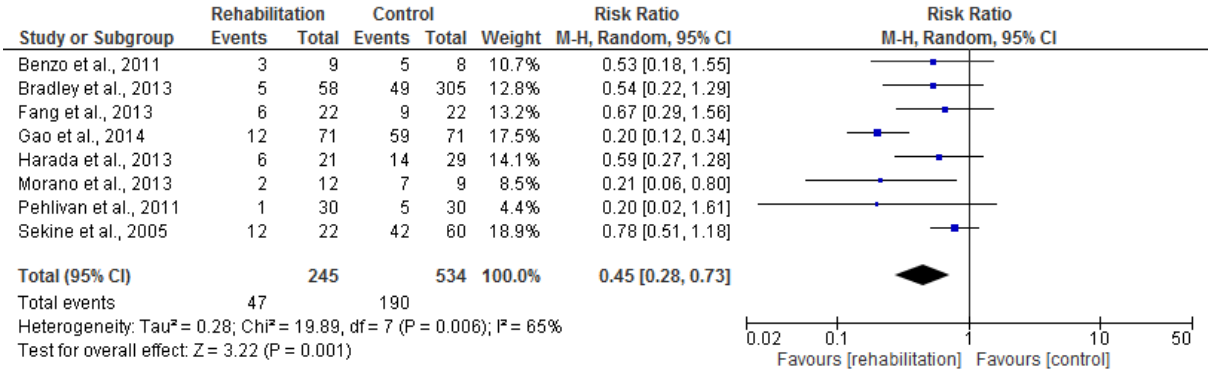


Figure 4.5: Forest plot and pooled estimated effect size for post-operative LOS in the intervention and control groups.

A



B

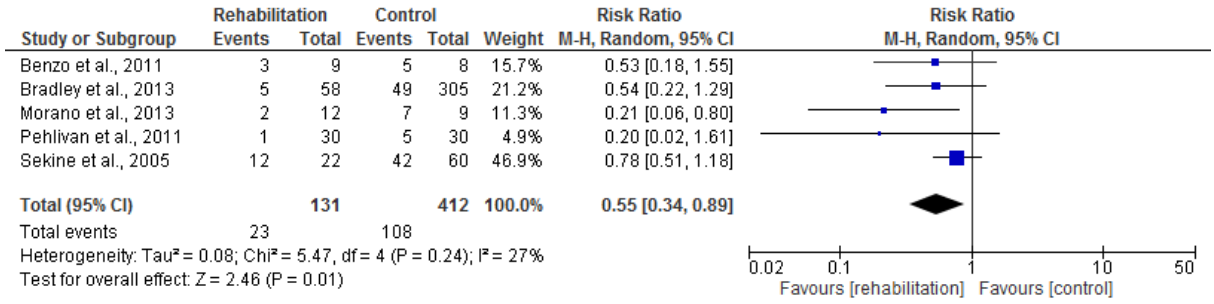


Figure 4.6: Forest plot and pooled estimated effect size of the interventions on overall post-operative complications (A) and pulmonary complications alone (B).

We also conducted a sub-group analysis in LOS and post-operative complications to compare the results obtained with randomized or pseudo-randomized controlled trials versus cohort studies. For the first outcome, we did not find any significant difference between both types of designs (MD = -4.06; 95% CI:-5.22, -2.90 and MD = -6.11; 95% CI: -7.85, -4.36 for RCTs and cohort studies respectively). In both cases, heterogeneity was low. For the post-operative complications however, the mean effect in terms of RR was almost identical but heterogeneity was significantly higher in the cohort studies (I^2 = 82% vs. 0%) (Figure 4.7).

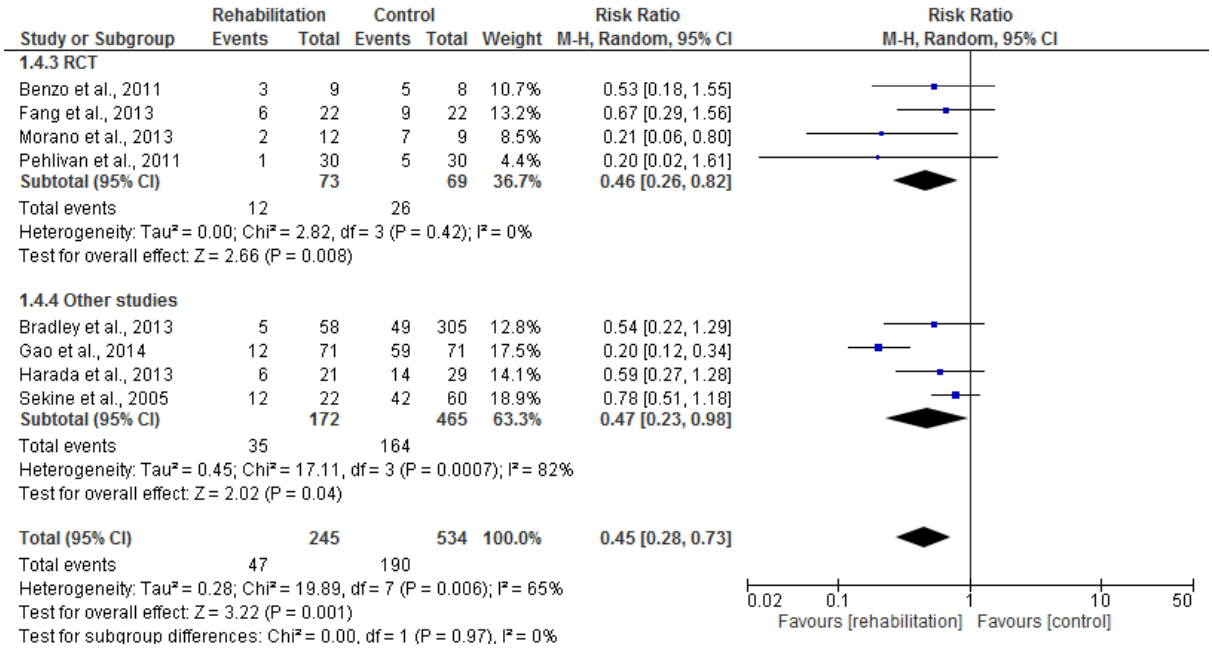


Figure 4.7: Forest plot and pooled effect size of the interventions on post-operative complications in RCTs and cohort studies.

4.5 DISCUSSION

This systematic review aimed to examine the current body of evidence on the benefits of engaging in a preoperative exercise-based intervention for individuals with lung cancer. The results drawn support the hypothesis that preoperative exercise training can significantly reduce hospital stay and the incidence of PPCs, as well as minimize post-operative risk by enhancing pulmonary

function and most likely, exercise capacity. These findings are consistent with the other systematic review conducted in patients awaiting lung resection surgery (Pouwels et al., 2015) and strengthen the evidence for the implementation of such interventions in this population.

When setting up a preoperative pulmonary rehabilitation programme in oncological patients there are several factors that should be taken into consideration. The individual components of the intervention including the modality of training, intensity, frequency and total duration as well as the clinical features of the participants (stage of the disease, presence of co-morbidities, performance status) and the instruments used to measure the intervention-related changes can significantly affect the results obtained. Given the paucity of research in this particular population, the current recommendations in lung cancer stem from those reported for COPD. For instance, duration of the intervention has been conventionally stablished in eight to 12 weeks, with longer training periods usually associated with larger improvements (Jenkins et al., 2010, Spruit et al., 2013). However, in the oncologic setting, the urge to proceed with surgery as soon as possible demands for shorter interventions. In a recent systematic review of the effects of prehabilitation in post-operative outcomes, six to eight weeks have been proposed as an adequate balance between feasibility and efficacy (Debes et al., 2014). This suggestion is consistent with the available literature and the current therapeutic delay reported in lung cancer. According to a retrospective analysis conducted in the UK, the median waiting time in lung cancer to receive the first line of treatment was 48 days (6.8 weeks) which didn't affect the long-term outcomes at any stage of the disease (Bozcuk and Martin, 2001). In another retrospective study, patients with stage I NSCLC undergoing surgical resection with a delay in care of more than eight weeks had an increase in 30-day mortality and a decrease in median survival comparing to those receiving surgical resection within the first eight weeks (57.7±1 months versus 69.2±1.3; p <.001). Therefore the suggested time frame of six – eight weeks seems optimal for delivering a preoperative pulmonary

rehabilitation programme without affecting cancer-specific outcomes. In this systematic review, only one study assessed the feasibility of the intervention (Coats V, 2013) and concluded that a home-based rehabilitation programme for four weeks was safe and feasible. In contrast, study #1 in the RCT of Benzo et al., (Benzo et al., 2011) was promptly closed after one year of recruitment mainly due to the fact that patients or providers were not willing to delay surgery for four weeks. However, based on the results found in some studies included in the systematic review, only two to three weeks of intense pulmonary rehabilitation seem to be enough to yield some improvements in exercise capacity and pulmonary function (Bagan et al., 2013, Fang et al., 2013, Mujovic et al., 2014). Adherence was also scarcely assessed in the studies included ranging from 72 to 80 % (Coats V, 2013, Peddle et al., 2009a, Jones et al., 2009c, Jones et al., 2007) although two more investigations reported 100% of adherence (data provided by the authors upon request) (Bagan et al., 2013, Bobbio et al., 2008). One study recorded two adverse effects and both were reversed after discontinuing the training (Jones et al., 2007). Altogether, these findings suggest that exercise training can be safely achieved before surgery although further research is needed to examine patients' preferences and perceived barriers to improve adherence an optimize results.

Features of training including mode of delivery, duration, intensity and frequency are also crucial when designing a pulmonary rehabilitation programme to achieve the desirable results. Traditionally, endurance training has been the cornerstone of pulmonary rehabilitation but more recently resistance training has also been acknowledged as an essential component to prevent or reverse muscle atrophy and enhance physical functioning. Nowadays, a combination of both endurance and resistance training is regarded as the best strategy to treat peripheral muscle dysfunction in patients with chronic respiratory diseases (Nici et al., 2006). However, the mode of delivery for each component has been poorly assessed and therefore there are no solid recommendations to be made. For example, endurance training can be performed at a constant load

or combining bouts of different intensity. Interval training has been suggested as an alternative to constant training for those patient who are unfit to achieve the targeted intensity for the total duration of the training. Few studies have been published comparing both approaches but it seem that they are equally effective in terms of improving the peak power or VO_{2peak} (Beauchamp et al., 2010). However, interval training could be more easily tolerated given that it facilitates a decrease in end-expiratory lung volume resulting in lower ventilation and less dyspnoea (Andrianopoulos et al., 2014, Puhan et al., 2006). The majority of the studies included in this review used a continuous protocol to deliver the endurance training with intensity ranging from 60 to 100 % of the peak workload. The studies conducted by Jones et al. used a combination of constant and interval training up to 100% of the VO_{2peak} where intensity and duration of the training were increased according to the patient's progression (Peddle et al., 2009a, Jones et al., 2007, Jones et al., 2009c). Given that we could not perform a meta-analysis for this outcome, we cannot compare the effect size of each training modality and examine potential differences in terms of VO_{2peak} but according to the results obtained in each individual study, it appears that there are no differences between the two approaches. Intensity was also very variable in the studies included but it generally achieved 60% of the maximal workload as recommended by the international guidelines (Nici et al., 2006). Only the study by Bagan et al. delivered a low-intensity programme where patients trained for 30 minutes at an intensity of 20 to 30 Watts (Bagan et al., 2013). Even so VO_{2max} and PPO VO_{2max} were significantly increased after the intervention. This demonstrates that cardiopulmonary fitness can be improved even with low-intensity programmes in patients with severe deconditioning and/or at high risk of post-operative morbidity and mortality. With regard to resistance training only five studies included strength exercises in their protocols (Bobbio et al., 2008, Benzo et al., 2011, Morano et al., 2014, Morano et al., 2013, Coats V, 2013). According to the current recommendations, in patients with chronic respiratory diseases, resistance training should be

delivered at medium intensity (55 – 60 % of maximal one repetition) and include two to four sets of 6 to 12 repetitions. Again, there is no current evidence of which training load and/or modality of resistance training provides the optimal results in patients with lung cancer. Overall, in the studies included, patients trained using free weights or elastic bands focusing on low loads and a relatively high number of repetitions. In summary, given the lack of consistency between the studies included in the review in terms of modality of training (continuous vs. interval), type of exercise prescribed (endurance vs. resistance or both), intensity and frequency no conclusions can be extracted and future research is needed to provide specific guidelines in the lung cancer population.

Measurement tools in the lung cancer setting are diverse and their responsiveness is more likely related to the stage of the disease (Granger et al., 2013a). Peak Oxygen Consumption (VO_{2peak}) provides the gold standard for evaluating cardiorespiratory fitness in healthy subjects (Jones et al., 2010) and is a key measurement in the preoperative evaluation of individuals undergoing lung resection surgery, especially for those who exhibit poor lung function (Benzo et al., 2007, Brunelli et al., 2009b, Brunelli et al., 2013a). In addition, it has been acknowledged that VO_{2peak} is a strong and reliable predictor of post-operative mortality and morbidity, HRQoL and long-term survival in NSCLC (Benzo et al., 2007, Loewen et al., 2007, Bobbio et al., 2008, Jones et al., 2010, Brunelli et al., 2014, Bolliger et al., 1996). Endurance training is considered the best way to improve VO_{2peak} in healthy subjects (Jones, 2011) and it has also been successfully prescribed to individuals with several chronic diseases (Gimenez, 2000, Corhay et al., 2012, Lan et al., 2013). The studies included in this systematic review support the premise that endurance training is also able to improve cardiopulmonary fitness in patients with NSCLC. However, due to the large heterogeneity found in the studies, estimated of pooled effect sizes were not obtained and we cannot draw any definitive conclusion. There was only one study that found no change in

VO_{2peak} after the training (Coats V, 2013). In this investigation, Coats et al. examined the effects of a home-based rehabilitation programme consisted of three to five weekly sessions of aerobic and strength training for four weeks. We believe that there are two possible explanations for the lack of results in this study. One, the reported lack of responsiveness of an incremental exercise test to quantify intervention-related changes (Borel et al., 2013), which seems reasonable in this case given that patients did improve their endurance time and functional performance (6MWT). Furthermore, in this study patients were already fit at baseline in terms of exercise capacity (VO_{2peak} 107% of predicted), therefore the intensity and/or total duration of the programme could have been insufficient to yield the physiological adaptations to exercise.

Similarly to exercise capacity, functional capacity was significantly enhanced across studies but heterogeneity was also found to be substantial and thus a meta-analysis was considered not appropriate. The 6MWT was the most common field test used in the studies in consistent with the literature (Granger et al., 2013a). The test has shown a good correlation with VO_{2peak} and perceived physical functioning in people with a variety of chronic diseases and cancer patients and has also proven effective to measure changes after a pulmonary rehabilitation programme (Ross et al., 2010, Schmidt et al., 2013). In this systematic review, four out of six studies reported an increment of more than 42 meters in the 6MWT, which is greater than the minimally clinical important difference (MCID) for individuals with lung cancer (Granger et al., 2015b). Only one study did not find any improvement in the functional capacity after the intervention. In this investigation, Benzo et al. examined the effects of a ten-session, twice-daily intervention of moderate aerobic and strength training using the Incremental Shuttle Walk Test (ISWT) (Benzo et al., 2011). Although the ISWT has shown moderate validity and correlation with the VO_{2peak} measured with a CPET in individuals with lung cancer (Granger et al., 2015a), incremental test are less sensitive to detect changes after an exercise-based intervention (Borel et al., 2013). This has lead researchers to

asseverate that the ISWT can be a good surrogate to CPET to assess functional capacity and stratify patients in the preoperative setting of lung cancer surgery but constant-work rate protocols are probably more responsive to detect changes after a pulmonary rehabilitation programme.

Pulmonary function is considered the key assessment in the physiologic evaluation of the lung resection candidate since both FEV_1 and predicted PPO FEV_1 have been traditionally applied for stratification of perioperative risk (Brunelli et al., 2013a). Similar findings have been reported for the diffusing capacity of carbon monoxide (D_LCO) and particularly, for the PPO D_LCO. Studies have shown that a PPO D_LCO below 60% is a strong predictor of cardiopulmonary complications and mortality even in patients with otherwise normal pulmonary function (Brunelli et al., 2013a, Brunelli et al., 2007a). Optimizing FEV_1 and D_LCO through targeted exercises in the preoperative period of lung cancer might result in an increase in surgical rates, improving patients' prognosis and prolonging disease-free and overall survival. In a preoperative randomized controlled trial published by Weiner et al., IMT plus incentive spirometry resulted in an improvement in pulmonary function in COPD patients awaiting lung resection surgery although this wasn't translate into a reduction in hospital stay or post-operative pulmonary complications (Weiner, 1997). Results of this meta-analysis showed that a significant increase both in FEV_1 and FVC can be achieved after a preoperative exercise-based intervention. These findings are consistent with another systematic review and meta-analysis conducting in post-surgical lung cancer patients. In this study, breathing exercises improved pulmonary function in terms of FEV_1 (SMD = 3.37; 95% CI: 1.97-4.77; p <.001) and FEV_1/FVC (SMD = 1.77; 95% CI: 0.15-3.39; p =.032) (Liu et al., 2013). In another systematic review involving patients with COPD, breathing exercises (including IMT, deep breathing exercises, pursed lips breathing and incentive spirometry) significantly enhanced functional capacity (MD = 45 meters; 95% CI: 29-61) but had no effect on HRQoL or dyspnoea (Holland et al., 2012). Despite this, breathing exercises are not systematically

recommended for patients with chronic respiratory diseases. It is worth noticing though, that breathing exercises have been insufficiently described in the literature and are arbitrarily used to refer to several interventions, which can lead to undesirable and biased results (Garrod and Mathieson, 2013).

The HRQoL was infrequently assessed in the studies included. This is not entirely surprising since according to one systematic review of randomized trials for the treatment of lung cancer, only 36% of the studies published contained information about HRQoL (Sarna and Riedinger, 2004). However, a growing interesting in the subject has emerged given the prognostic role of HRQoL in lung cancer survival (Pompili et al., 2013, Li et al., 2012, Moller and Sartipy, 2012). Unfortunately, studies examining the effects of exercise training on HRQoL have yielded disappointing results, showing little to no change in the majority of the domains (Jones et al., 2008, Arbane et al., 2011, Stigt et al., 2013). In this line, the studies included in our review have also failed to find any significant improvement in HRQoL after the prehabilitation (Peddle et al., 2009a, Morano et al., 2014, Coats V, 2013). More interestingly, the only study which compared HRQoL to a control group during the post-operative period found significant differences in global health, physical functioning and symptom severity both at three and six months after the surgery (Li et al., 2013). However, this was a non-randomized study with several methodological flaws, so these findings should be interpreted carefully.

Finally, post-operative morbidity is regarded as the main cause for increased hospital costs and long-term impairments. PPCs are particularly the most costly and are associated with prolonged hospital stay in comparison to patients without pulmonary complications (Cassidy et al., 2013, Sabate et al., 2014, Branson, 2013). In the long-term, PPCs have been also shown to impact cancer-related survival reducing disease-free and overall survival across all stages (Rueth et al., 2011). Risk factors associated with post-operative complications include advanced age (≥75 years

old), PPO FEV_1 or PPO D_LCO ≤60%, cardiovascular morbidity, neoadjuvant therapy, low cardiorespiratory fitness, smoking status, obesity and the presence of COPD (Brunelli et al., 2007a, Brunelli et al., 2013b, Jones, 2011, Stephan et al., 2000, Agostini et al., 2010, Amar et al., 2010). Several studies have been undertaken to assess the efficacy of perioperative interventions to prevent complications after cardiothoracic surgery but results are conflicting (Agostini et al., 2010, Reeve et al., 2010, Varela et al., 2006, Weiner, 1997, Yañez-Brage et al., 2009, Sobrinho et al., 2014). Yañez et al., in an observational study conducted in patients undergoing off-pump CABG found that preoperative chest physiotherapy including breathing exercises and incentive spirometry effectively reduced the incidence of atelectasis (17% vs. 36%; p =.01) (Yañez-Brage et al., 2009). Sobrinho et al., in another prospective study involving patients undergoing myocardial revascularization found a significant reduction in post-operative LOS in patients undergoing preoperative physiotherapy (IMT and breathing exercises) comparing to the control group (Sobrinho et al., 2014). In this meta-analysis, a significant reduction both in post-operative LOS and post-operative complications was found, with the latter showing a Relative Risk Reduction (RRR) of 55% in those patients undergoing prehabilitation in comparison to the standard care. Furthermore, when pulmonary complications were assessed separately, we observed that the mean effect size was maintained and heterogeneity across studies was remarkably reduced (from I^2=65%; p =.02 to I^2=27%; p =0.24). The lack of consensus in the definition of PPCs is most likely the main responsible for the controversial results found in the literature. Several diagnostic tools have been proposed to homogenously assess the frequency and severity of PPCs such as the MGS, which aims to identify those complications that are more likely to be prevented with a physiotherapy intervention (Reeve et al., 2010). Unfortunately, only one study in this review used this scale to assess post-operative complications (Bradley et al., 2013). The majority of the studies included as PPCs events of different severity and therapeutic management, such as pulmonary embolism,

bronchopleural fistula, atelectasis, prolonged air leak, pneumonia, respiratory failure or re-intubation, which considerably hinder the comparison and generalization of results.

4.6 LIMITATIONS

This systematic review and meta-analysis has several limitations that must be acknowledged. First, given the lack of RCTs published in the field, we also included non-randomized controlled trials and observational studies, which are more easily biased and can potentially affect the validity and reliability of the findings. Notwithstanding, in the sub-group analysis performed comparing RCTs with cohort study, both LOS and PPCs showed little change in the mean effect size. In addition, because most studies were series of cases, the principal summary measurements (exercise capacity and functional capacity) were calculated pre to post-intervention, so it remains unclear whether a preoperative pulmonary rehabilitation programme provides better functional outcomes in the post-operative period in comparison to the standard care. Furthermore, the between-studies heterogeneity has prevented us from conducting a meta-analysis in those outcomes. Finally, assessment of publication of bias was not considered appropriate in the meta-analysis because of the small number of studies involved. However, the novelty of the research field (the oldest article being published in 2005), plus the differences found in the results (with some studies showing little to no results) suggest that most likely publication of bias has not influenced our findings.

4.6 CONCLUSIONS

The results of this systematic review are indicative that an exercise-based intervention performed in the preoperative period of lung cancer surgery improves pulmonary function and most likely exercise and functional capacity before surgery. Furthermore, prehabilitation of patients with lung cancer appears effective in reducing post-operative pulmonary complications and length of

hospital stay in patients undergoing thoracotomies. However, further research involving larger RCTs are needed to validate these results and elucidate the effectiveness of the intervention on other outcomes such as HRQoL and survival.

CHAPTER FIVE: Feasibility of a preoperative pulmonary rehabilitation programme in patients awaiting VATS for lung malignancies: a single-arm pilot study.

5.1 INTRODUCTION AND RATIONALE

The main concern for implementing a prehabilitation programme in oncological patients is the need to proceed with surgery as soon as possible. As discussed in the previous chapter, traditional exercise programmes should last between eight to 12 weeks, with longer training periods usually leading to better results (Spruit et al., 2013, Nici et al., 2006, Ries et al., 2007). However, in individuals with cancer who are waiting to undergo surgery, the urge to proceed with the planned treatment calls for shorter interventions. Six weeks of pulmonary rehabilitation are the minimum recommended to achieve sustainable effects, although physiologic improvements have been seen as early as two – four weeks (Shannon, 2010). The Swedish Lung Cancer Study Group recommend that 80% of all diagnostic test should be completed within four weeks from the first consultation and treatment should start within two weeks thereafter (Myrdal et al., 2004). A therapeutic delay of > eight weeks has been associated with poor disease-free and overall survival in patients with stage I NSCLC undergoing lung resection surgery with curative intent (Samson et al., 2015). Consequently, six to eight weeks have been proposed as an optimal time frame to deliver a preoperative intervention both in terms of feasibility and efficacy (Debes et al., 2014).

Feasibility refers to the ultimately capacity of something to be done or undertaken considering all the variables involved. Feasibility in the context of an exercise intervention is usually assessed in terms of cost-effectiveness, tolerability, safety, adherence to the protocol prescribed and preliminary responsiveness. Adherence is define by the WHO as the extent to which a person's behaviour corresponds with agreed-on recommendations by the health care provider and is a crucial health behaviour in the management of chronic respiratory diseases (Nici et al., 2006). Feasibility studies are usually designed to determine if an intervention is appropriate for further

testing in a larger sample. These investigations are necessary when there is not enough evidence on the effectiveness of a particular treatment. There are eight major areas in which a feasibility study can be focused on (Table 5.1) (Bowen et al., 2009). In this pilot study, we specifically focused on the implementation, practicality and preliminary efficacy.

Table 5.1: Key areas of focus of feasibility studies and possible outcomes; adapted from Bowen et al., 2010

Area of focus	Outcomes of interest
Acceptability	• Satisfaction • Intent to continue use • Perceived appropriateness • Perceived positive or negative effects on organization
Demand	• Actual use • Perceived demand
Implementation	• **Degree of execution (recruitment rate, adherence)** • Success or failure of execution • **Amount, type of resources needed to implement** • Factors affecting implementation ease or difficulty
Practicality	• **Positive/negative effects on participants (safety)** • **Ability of participants to carry out the intervention** • Cost analysis
Adaptation	• Degree to which similar outcomes are obtained in new format
Integration	• Perceived fit with infrastructure • Perceived sustainability • Cost to organization and policy bodies • Fit with organizational goals and culture • Positive or negative effects on organization
Expansion	
Limited Efficacy	• **Intended effects or programme or process on key intermediate variables** • Effect-size estimation • **Maintenance of changes from initial change**

Safety is also a critical aspect when implementing an exercise-based intervention, especially in frail populations such as COPD or cancer. Before starting an exercise programme, a comprehensive evaluation of the exercise capacity and health status is needed to individualize the

exercise prescription and explore potential limitations (Spruit et al., 2013). There is accumulating evidence that exercise in the context of cancer is effective and safe across all stages, although the majority of the research has been conducted in cancer survivors or patients undergoing active treatment (Granger et al., 2013b, Cheema et al., 2014, Jones et al., 2008, Hoffman et al., 2013, Schmitz et al., 2010). Few studies have been undertaken in patients with lung cancer awaiting surgery thus the feasibility and safety of the intervention in this particular context is still not clear (Jones et al., 2007). Moreover, no study has focused on patients undergoing videothoracoscopic surgery. Given these circumstances, we conducted a pilot single-arm study to test the feasibility, tolerability and safety of a supervised preoperative exercise intervention in patients awaiting VATS for lung malignancies.

5.2 OBJECTIVES

The primary aim of this study was to assess the feasibility and safety of a preoperative pulmonary rehabilitation programme in patients undergoing videothoracoscopic surgery for lung malignancies. Secondary objectives included:

- To explore the changes in functional capacity, muscle strength and HRQoL before and after the intervention.
- To depict the decline in physical and psychological functioning during the first post-operative months after VATS.
- To determine if three months after the surgery the patients have reached their baseline values in terms of fuctional capacity, muscle strength and HRQoL.

5.3 HYPOTHESIS

We hypothesized that 1) a preoperative exercise programme was feasible (patients achieved at least 80% of adherence) and safe (not associated with any severe adverse effect and 2) the

intervention was optimal in frequency and intensity to yield significant and clinical changes in the main outcomes.

5.4 MATERIALS AND METHODS

5.4.1 Design

This was a non-randomized single-arm pilot study.

5.4.2 Participants

From February 2013 to June 2013 we screened all patients being considered for lung resection surgery for lung malignancies at the University Hospital of A Coruña, Spain. Inclusion and exclusion criteria are shown in Table 5.2.

Table 5.2: Inclusion and Exclusion Criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
- Adults only (>18 years old) - Suspected or histological diagnosed of NSCLC either primary or metastatic - Health area of A Coruña - No contraindications for exercise therapy	- Neoadjuvant therapy with chemotherapy or radiotherapy in the 6 months prior to surgery - Not signed the informed consent - Inability to perform the PPRP, no cooperation or no capacity to adhere the programme

Potentially eligible patients were initially contacted by phone and scheduled for an interview with a specialized physiotherapist. In this first interview, an information sheet was given to the patients explaining the purpose of the study (Supplemental file no.3). Those who agreed to participate gave written informed consent prior to any formal testing.

The research protocol was approved by the local ethics committee in the context of a larger randomized controlled trial (CEIC Galicia, 2011/395) (Supplemental file no.1).

5.4.3 Intervention

The PPRP consisted of one and a half hour session, three to five times per week, during the preoperative waiting period (ranging from four to 12 weeks) including endurance and resistance training as well as conventional chest physiotherapy and breathing exercises.

Endurance training

Endurance training was performed using a calibrated cycle-ergometer (Monark 818 E, Monark Exercise AB, Sweden) with an initial targeted duration of 30 minutes.

In the first session, an incremental exercise test was conducted according to the American College of Chest Physicians guidelines (ATS/ACCP, 2003) to determine the peak workload (W_{peak}). Each training session patients completed an interval protocol combining four minutes at low intensity (45 – 50% of the W_{peak}) with one minute at high intensity (80 - 85% of the W_{peak}). A five-minute warm-up and a four-minute cool down at 30% of the W_{peak} were also included in the 30 minutes. After the first 10 sessions, intensity was maintained and the goal was to increase total duration to 40 minutes.

Resistance training

Resistance training was performed using elastic bands (Thera-Band®, The Hygienic Corporation, Akron, Ohio, USA) and bodyweight exercises. Patients performed six out of ten exercises proposed by the investigators targeting the main muscle groups involved in daily life

activities. A detailed description and illustration of the exercises can be found in the Supplemental file no. 7. The initial goal was to perform three sets of 15 repetitions of each exercise during the first 10 sessions; from the 10th session onwards number of sets increased to four – five if possible. Training load for the Thera-band® exercises was determined after a 25 maximal repetition test (Newsam, 2005) and patients were asked to maintain a moderate rate of exertion (five - six) according to the OMNI-Resistance Scale of Perceived Exertion during the training. The OMNI-RES is a tool that helps to control intensity during strength training exercises that can be applied to men, women, boys and girls alike and has been validated to use with elastic bands (Figure 5.1) (Colado et al., 2012).

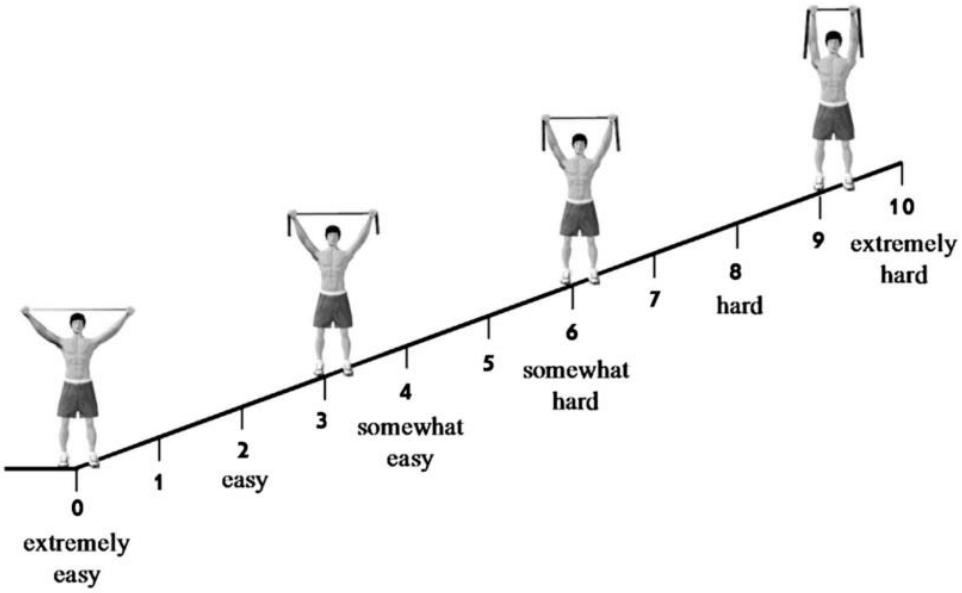


Figure 5.1: The OMNI-RES of perceived exertion with elastic bands; Colado, 2012.

Breathing exercises

Breathing exercises and airway clearance techniques were provided at the end of the session according to the patients' needs. Participants were also encouraged to do breathing exercises at home with a volume-oriented incentive spirometer (Coach 2 Incentive Spirometer 22-4000 HD, Smith Medicals, USA). The protocol consisted of 30 sustained inspirations at 80% of the maximal Vital Capacity (VC) with an end-inspiratory hold of two to three seconds (Westerdahl et al., 2005,

Yañez-Brage et al., 2009). Patients were taught to perform six cycles of five repetitions each, with one minute rest between cycles. Participants were asked from time to time about the performance of the exercises to ensure compliance and understanding of the protocol.

Each training session was recorded and kept in a codified data sheet (Supplemental file no. 4).

5.4.4 Outcomes

Patients were evaluated at four points during the study period: T1: at baseline; T2: after the preoperative rehabilitation programme; T2: immediately after surgery (one week after hospital discharge) and T3: three months after surgery. The results of each evaluation were kept in an individual, codified data collection sheet.

Safety and feasibility

Feasibility of the intervention was determined using the following criteria: on one hand, we calculated the percentage of patients who consented from those who fulfilled the inclusion criteria (recruitment rate) and on the other hand, the percentage of sessions attended relatively to the number of sessions scheduled (adherence). Mean preoperative time was estimated in 6 weeks. Using a training frequency of at least 3 times per week, the number of sessions planned was 18.

Safety was described as the absence of any adverse events requiring medical consultation or additional treatment.

Functional capacity

Functional Capacity refers to a person's ability to perform daily life activities that require sustained aerobic metabolism and it's a reflection of the integrated efforts and health status of the pulmonary, cardiovascular and skeletal muscle systems (Arena et al., 2007). The gold standard for the assessment of functional capacity is VO_{2peak} using a CPET (Arena et al., 2007, Jones et al., 2009a). However, the CPET is expensive and time-consuming and therefore is not available in

most clinical and rehabilitation settings. The 6MWT is a field test derived from the 12-minute run test developed by Cooper et al. in the late 1960's, which was later adapted to fast walking and accommodated to patients with respiratory disease who found the 12-minute walk too exhausting. The test has proven to be safer, easier to administer, better tolerated and more reflective of the activities of daily living than other walk tests (American Thoracic Society, 2002, Enright, 2003). The 6MWT is a self-paced test and therefore is considered a submaximal test (contrary to the CPET); however, since the majority of the activities of daily living are performed at sub-maximal level of exertion, the test may be more adequate to measure functional capacity (Enright, 2003, American Thoracic Society, 2002). The 6MWT has shown good correlation with the measured VO_{2Peak} in patients with diverse cardiopulmonary disorders (correlation coefficient (r) ranging from .21 to .7) and cancer (r =.67) (Ross et al., 2010, Schmidt et al., 2013). In NSCLC, the 6MWT is the most common field test used to assess functional capacity (Granger et al., 2013a) and it has shown to predict post-operative complications and survival (Marjanski et al., 2015, Jones et al., 2012). The test has also shown good sensitivity to measure changes after a pulmonary rehabilitation programme in chronic respiratory diseases (Holland et al., 2014, Singh et al., 2014).

To perform the test, the Spanish Society of Respiratory Medicine and Thoracic Surgery (SEPAR) and the ATS guidelines were applied (American Thoracic Society, 2002, Burgos-Rincon and Casan Clara, 2004). Patients were asked to walk as fast as they could during six minutes between two marks on an inside 40-meter corridor. Heart rate, oxygen saturation, dyspnoea and fatigue were recorded at the beginning and at the end of the test. Oxygen saturation and heart rate were also monitored during the test using a portable pulse oximeter. Encouragement was given every one minute according to the international recommendations. Total walked distance was calculated once the test was finished. Duplicate tests were performed at baseline for reliability and the maximum distance covered was used for the analysis.

Muscle strength

Muscle strength was assessed using a modified version of two items included in the *Senior Fitness Test* (SFT) developed and validated by Rikli and Jones (Rikli and Jones, 2013). The SFT is a battery of tests specifically designed to measure functional fitness in older adults. Functional fitness is defined as having the physiologic capacity to perform normal everyday activities safely and independently without undue fatigue (Rikli and Jones, 2013). Selection of the items included in the SFT was made basing on two principles: a) validity and reliability and b) easy to administer and feasible. With that in mind, two items were selected to measure muscle strength: the *Arm Curl Test* and the *30's Chair to Stand Test*. The first examines upper body strength by counting the number of times a hand weight of 5lb for women and 8lb for men can be curled through a full range of motion in 30 seconds (Figure 5.2A). In our study, two dumbbells of two and 3.5 kg were used for females and males respectively according to the estimated equivalence in the International Unit System (IUS). The *30's Chair to Stand Test* evaluates lower body strength by counting the number of times within 30 seconds that an individual can rise to full stand from a seated position without pushing off with the arms (Figure 5.2B). For this test chair height was 43.5 cm according to the metric equivalent of the original height (Rikli and Jones, 2013).

The SFT was performed in the same sequence for all the evaluations: first, the Arm Curl test followed by the Chair to Stand Test. Only one trial with partial practice the same day was allowed for each of the tests and the obtained values were compared to the normative scores (Rikli and Jones, 1999).

Figure 5.2: Curl Arm (A) and Chair to Stand (B) to assess muscle strength with the SFT; Rikli and Jones, 2001.

Health-related quality of life

HRQoL was assessed using the second version of the Short Form 36 Health Survey (SF-36). This generic questionnaire encompasses 36 items offering an overview of an individual's health status in eight major dimensions: 1) limitations in physical activities because of health problems; 2) limitations in social activities because of emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being; 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue) and 8) general health perceptions (Ware and Sherbourne, 1992). The test was developed in 1992 to be either self-administrated or by a trained interviewer in person or by telephone (Ware and Sherbourne, 1992). In 1996 the second version of the questionnaire was released which among other improvements included a summary of the eight dimensions into two major categories: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) which provide an easiest evaluation of the physical and psychological well-being (Figure 5.4).

The items in the SF-36 represent both positive and negative health status, so for each dimension they are codified, aggregated and transformed into a 0 – 100 score (where 0 represents the worst possible health status for that particular dimension). The questionnaire was validated into Spanish in 1995 and the normative data for the Spanish population including those over 60 years was extracted in two subsequent samples (Alonso et al., 1998, López-García et al., 2003). To facilitate the interpretation of the results, the scores are usually presented as the standardized mean, where 50 represent the general population mean and 10 the standard deviation (SD) (Vilagut et al., 2008).

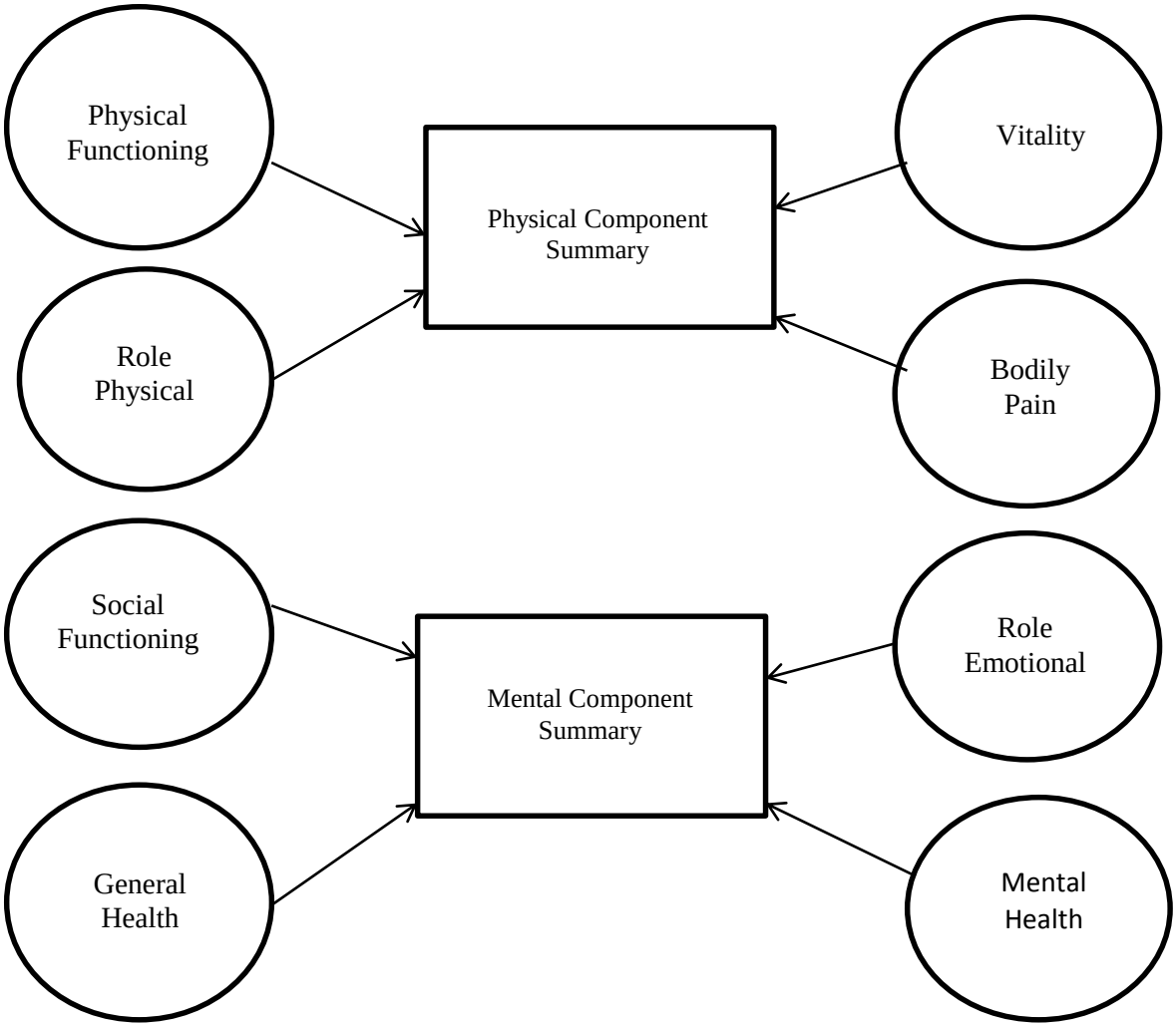


Figure 5.3: SF-36 Health domains

In this study, the questionnaire was self-administrated whenever possible but patients were assisted if they required further explanations of the questions. The SF-36 can be found in the Supplemental file no.6.

Post-operative outcomes

Data from the medical records was reviewed regarding the Length of Hospital Stay (LOS) and the number of Post-operative Pulmonary Complications (PPC) along with other perioperative features.

5.4.5 Sample size calculation

This study was not powered to detect any specific difference in the outcomes measured so there was no real estimation of the sample size. Instead, a pragmatic sample of ten patients was chosen to assess the feasibility of the study and preliminary effects of the intervention.

5.4.5 Statistical analysis

Initially, a descriptive analysis of the participants regarding the main socio-demographic and clinical variables was performed. Despite the normal distribution of the main variables, non-parametric tests were used due to the small sample size. At first, a Friedman Test was conducted to compare the main outcomes at T_0, T_1, T_2 and T_3. If a significant difference was found, then the Wilcoxon Signed rank Test was used in order to examine specific pairwise differences.

Univariate and multivariate regression analysis were used to identify the potential risk factors associated with a decrease in the post-operative functional capacity.

All statistical analyses were performed using the SPSS package for Windows (Version 20; IBM Corporation, Chicago IL, USA) and a p value of $<.05$ was considered statistically significant.

5.5 RESULTS

During the study period, 23 potentially eligible patients were evaluated, and 12 met the inclusion criteria and provided informed consent (recruitment rate 56.2%). Reasons for exclusion were not interested (n=4), lack of transportation (n=2), severe musculoskeletal impairment (n=2), urgent surgery (n=2) and referral to neoadjuvant therapy (n=1). Two patients withdrew during the study due to difficulties to attend the PPRP and another patient was excluded because surgery was declared urgent. A flow diagram of the study is shown in Figure 5.4. Finally, nine patients were enrolled. Baseline characteristics are shown in Table 5.3.

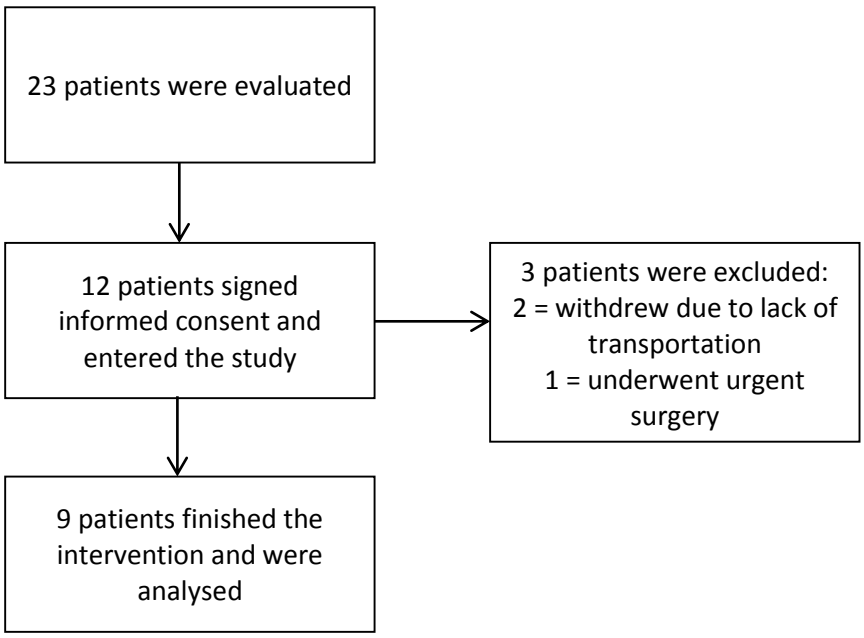


Figure 5.4: Flow diagram of the study.

Table 5.3: Baseline characteristics

VARIABLE	**VALUE (n=9)**
Age (years)	68.56 (10.36)
Sex (% men)	88.9%
BMI	29.15 (3.83)
History of Smoking	
No	1 (11.1%)
Former	6 (66.7%)
Current	2 (20.2%)
Co-morbidities (%)	
COPD	6 (66.6%)
Arterial Hypertension	3 (33.3%)
Diabetes Mellitus	1 (11.1%)
Cardiovascular Disease	2 (22.2%)
Previous History of Cancer	2 (22.2%)
CCS	7.56 (3.35)
Symptomatology (%)	
None	4 (50%)
Cough	2 (25%)
Dyspnoea	2 (25%)
Expectoration	4 (50%)
Other	0
Lung Function (% of predicted)	
FVC	83.11 (14.45)
FEV1	69.89 (13.92)
FEV1/FVC	62.22 (9.74)
6MWT (meters)	557.56 (74.43)
6MWT (% predicted)	89.35%
Curl Arm Test (nº)	16.89 (5.35)
Chair Sit-to-Stand Test (nº)	14.56 (5.91)
Maximal Workload Achieve (Watts)	72.77 (20.28)
Extension of resection (%)	
Lobectomy	6 (66.7%)
Wedge Resection	3 (33.3%)
Post-operative Diagnosis (%)	
Adenocarcinoma	2 (22.2%)
Squamous Cell Carcinoma	4 (44.4%)
Lung Metastases	2 (22.2%)

Benign	1 (11.1%)
Stage of Disease	
IA-IB	4 (50%)
IIA-IIB	2 (25%)
Lung metastases	2 (25%)

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FVC: Forced Vital Capacity; FEV_1: Forced Expiratory Volume in 1 second; CCS: Colinet Co-morbidity Score; 6MWT: 6 Minute Walking Test

Overall adherence was 109.9% with patients attending a median of 21 sessions of the 18 initially scheduled (range 11 – 27). Only one patients achieved <80% of adherence. The improvement in the 6MWT and muscle strength experienced by this participant was similar than that observed in patients with overall adherence ≥80%. No adverse events were recorded.

All patients underwent surgery by VATS through one or two ports. The mean waiting period before surgery was 71.44±17.55 days. Mean LOS was 5.11±4.01 days. Two patients (22.2%) experienced one or more PPC: prolonged air leak >7 days in both cases, and pneumothorax in one case.

Results of the functional outcomes are summarized in Table 5.4 and Figures 4.4 and 4.5. A borderline significant improvement of 22.55±30.11 meters (p =.050) was achieved in the 6MWT after the PPRP (T_0 to T_1). Upper and lower body strength were significantly enhanced after the intervention, from 16.89±5.35 to 20.67±2.64 repetitions (p =.028) and from 14.56±5.92 to 15.86±3.93 repetitions (p =.016) respectively. The *Chair Sit-To-Stand* Test was obtained only for seven patients because another participant was unable to complete the test due to knee discomfort.

Table 5.4: Results for the functional capacity and muscle strength

Variable	**T0**	**T1**	**T2**	**T3**
6MWT (m)	557.56±74.43	580.11±80.67	489.67±98.69** †	529.63±83.23
Curl Arm Test (nº)	16.89±5.34	20.67±2.64*	20±3.28**	19.25±3.19††
Chair Sit-To-Stand Test (nº)	14.56±5.91	15.86±3.93*	16.11±4.98	13.22±6.98

*p <.05 between T_0 and T_1; **between T_0 and T_2; †between T_1 and T_2 ††between T_0 and T_3;

After the surgery, all measurements significantly decreased both comparing to baseline and pre-surgery. Functional capacity decreased by 67.88±65.52 meters (p =.011) from T_0 to T_2 and by 90.44±63.35 meters from T_1 to T_2 (p =.08). Upper body strength also decreased from T_0 to T_2 (p =.050) while no change was found for lower body strength (p >.05). At T_3, functional capacity and muscle strength were fully recovered (the 6MWT was 105.5 ± 6.8% of the baseline values and upper and lower body strength were 80 ± 14% and 88±13.4% respectively)

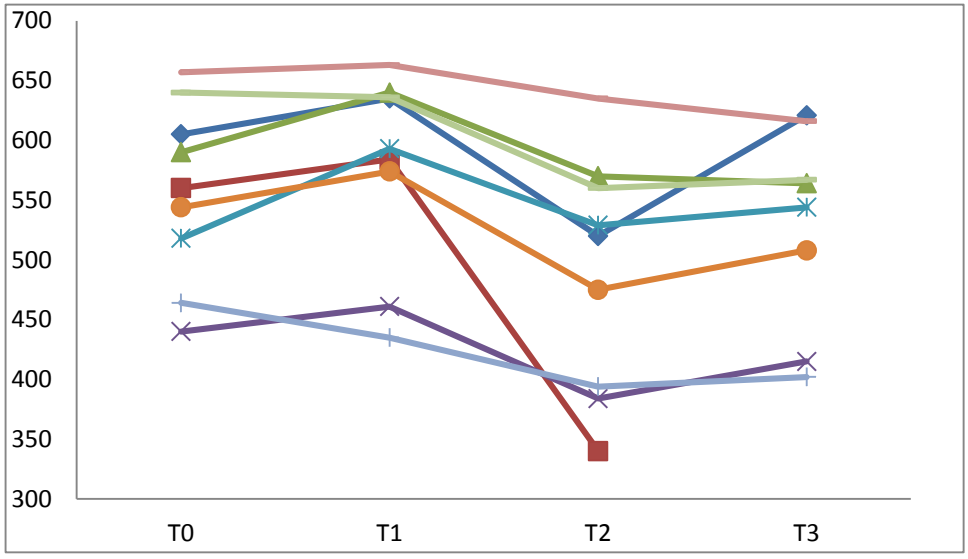


Figure 5.5: Individual tendency for the 6MWT during the study period.

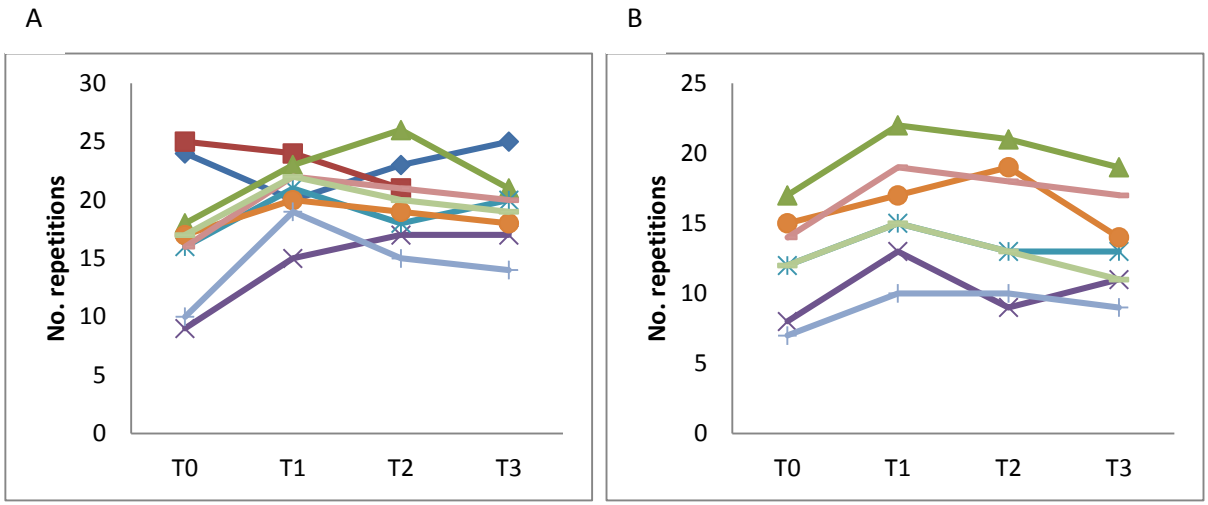


Figure 5.6: Individual changes for the Curl Arm Test (A) and The Chair to Stand Test (B) during the study period.

Results from the HRQoL are shown in Table 5.4. At baseline, HRQoL scores were below normative data. At T_1 all items were improved, although the difference was only statistically significant for the Mental Health Subscale (72±11.3 to 80±10.2; p =.041). In the early post-operative period (T_2), all items decreased comparing to baseline and pre-surgery, especially the physical role (from 61.66±18.04 pre-surgery to 37.77±21.37 post-surgery; p =.012). Three months after surgery, all items were restored comparing to baseline (P>.05). A summary of tendency for PCS and MCS throughout the study period is shown in Figure 5.7. One patient did not complete the three-month follow-up due to hospitalization for other causes.

Table 5.5: Changes in HRQoL throughout the study period

HRQoL Domain	T0	T1	T2	T3
Physical Functioning	79.4±4.4	79.4±12.6	67.2±23.1	82.5±15.1
Role Physical	56.1±26.2	62.2±18.1	37.8±21.4 ¥	59.4±14.5
Bodily Pain	71.8±28.8	76.5±28.1	64.4±30.1	74.5±23.7
General Health	52.9±37.7	68.9 ±18.5	64.1±24.8	68.7±22.6
Vitality	61.7±24.6	65.6±14.9	59.4±19.1	71.2±14.3
Social Functioning	83.3±25.8	91.7±16.5	84.7±25.6	87.5±22.2
Role Emotional	71.8±13.2	71.85±13.2	54.8±24.2 ¥	69.2±21.9
Mental Health	72±11.3	80±10.2*	69.8±22.5 ¥	73.5±18.4

*p <0.05 T0 to T1; ¥p <0.05 T1 to T2

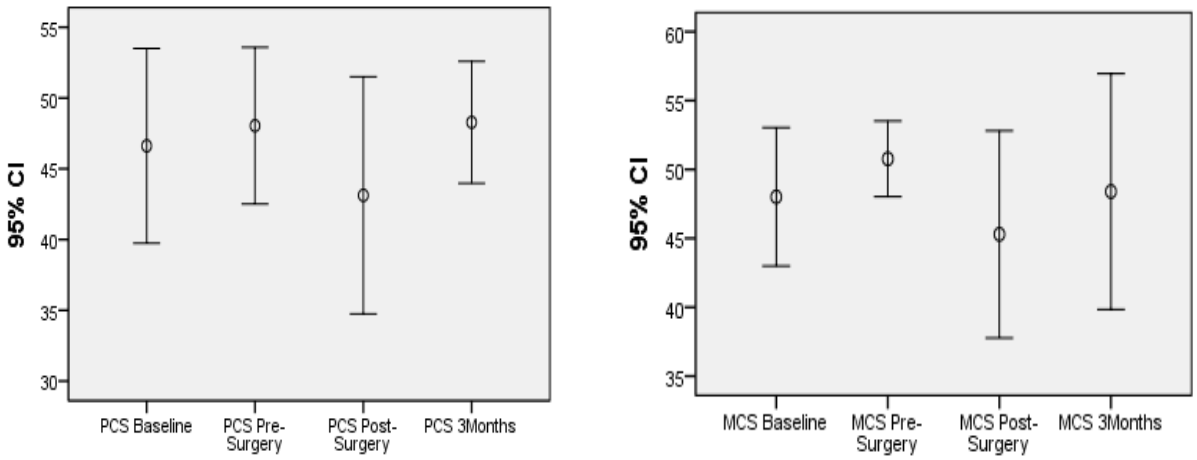


Figure 5.7: PCS and MCS tendency throughout the study period.

Univariate analysis indicate that after surgery, the 6MWT was highly correlated to the baseline FEV_1, baseline physical functioning and baseline PCS. In the multivariate analysis the PCS was identified as an independent factor for the post-operative 6MWT (R^2 = .58).

5.6 DISCUSSION

The results of this preliminary pilot study suggest that a PPRP for patients awaiting VATS is feasible, safe, and can potentially improve functional capacity and muscle strength, optimizing the patients' baseline status before lung resection surgery.

Eligibility and recruitment rate, adherence and completion rate are key components in assessing the feasibility of an exercise protocol. The eligibility rate is fundamentally affected by the inclusion and exclusion criteria established by the investigators but also by the designated location from where the participants are picked. For instance, Granger et al. in a pilot randomized trial in patients with NSCLC, reported an eligibility rate of only 18% in a general thoracic clinic, reflecting the heterogeneity of the institution and significantly affecting the potential number of participants eligible for the study (Granger et al., 2013b). The recruitment or consenting rate refers to the number of patients from those eligible who participate in the study and is a reflection of the willingness of the patients to exercise. In our study, we achieved a recruitment rate of 52.2% which although it could be considered as low, it is similar to other feasibility studies conducted in lung cancer patients (Coats V, 2013, Granger et al., 2013b, Jones et al., 2008, Kuehr et al., 2014). In contrast, completion rate was 75%, superior to some other studies including patients with NSCLC (Missel et al., 2015, Temel et al., 2009, Kuehr et al., 2014, Andersen et al., 2013) but certainly improvable. For instance, in the study conducted by Coats el at., a home-based programme in lung cancer patients awaiting surgery resulted in a 81% completion rate (Coats V, 2013). Jones et al. also reported a 90% completion rate in a preoperative exercise-based intervention and a 95% after a post-operative 14-week training programme (Jones et al., 2008, Jones et al., 2007). The modality of exercise prescribed, timing and setting of the intervention as well as the baseline status of the participants are features that can affect the completion rate in patients with lung cancer and need to be specifically addressed in the future.

For an exercise intervention to be successful it is fundamental that participants adhere to the prescribed programme. Adherence in the oncological setting is challenging to say the least and is most likely influenced by numerous clinical, demographical and socio-economic factors. In a meta-analysis looking at the factors influencing adherence in cancer survivors, inconsistent results were found in the majority of the factors studies. As a matter of fact, the only factor positively associated across studies was exercise history (referring to a past habit of engaging in exercise training or physical activity). Correlates of adherence in NSCLC have been scarcely investigated. According to a study conducted by Peddle et al. in NSCLC survivors, females were at higher risk of poor exercise adherence comparing to males (Peddle et al., 2009b). In another study looking at the adherence trajectory in patients undergoing treatment for breast cancer, the authors found that women with higher perceived importance of exercise, early-stage disease and employed status were more likely to be classified as good intensity adherents (Huang et al., 2015a). In our study adherence exceed our own expectations and achieved a mean of 109%, with only one patient attending <80% of the prescribed sessions. This adherence rate is better than reported in other preoperative studies (Jones et al., 2007, Peddle et al., 2009a, Peddle et al., 2009b) but we must acknowledge that the therapeutic delay observed in our study was longer than predicted (71.4±17.50 days). Again, timing of the intervention (pre, post- or during active treatment), setting and type of exercise prescribed can also significantly influence the compliance of the patients to an exercise intervention. For example, Hoffman et al. in a pilot investigation examining the adherence to a virtual reality home-based training programme in postthoracotomy lung cancer patients reported an 88% adherence (Hoffman et al., 2014). Most likely, exercise interventions which are designed to be conducted at home or using a combination of supervised and unsupervised exercise sessions would result in better overall adherence in this population across the cancer continuum.

Although this is the first preoperative intervention to include only patients undergoing VATS, other similar studies have been conducted in recent years in patients submitted to thoracotomy which allows us to compare our findings in the outcomes examined. Between 2007 and 2009, Jones *et al*. published the results of a preoperative pulmonary programme on exercise tolerance, inflammatory markers and other functional variables. They found a significant increase both in the distance covered with the 6MWT and VO_{2peak} after a median of eight weeks of aerobic training (Jones et al., 2009c, Jones et al., 2007). Cesario *et al*., in 2007, conducted a small pilot study evaluating the effects of a 4-week intervention in patients who were denied surgery because of their poor lung function and reported a significant increase of 79 meters in the 6MWT along with an improvement in pulmonary function (Cesario et al., 2007a). More recently, Mujovic et al. conducted an intense preoperative rehabilitation programme of three daily sessions of aerobic training lasting two to four weeks and found an improvement of 56 meters (p =.0001) in the 6MWT (Mujovic et al., 2014). In the same line, Divisi et al. examined the effects of a four-week preoperative pulmonary rehabilitation programme in patients with lung cancer and COPD and reported a significant improvement in the 6MWT from 220 to 390 meters (Divisi et al., 2013). Bradley et al. in a cohort study of patients undergoing lung resection surgery found a significant improvement in the 6MWT of 20 meters after a low frequency training programme (p =.001) (Bradley et al., 2013). Finally, Morano et al. in a randomized controlled trial comparing conventional chest physical therapy with pulmonary rehabilitation for four weeks, found that there was a significant change in the 6MWT of 50 meters only for the PR group (p <.001). These results are consistent with our research, since we also found an increase in the distance walked with the 6MWT of 22.55±30.11 meters (p =.050) after the training. Although this difference did not reach statistical significant importance by a very small margin, the improvement was clinically meaningful according to the minimal clinical important difference (MCID) reported for lung cancer

patients (Granger et al., 2015b). Postoperatively, we found a significant decrease in the 6MWT comparing to baseline of 67.9±65.5 meters (p =.01). Even so, patients were over 80% of the preoperative values, which is consistent with previous research and demonstrates that in contrast to open surgery, functional exercise capacity is restored within the first week after VATS (Ueda et al., 2006).

We also found a significant improvement in muscle strength after the PPRP according to the SFT. The SFT is a battery of test designed to measure functional fitness in older adults. Considering that the lung cancer population is mostly old and carries a significant history of co-morbidities, the test seems an appropriate and affordable choice to measure changes in functional fitness after an exercise programme. Plus, each item included in the SFT has been successfully measured against the gold standard in the field. For example, both the *Arm Curl Test* and the *30's Chair to Stand Test* have been compared with the maximal one-repetition test (1RM) showing an intra-class correlation coefficient (ICC) of .79 and .77 respectively (Rikli and Jones, 2013). The SFT has been used in several populations, including dwelling elderly people and individuals with chronic diseases. Alexander et al. in a study comparing the effectiveness of two training modalities in older patients with COPD observed that both groups improved all SFT items with no significant differences between groups (Alexander et al., 2008). Peddle et al., in a study conducted in post-surgical lung cancer patients, reported significant improvements in several items of the SFT (*Arm curl, Chair sit to stand* and 6MWT) after a resistance training programme with weight machines (Peddle-McIntyre et al., 2012). Finally, Fahlman et al. studied the effects of a 16-week semi-supervised strength training programme using elastic bands on functional fitness in older but otherwise healthy individuals and found significant improvements both in the *Arm Curl* and the *30's Chair To Stand Test* pre to post intervention and in comparison to a control group (Fahlman et al., 2011). These findings are consistent with our results since we also reported significant

improvements in both items of the SFT, but especially in the *Arm Curl Test*, which shows that elastic bands can improve muscle strength and that the SFT is sensitive to change after an exercise-based intervention in the lung cancer population.

Another secondary endpoint in this study was changes in HRQoL after the training. As previously reported, lung cancer patients frequently exhibit low levels of quality of life both in comparison to healthy individuals and other cancer survivors and are also considered at higher risk of experience functional decline after surgery (Granger et al., 2014). Unfortunately, as discussed in the previous chapter, so far the effects found after an exercise-based intervention are inconsistent and not very encouraging. Riesenberg et al. in a study conducted in patients with lung cancer after surgery and/or after radio- or chemotherapy found overall significant improvements in HRQoL according to the EORTC QLQ-C30 L13 and the SF-36 (Riesenberg and Lubbe, 2010). In another longitudinal single-arm study involving patients after lung cancer surgery, participants improved their HRQoL from 56.3 to 65.9 (p <.05) and more importantly, the improvements were maintained six months after the rehabilitation (Vandenbos et al., 2015). On the contrary, Arbane et al. in a randomized controlled trial in postthoracotomy patients found no changes in HRQoL pre to post intervention or between groups (Arbane et al., 2011). Morano et al. in another randomized controlled trial in preoperative lung cancer patients found an improvement of eight points in the PCS after four weeks of endurance and resistance training but the interaction effect between time and group was not statistically significant (Morano et al., 2014). Features of the training including intensity, frequency, mode of delivery and the number of participants could partially explain the variation observed across studies. Also, the instrument selected to measure HRQoL can substantially affect the results obtained. In our study, we chose the SF-36 given the heterogeneity of the lung resection candidate and to facilitate the external comparison of our results (Nici et al., 2006). Our results showed an overall improvement in HRQoL but only the mental health domain

achieved statistical significance. Nevertheless, our sample size was too small to detect any significant improvement in HRQoL. Given that most studies conducted in cancer patients have reported positive changes in quality of life after the interventions, larger sample sizes would likely result in both statistical and clinically meaningful improvements. Therefore, we encourage researchers to undertake powered randomized controlled trials to confirm the effects of exercise on HRQoL.

5.7 LIMITATIONS

This is study has several limitations that must be addressed. First, this was a non-randomized single-arm study, so we lack of a control group to confirm that our results are due to the prescribed intervention. Second of all, our sample size was too small to detect significant differences in some of the outcomes of the study, such as functional capacity and HRQoL. Also, inclusion criteria were broad and thus the baseline characteristics of the patients were heterogeneous, especially in terms of age and pulmonary function. Finally, due to lack of financial support we weren't able to obtain a more accurate measurement of the selected outcomes although, as previously discussed, the instruments used instead have been extensively validated in the literature and therefore they shouldn't affect the validity of our results.

5.8 CONCLUSIONS

In conclusion, we believe that a preoperative rehabilitation programme for patients awaiting lung resection for VATS is safe and feasible and has the potential to improve functional fitness and enhance exercise performance. Larger randomized controlled trials are warrant to determine whether or not these findings can enhance post-operative functional recovery and reduce length of hospital stay and post-operative complications.

CHAPTER SIX: Effectiveness of a preoperative pulmonary rehabilitation programme to improve exercise capacity and enhance post-operative recovery in patients undergoing VATS: a randomized, single-blind controlled trial.

6.1 INTRODUCTION AND RATIONALE

Throughout this thesis, it has been well-documented that individuals with NSCLC frequently experience functional deconditioning across the lung cancer continuum which can lead to increased dyspnoea, decreased physical activity and impaired HRQoL. Additionally, these clinical features can be further aggravated by anti-cancer therapies, especially after lung resection surgery. Fortunately, low exercise capacity and functional deconditioning are two modifiable risk factor in the onset of thoracic surgery (Jones et al., 2009a); therefore, interventions designed to improve pre-surgical exercise capacity should be of clinical benefit in lung cancer (Shannon, 2010).

Pulmonary Rehabilitation (PR) is a comprehensive, interdisciplinary intervention aimed to restore the patient to his or hers highest possible level of independent function (Ries et al., 2007). One salient aspect of this definition is that the programme must be individually tailored according to the patient's baseline status (Celli, 2003). Plus, rather than only focusing on reversing the progress of the disease, a pulmonary rehabilitation programme is designed to reduce the symptoms and disabilities associated with the disease and enhance functionality.

In 1974 the American College of Chest Physicians (ACCP) defined PR for the first time. In 1980, the American Thoracic Society (ATS) issued its first official statement on the topic in which the pulmonary rehabilitation components were described in detail and the list of benefits were specified. More recently, a task force from the European Respiratory Society (ERS) and the ATS updated the pulmonary rehabilitation definition to *"a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited*

to, exercise training, education and behaviour change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours". This new definition entails two important modifications regarding the previous one stated in 2006. First, the shift from a multidisciplinary to an interdisciplinary intervention, in the sense that the latter involves analysing, synthetizing and harmonizing links between disciplines into a coordinated and coherent whole instead of them working separately. Secondly, the new definition highlights the importance of behaviour changes as a mean to achieve long-term results and promote a new lifestyle.

The ultimately goals of PR are a) to control, alleviate and as much as possible reverse the symptoms and pathophysiologic processes leading to respiratory impairment and b) to enhance the patient's physical and psychological well-being. To achieve those goals, PR includes several components such as exercise training, nutrition, self-management education and psychological support. Exercise is considered the cornerstone of PR and therefore is an essential, mandatory aspect of the programme (Ries et al., 2007, Nici et al., 2006, Nici and ZuWallack, 2014, Wilson, 1997, Celli, 2003). Conventionally, exercise training in PR was delivered in the form of endurance training for the lower limbs, given their role in performing the majority of the daily life activities such as walking. Endurance training can be defined as an activity in which the body's large muscle groups are moved in a rhythmic manner for sustained periods of time (Chodzko-Zajko et al., 2009). The specific aims of endurance training are to re-condition the muscles of ambulation and improve cardiorespiratory fitness to increase physical activity and eventually reduce breathlessness and fatigue (Spruit et al., 2013). Endurance training is most commonly prescribed in the form of cycling or walking (Figure 6.1). Walking has the benefit of being a more functional exercise and benefits can be easily translated into daily life. Biking, on the other hand, places a greater specific load on the quadriceps muscles and results in less exercise-induced oxygen desaturation, thus is usually

advocated for patients with moderate to severe chronic respiratory diseases (Spruit et al., 2013). Aerobic training at high intensity (≥60% of peak exercise capacity) for at least 30 minutes three times per week is the minimum recommended by the main guidelines to elicit physiologic changes (Nici et al., 2006, Andrianopoulos et al., 2014). However, less than 20% of patients with severe chronic disease may be able to sustain this continuous high-intensity exercise throughout the PR (Andrianopoulos et al., 2014). In this case scenario, interval training can be a more reasonable alternative for this population. This modality of training consists of repeated short periods of exercise at high intensity alternated with rest (Andrianopoulos et al., 2014). Both regimes have shown to elicit similar physiologic improvements in healthy individuals but interval training could be a better choice for those patients with severe respiratory impairment or advanced muscle atrophy that have difficulty in achieving their targeted intensity or total duration.

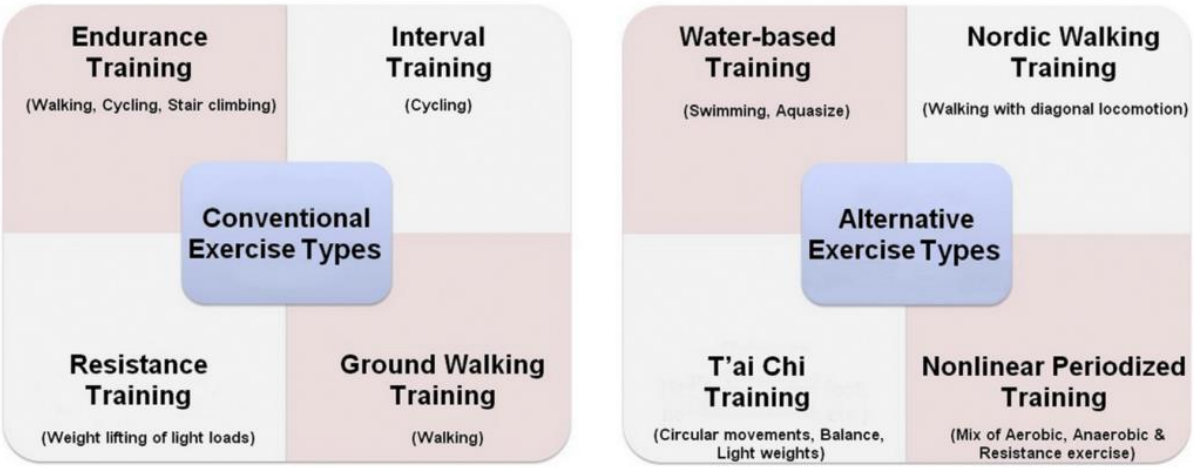


Figure 6.1: Training modalities in PR; Andrianopoulos et al., 2014.

More recently, resistance training has been acknowledged as another key component in PR given the peripheral muscle dysfunction shown by patients with COPD. Resistance training is a type of exercise modality in which local muscle groups are trained by repetitive lifting of relatively heavy loads and it is designed to enhance several aspects of muscle performance (such as maximal strength, muscle endurance or muscle mass) (Andrianopoulos et al., 2014, Spruit et al., 2013). It is

well-established that COPD also affect the peripheral muscles by decreasing muscle mass and muscle force, aggravating general weakness, fatigue and dyspnoea. The role of resistance training in PR to reverse this muscle deconditioning is crucial since aerobic training alone is only able to induce suboptimal increases in muscle mass or muscle strength. However, resistance training should never be regarded as a replacement for endurance training. Given this rationale, the combination of endurance and strength training is probably the best strategy to treat peripheral muscle dysfunction in chronic respiratory disease (Nici et al., 2006).

The minimum duration of exercise training in pulmonary rehabilitation has not been specifically investigated but current recommendations agreed that a minimum of 20 sessions or 8 to 12 weeks are preferable, with longer training periods resulting in overall larger improvements, especially in exercise capacity. Patients should exercise at least three times per week, and regular supervision is strongly advocated to achieve optimal physiologic benefits (Nici et al., 2006, Jenkins et al., 2010). General recommendations for endurance training are shown in Table 6.1.

Table 6.1: Recommendations for endurance training; Jenkins et al. 2010

Prescription for physiologic benefits	
Mode	Walking, cycling
Frequency per week	Two supervised sessions Encourage patients to perform two or three unsupervised sessions
Duration	At least 30 min
Intensity	>60% maximum work rate
Progression	According to symptoms

PR is a relatively inexpensive, low-tech therapy for patients with chronic diseases. However, when setting up a pulmonary rehabilitation programme there are minimum requirements that should be fulfilled. In addition to an adequate space to perform the exercise training such as a rehabilitation room or a gym, minimal equipment is required to perform the training and monitor basic vitals (Table 6.2).

Table 6.2: Equipment required for a pulmonary rehabilitation programme; Jenkins et al., 2010

Minimum requirement	Optional
Pulse oximeter	Weights machine/multigym
Polar heart rate monitor	Stationary cycle
Sphygmomanometer	Spirometer
Odometer (for walking test/track)	Glucometer
Stopwatch	Inspiratory muscle training device
Walking track/treadmill	Rollator
Hand weights	
Stairs/step	
Portable oxygen and nasal prongs	

Evidence of the effectiveness of PR fundamentally stems from studies in COPD and other chronic respiratory diseases. During the past decade, a growing interest in the potential role of PR in lung cancer patients has emerged and preliminary results are promising (Edvardsen et al., 2015, Shannon et al., 2010, Granger et al., 2013b). Patients with lung cancer could benefit from PR across the whole lung cancer continuum (Jones et al., 2009a). Particularly, in the preoperative period, PR could increase exercise and functional capacity leading to an improvement in lung resection outcomes (Benzo, 2007, Rivas-Perez and Nana-Sinkam, 2015). PR has also been recommended for patients who are considered unfit to undergo surgery in an attempt to improve their baseline cardiorespiratory fitness with satisfactory results (Jones et al., 2013, Cesario et al., 2007a). In a

retrospective study involving post-pneumonectomy patients, the lack of preoperative physiotherapy was also an independent predictor of post-operative pulmonary complications (Algar et al., 2003). Combining PR with conventional chest physiotherapy also decreases the incidence of relevant respiratory complications such as atelectasis (Nagarajan et al., 2011). As a result of fewer post-operative complications, length of hospital stay can also be shortened in patients undergoing PR (Morano et al., 2013, Pehlivan et al., 2011). However, these studies have been mostly conducted in patients undergoing thoracotomy. With the advent of VATS, new randomized controlled trials are warrant to examine the effects of a preoperative pulmonary rehabilitation programme (PPRP) in this surgical context.

6.2 OBJECTIVES

The two main purposes of this randomized controlled trial were 1) to assess the effects of a PPRP on exercise tolerance (endurance time) in patients awaiting VATS and 2) to compare the effectiveness of the intervention to enhance post-operative recovery in comparison to the standard care (no intervention).

Secondary study endpoints included:

1. To measure changes in muscle strength and HRQoL before and after the intervention.
2. To compare functional capacity, muscle strength and HRQoL in the rehabilitation and control groups in the post-operative period to assess the effectiveness of the intervention to enhance functional recovery after VATS.
3. To compare the incidence of post-operative pulmonary complications (PPCs) and length of hospital stay between the rehabilitation and the control group.
4. To examine the risk factor associated with a decrease in functional capacity and exercise tolerance after VATS for lung cancer.

6.3 HYPOTHESIS

Our hypothesis for this study was that a preoperative exercise-based pulmonary rehabilitation programme would improve exercise tolerance, muscle strength and health-related quality of life in patients with confirmed or suspected lung cancer awaiting VATS. We also hypothesized that patients in the intervention group would performed better in the exercise testing in the post-operative period in comparison to the control group.

6.4 MATERIAL AND METHODS

This research protocol was designed according to the Consolidated Standard of Reported Trials (CONSORT) guidelines and was registered in the database of clinical trials (clinicaltrials.gov) under the registration number NCT01963923. The protocol was approved by the local Ethics Committee (CEIC Galicia, 2011/395).

6.4.1 Design

This was a randomized (1:1 ratio), assessor-blinded controlled trial conducted at the University Hospital of A Coruña (Spain) serving a population of 550.000 inhabitants.

6.4.2 Participants

From October 2013 to April 2015 (18 months) patients who were scheduled for lung resection surgery at the Thoracic Department of the hospital were assessed for eligibility. Inclusion and exclusion criteria are summarized in Table 6.3.

Table 6.3: Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
- Adults only (>18 years old) - Suspected or histological diagnosis of NSCLC. - Having, at least, one of the following conditions: $FEV_1 \leq 80\%$ of predicted value; and/or BMI ≥ 30; and/or age ≥ 75 years and/or having two or more co-morbidities such as AH, Diabetes, COPD, cardiovascular disease, renal impairment and/or past history of cancer. - Distance to the facility centre ≤ 80 km.	- Neoadjuvant therapy with chemo- or radiotherapy in the 6 months prior to surgery. - Reconversion to open thoracotomy during surgery. - Bilobectomies or pneumonectomies. - Inability to perform the exercise training; no cooperation or lack of adherence. - Not signed the informed consent.

*NSCLC = Non-Small Cell Lung Cancer; FEV1 = Forced Expiratory Volume in the 1 second; BMI = Body Mass Index; AH = Arterial Hypertension; COPD = Chronic Obstructive Pulmonary Disease

Patients were considered eligible if they have confirmed or suspected resectable NSCLC and presented at least with one of the conditions listed in table 6.3. The clinical features selected as inclusion criteria were chosen based on the current evidence of the potential risk factors associated with poor post-operative outcomes and/or poor prognosis (Amar et al., 2010, Barrera et al., 2005, Agostini et al., 2010, Wilson, 1997).

Potentially eligible patients were initially contacted by phone and scheduled for an interview with a specialized physiotherapist. After carefully reading the information sheet and posed any questions they might have, those who agreed to participate gave written informed consent prior to any formal testing (Supplemental file no.3).

Patients were randomized using a 1:1 ratio after they completed the baseline assessments. Group allocation was revealed to the patient by same investigator responsible of the PPRP but only after the initial evaluations were completed.

6.4.3 Intervention

Patients were randomly allocated to receive either a PPRP (rehabilitation group) or standard care (control group). Patients in the control group were monitored by their general practitioners during the preoperative period and only if required. Meanwhile, patients in the experimental group engaged in a 1-hour, three to five times per week exercise-based intervention including the following:

Endurance training

The general principles of exercise training in individuals with chronic diseases are no different from those for healthy individuals or even athletes. These basic principles are: a) overload (only loads higher than those imposed in daily life activities will provoke physiological changes); b) specificity (the acquired physiological changes are only shown in the exercise practiced); c) periodization and variation of the training (in order to achieve progress as the physiologic changes occur) and d) reversibility (meaning the total or partial loss of the effects achieved after discontinuing the training) (Spruit et al., 2013, Celli, 2003).

Intensity is an important determinant of the physiological responses to exercise training (Garber et al., 2011). According to the principle of overload, intensities below a minimum threshold will not result into the physiological changes required to increase VO_{2peak} and exercise capacity. As aforementioned, a training intensity that exceeds 60% of the peak exercise capacity is empirically considered sufficient to elicit some physiologic training effects when the total effective training exceeds 30 minutes (Nici et al., 2006). Lower intensities (50% of peak work rate) have also shown to improve symptom management and HRQoL, and could also increase exercise capacity in more deconditioned patients (Garber et al., 2011). However, in some cases, it may be impossible for the patient to achieve the targeted intensity and/or duration due to severe ventilatory limitation and/or muscle atrophy. Interval training has been proposed as a more suitable alternative

in this population given that the placement of rest periods decreases ventilatory requirements and exercise-associated dyspnoea (Andrianopoulos et al., 2014). A recent meta-analysis conducted in healthy individuals aged 18 to 45 found that both continuous and interval training elicit large improvements in VO_{2max} when comparing to no training. In addition, the authors observed that for subjects with typically lower baseline fitness, the improvements were greater with the interval training. Furthermore, when comparing both training modalities, there was an increased benefit of the high interval training comparing to continuous modality on VO_{2max} (MD: 1.2 ml/kg-1/min-1 ±0.9) (Milanović et al., 2015). In contrast, in patients with COPD interval training appears equally effective to continuous training to increase cardiorespiratory fitness (Beauchamp et al., 2010). Additionally, attendance rates and dropouts did not differ between groups. The variation in the modality used to deliver the interval training including work: rest ratio, peak intensity and total duration of the exercise could largely affect the results of the comparison.

In this study, endurance training was performed using a calibrated cyclo-ergometer (Monark 818 E, Monark Exercise AB, Sweden) with an initial targeted duration of 30 minutes according to the previous recommendations. Training load (Watts) was determined after a symptom-limited incremental cycle test. The test was performed according to the American

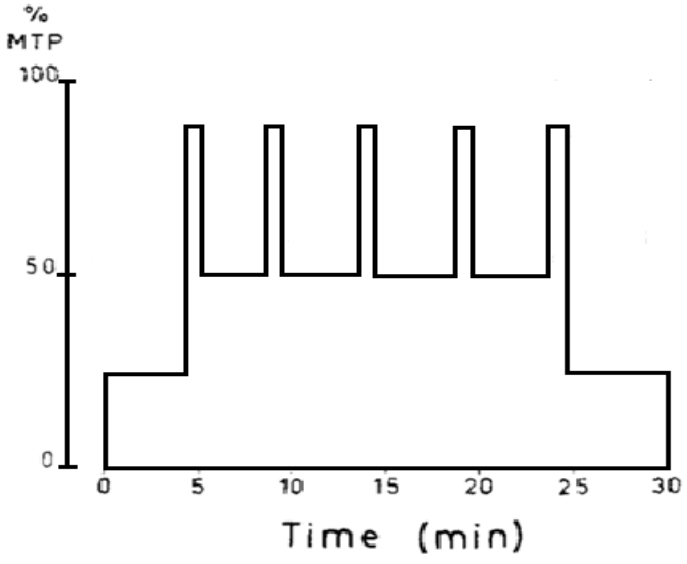


Figure 6.2: Square-Wave Endurance Exercise Test; adapted from Giménez et al., 1982.

College of Chest Physicians (ACCP) guidelines (ATS/ACCP, 2003): after a two-minute unload cycling at 50 - 70 rpm, intensity was increased by 12.5 W each minute until maximal exhaustion was achieved. Patients were asked to discontinue if they couldn't maintain the rhythm of cycling due to increased dyspnoea, muscle fatigue or any symptom of discomfort. The maximal load maintained for at least 30 seconds was recorded as the Peak Work Load (W_{peak}). Heart rate and oxygen saturation were monitored during the test whilst blood pressure, dyspnoea and leg fatigue were recorded only before and after the assessment. Each training session patients were encouraged to perform 30 minutes of interval aerobic training adapting the principles of the SWEETraining developed by Giménez et al. for chronic respiratory diseases, which consisted of a one-minute bout at a high intensity load (≥80% W_{peak}) combined with a four-minute, low-intensity active rest (50% W_{peak}) (Figure 6. 2) (Giménez et al., 1982). A five-minute warm-up and a four-minute cool down were also included in the 30 minutes time frame.

At the beginning and at the end of the test dyspnoea and leg fatigue were logged using the modified version of the Borg Scale (Table 6.4). After the 10^{th} session, if either dyspnoea or leg fatigue were below the targeted intensity (four to five), a new incremental cycle test was conducted in order to re-evaluate the peak work rate and maintain an optimal training stimuli.

Table 6.4: Modified version of the Borg Scale; Borg, 1982

Rating of Perceived Exertion	Intensity
0	Nothing at all
0.5	Extremely light (just noticeable)
1	Very Light
2	Light
3	Moderate
4	Somewhat severe
5	Severe
6	
7	Very Severe
8	
9	Extremely Severe (almost maximal)
10	Maximal

Resistance training

The same principles of overload, specificity and variation also apply for resistance or strength training (Ratamess et al., 2009, Andrianopoulos et al., 2014). Resistance training is oriented to enhance muscle mass, maximal strength or muscle endurance. According to this, the addition of resistance training to a PR programme can help preventing or reversing peripheral muscle weakness in patients with respiratory chronic diseases who suffer from muscle weakness or atrophy. Intensity is considered the most important variable and should be inversely related to the training volume (Andrianopoulos et al., 2014). Depending on the specific goal, training volume (which encompasses intensity, number of repetitions and sets and frequency of the training) can slightly vary. Conventionally, resistance training is performed using weight machines or free weights as they allow clinicians to accurately measure the intensity of the training. International guidelines recommend that for healthy adults, an intensity of ≤50% of the maximal one repetition

(1RM) is the optimal to improve muscle endurance and it could also be beneficial for improving muscle strength and power in sedentary and older people beginning a resistance programme (Garber et al., 2011). Two to four sets of 10 – 15 repetitions each, at least two times per week are recommended in this population (Garber et al., 2011). Progression can be achieved by increasing the intensity, the number of repetitions per set, the number of sets, decreasing the rest between sets or increasing speed of the movement (Ratamess et al., 2009). Unfortunately, the availability of free weights or weight machines is limited in many clinical settings thus other alternatives are warrant. Elastic bands have been recently acknowledged as a valid training modality by the international guidelines (Garber et al., 2011, Nici et al., 2006). Studies have shown that elastic bands induce similar muscle activation than traditional equipment and are as effective as weight machines or free weights to increase muscle strength in sedentary but otherwise healthy individuals (Colado and Triplett, 2008, Colado et al., 2009, Andersen et al., 2010). The main disadvantage of elastics bands is the difficulty to accurately measure training intensity and progression. According to the first manufacturer (Thera-Band®, The Hygienic Corporation, Akron, Ohio, USA) there are eight band colours each one providing different resistance (tan – yellow – red – green – blue – black – silver and gold). In 2000, Page et al. measured the specific force developed by each one of the bands and generated regression equations according to the percentage of elongation (Page et al., 2000) (Table 6.5). The results provided clinicians and researchers with a more precise estimation of the real intensity generated by each band and enable comparison to other training modalities.

Resistance in Kilograms

Percent Elongation	Yellow	Red	Green	Blue	Black	Silver	Gold
25%	0.5	0.7	0.9	1.3	1.6	2.3	3.6
50%	0.8	1.2	1.5	2.1	2.9	3.9	6.3
75%	1.1	1.5	1.9	2.7	3.7	5.0	8.2
100%	1.3	1.8	2.3	3.2	4.4	6.0	9.8
125%	1.5	2.0	2.6	3.7	5.0	6.9	11.2
150%	1.8	2.2	3.0	4.1	5.6	7.8	12.5
175%	2.0	2.5	3.3	4.6	6.1	8.6	13.8
200%	2.2	2.7	3.6	5.0	6.7	9.5	15.2
225%	2.4	2.9	4.0	5.5	7.4	10.5	16.6
250%	2.6	3.2	4.4	6.0	8.0	11.5	18.2

Table 6.5: Resistance in Kilograms of Thera-Band® according to the percentage of elongation; Page et al., 2000.

In our study, four different bands (yellow – red – green – blue) of 1.25-m long were used. Percentage of elongation ranged from 50 to 125 % depending on the exercise performed and the height of the patient. Training load was determined during the first session after a 25 maximal repetition test, meaning that the patient could not perform more repetitions with the correct technique (Newsam, 2005). They started with the lightest resistance available and performed a maximal number of three consecutive attempts with a one-minute rest between to choose the adequate resistance.

Functional exercises that strengthen the lower and upper limbs are recommended for pulmonary rehabilitation programmes with limited equipment (Jenkins et al., 2010). According to this, ten exercises were selected targeting individual muscles or muscle groups involved in daily life activities: shoulder lateral raise, straight arm shoulder flexion, elbow flexion, row, chest press, latissimus row, single leg press, heel raise, step-up and/or squat. Upper and back exercises were

performed using the elastic bands while bodyweight exercises were used to train the lower body (Supplemental file no.7).

During each training session, patients performed six out of the ten proposed exercises according to their personal limitations and preferences balancing upper and lower body exercises. During the first session, patients performed one set of 15 repetitions of each exercise to familiarize with the technique. In the subsequent training sessions, the goal was to perform three sets of 15 repetitions for each exercise with a 40-second rest between sets (Chodzko-Zajko et al., 2009, Ratamess et al., 2009). From the 10^{th} onwards, number of repetitions was maintained and the number of sets was increased to four if tolerable. Patients were encourage to maintain a moderate perceived rate of exhaustion of (five to six) according to the OMNI-Resistance Scale described in the previous chapter (Colado et al., 2012).

Breathing exercises

As early as 1915, physiotherapists were including breathing exercises as part of their conventional regimes (Grant-Paterson and Buchholtz-Moodie, 1985). Breathing exercises aim to correct breathing errors, re-establish a proper breathing pattern, increase diaphragm activity, elevate the amount of alveolar ventilation, reduce work-imposed breathing and relieve shortness of breath in patients with respiratory diseases (Liu et al., 2013). The addition of a respiratory biofeedback to perform the exercises enables clinicians to select a determinate goal and provides the patients with more autonomy and self-evaluation of the progress. Incentive Spirometry (IS) was introduced by Bartlett and colleagues as a method to encourage deep breathing inhalations in post-operative patients (Bartlett et al., 1973). IS is accomplished when the patient inhales a pre-determinate flow and/or volume using the device and sustains the inspiration for three to six seconds (Restrepo et al., 2011). IS is usually recommended in the perioperative period of major surgery (especially abdominal, thoracic and cardiac) to prevent and/or reverse atelectasis and other

post-operative pulmonary complications. Despite the almost universal widespread of the technique, the evidence so far is at least controversial. There are several factors that could explain the inconsistent results found across studies. For instance, breathing exercises are insufficiently described in the literature, the terminology used to define them is arbitrary, and more frequently, the same name is given to different interventions (Garrod and Mathieson, 2013). Lack of standardization to perform the IS, the type of incentive spirometer used as well as the diaphragmatic and thoracic motion can contribute to the absence of consistent results (Grant-Paterson and Buchholtz-Moodie, 1985, Chang et al., 2010, Westerdahl, 2014, Weindler and Kiefer, 2001).

In this randomized controlled trial, patients in the experimental group were taught breathing exercises using a volume-oriented incentive spirometer (Coach 2 Incentive Spirometer 22-4000 HD, Smith Medicals, USA). Participants were asked to perform the exercises at home twice daily. The protocol consisted of 1) slow exhalation outside the device until the reserve volume was reached; 2) a deep, slow inhalation through the device up to 80% of the maximal vital capacity (flow rate approximately 0.5 – 1.5L/min); 3) an end-inspiratory hold of three seconds and 4) a normal exhalation outside the device. The sequence was repeated 30 times distributed in six cycles of five repetitions each, with a one-minute rest between cycles.

Also, when considered appropriate and according to the patients' baseline symptomatology, airway clearance techniques were provided at the end of the session.

Each training session was recorded and kept in a codified data sheet (Supplemental file no. 4).

6.4.4 Outcomes

The two main outcomes of the study were: 1) changes in exercise capacity (endurance time) before and after the PPRP and 2) mean difference between groups in endurance time in the post-operative period (early and late post-operative period).

Other secondary outcomes included 1) changes in muscle strength and HRQoL before and after the intervention; 2) mean difference between groups in muscle strength and HRQoL in the early and late post-operative period and 3) differences in length of hospital stay and post-operative pulmonary complications between groups. Patients in both groups were evaluated at three points during the study period: at baseline prior to randomization (T0) and in the early (T1) and late post-operative period (T2). The experimental group was also evaluated after the PPRP prior to surgery. The post-operative evaluations (T1 and T2) were undertaken by two blinded therapist who were not aware of the allocation of the participants.

Patients were evaluated at baseline on two separated days by one of the investigators. On the first day, medical and socio-demographic data were collected during a personal interview including: smoking history, symptomatology, number of medications, height, weight and BMI. Heart rate, blood pressure and oxygen saturation at rest were also recorded. An incremental symptom-limited exercise test was then performed followed by a Constant-load Cycle-Endurance Test (CCET) at 80% of the W_{peak}. On the second day, patients completed the rest of the assessment including determination of muscle strength, HRQoL and functional exercise capacity. Participants were asked not to drink alcohol or other caffeinated drinks the previous day of the tests. They were also encouraged not to perform any strenuous exercise 24 hours before the exercise capacity evaluation. Patients in the intervention group were re-evaluated prior to surgery to measure changes after the exercise programme (endurance time, muscle strength and HRQoL). Finally, post-operative evaluations including exercise capacity, functional capacity, muscle strength and HRQoL

were obtained at three weeks and three months (Figure 6.3). The results of the evaluations were kept individually in a codified data collection sheet shown in the Supplemental file no.5.

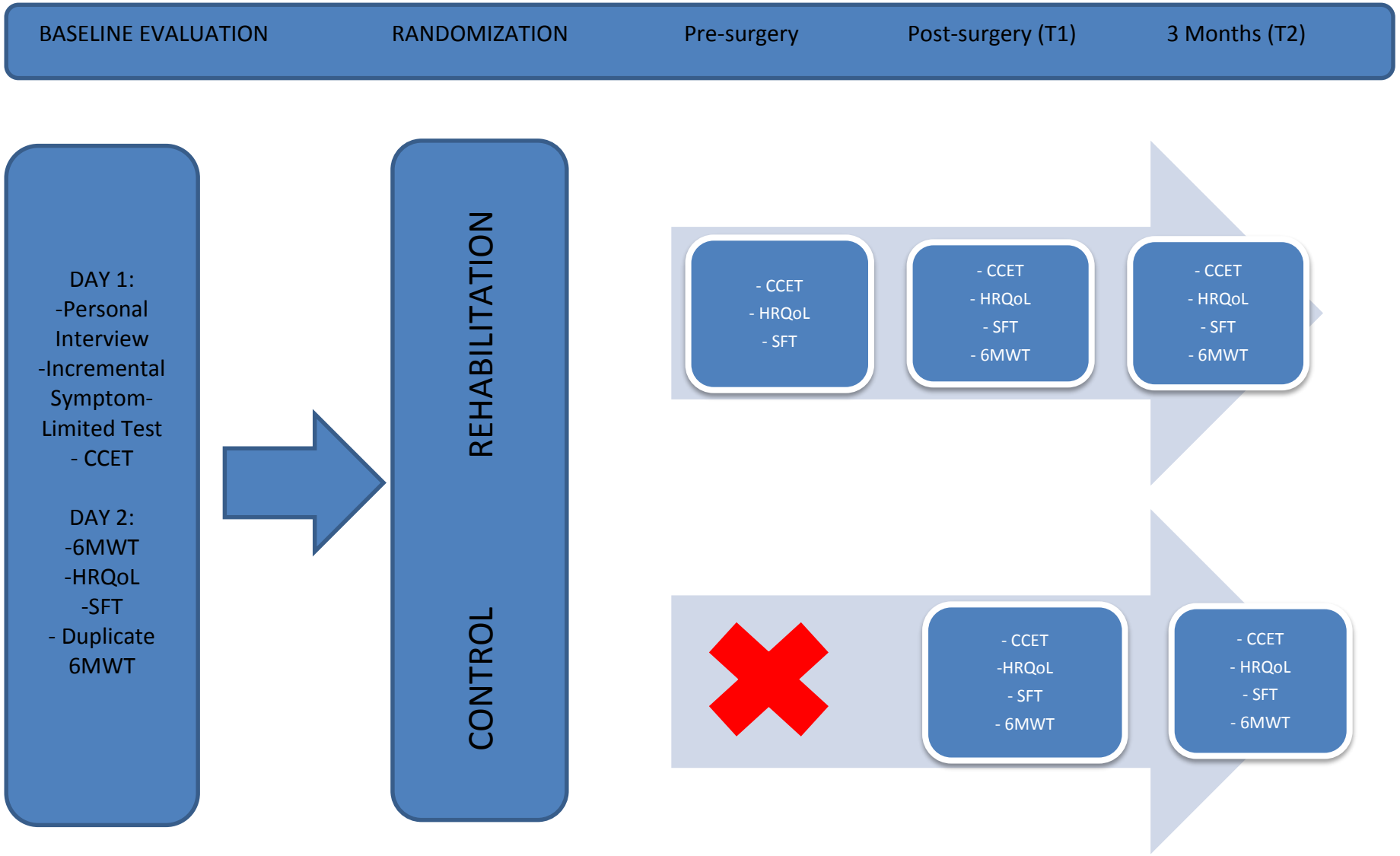


Figure 6.3: Chronogram of the study.

Exercise capacity

The principle of specificity in exercise training entails that individuals engaging in a training programme would only show improvements in the exercise practiced. According to this, it is essential both in clinical practice and in research to select the most sensitive tool to measure changes after an exercise training. Traditionally, incremental exercises tests were used both to assess cardiopulmonary fitness and to quantify the improvements after a given intervention. However, today we have sufficient data to believe that incremental protocols are not the most sensitive tool to evaluate the impact of an exercise-based intervention. As acknowledged by the ATS and the ACCP, although the incremental tests are the most widely used in clinical practice, constant-work rate protocols (6MWT, ESWT, Constant-Load Cycle-Endurance Test) are gaining popularity because of their clinical applicability for monitoring responses to therapy (ATS/ACCP, 2003). In 2009, the ERS statement on Pulmonary Rehabilitation recognized the superiority of the constant endurance test over the measurement of VO_{2peak} to quantify the effects of therapeutic interventions in COPD (Brunelli et al., 2009b). This asseveration is based on the results of some comparative studies showing that in patients with chronic diseases, endurance time has shown the largest improvement after a pulmonary rehabilitation programme (Ong et al., 2004). Given these findings, it appears that maximal exercise tests are more appropriate to assess the nature of the exercise limitation in patients with pulmonary diseases while constant protocols performed at a percentage of the maximal intensity should be used to measure changes after an intervention (Whipp and Ward, 2009, van 't Hul et al., 2003).

Constant-load Cycle Endurance Test (CCET) has shown to yield higher fractioned increases in exercise tolerance than other constant protocols (Casaburi, 2009). Intensity and duration of the CCET are the two more important features for the validity and reliability of the test. Optimal duration should fall between four and seven minutes (Casaburi, 2009) since durations

greater than the upper limit imply that the work rate is not much above the critical power while durations less than four minutes don't allow enough time to the cardiorespiratory system to adopt the physiological adaptations to exercise. Intensity, on the other hand, is a subject of continuous discussion. It is generally accepted that a higher intensity (≥60%) is preferred over a moderate one (≤60%), given that it has shown shorter exercise time, less variability and higher sensitivity (Oga et al., 2004). The most common intensities for the CCET vary between 75 and 85 % of the peak workload achieved during an incremental maximal test but no final consensus has been reached. The CCET has shown good intra-test reliability and validity in patients with COPD (Intra-class Correlation Coefficient ≥ .85 (van 't Hul et al., 2003) but further confirmation is needed in other chronic diseases.

Given the superiority of the constant endurance tests and the arguable responsiveness of the 6MWT reported by some authors (Borel et al., 2013), in our study, a CCET was used to measure changes in exercise tolerance after the PPRP. To perform the test, an incremental symptom-limited cycle-ergometry test was firstly performed to determine the peak workload (W_{peak}) according to the ATS/ACCP recommendations (ATS/ACCP, 2003) (a full description of the test is provided in the previous chapter). After a 45-minute rest, the CCET was performed at 80% of the W_{peak}: after two minutes of unloaded cycling, intensity was rapidly increased until the targeted percentage was reached. Patients were instructed to exercise for as long as possible at 50 - 70 revolutions per minute (rpm) until maximal exhaustion was achieved or the patient was unable to maintain the minimal pedalling rate. Encouragement was given every two minutes. If exercise time exceeded more than 15 minutes the test was terminated (van 't Hul et al., 2003). Heart rate, oxygen saturation, dyspnoea and leg fatigue were recorded at the beginning and at the end of the test. Heart rate and oxygen saturation were also monitored during the test. Reasons to discontinue the test were logged in the data collection sheet (Supplemental file no.5).

Functional capacity

Functional capacity was assessed at three points during the study period (at baseline and in the early and late post-operative period) using a 6MWT.

The 6MWT was performed in an indoor flat corridor with patients walking at self-pace between two marks separated by 30 meters according to the national and international guidelines (American Thoracic Society, 2002, Burgos-Rincon and Casan Clara, 2004). Patients were asked to walk as fast as they could for six minutes between the two marks (Figure 6.3). Heart rate, oxygen saturation, dyspnoea and fatigue were recorded at the beginning and at the end of the test. Oxygen saturation and heart rate were monitored during the test using a portable pulse oximeter. Total walked distance was calculated once the test was finished. Duplicate tests were performed at baseline for reliability and the maximum distance covered was used for the analysis.

The values achieved during the test were compared to the reference equations for the Spanish population (Gimeno-Santos et al., 2015) (Table 6.6).

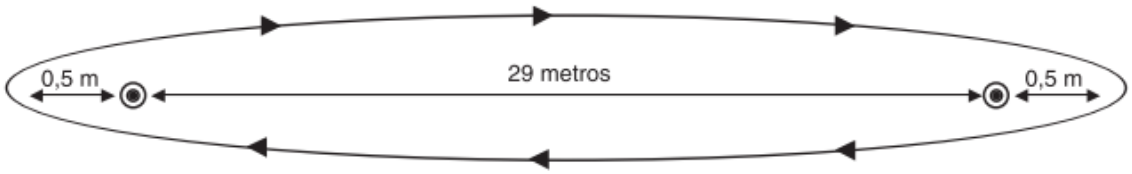


Figure 6.4: Trajectory of the 6MWT; Burgos-Rincón et al., 2004.

Table 6.6: Reference equations for the Spanish population aged 45 - 85; Gimeno-Santos et al., 2015

	Reference Equation
Males	$6MWD = 478 - (5.51*Age_{years}) + (4.15*Height_{cm}) - (1.78*Weight_{kg}) - (1.18*HR_{baseline}) + 84$
Females	$6MWD = 1107 - (5.78*Age_{years}) - 1.48*Weight_{kg}) - (1.27*HR_{baseline}) + 67$

Muscle strength

Muscle strength was assessed using two items of the Senior Fitness Test (SFT) designed and validated by Rikli et al.: the *Curl Arm Test* and the *30's Chair-Stand* Test (Rikli and Jones, 2013). The test was performed in the same sequence for every assessment: first the *Arm Curl* test followed by the *30's Chair to Stand* Test. Only one trial with partial practice the same day was allowed for each of the tests. For more details of how the test was performed refer to Chapter 5.

Health-related quality of life

HRQoL was assessed using the second version of the Short Form 36 Health Survey (SF-36) described in Chapter 5. The test as self-administrated whenever possible; if the patient was unable to read or understand the test, one of the investigators was responsible for reading the questionnaire and provide the participant with further explanations of the questions.

Post-operative outcomes

Post-operative outcomes included: a) length of post-operative hospital stay (LOS) from the day of surgery to hospital discharge and b) incidence of post-operative pulmonary complications (PPCs) assessed with the Melbourne Group Scale (MGS). As described in previous chapters, the MGS is a tool specifically designed to identify post-operative respiratory complications which are more likely to be prevented by a physiotherapy intervention (Reeve et al., 2008). Post-operative outcomes were retrospectively reviewed by using the medical records. We also recorded other common complications (prolonged air leak, atrial fibrillation, pneumothorax, pleural effusion) and

other perioperative relevant data: number of post-operative physiotherapy interventions, pathological diagnosis, stage and post-operative adjuvant therapy.

6.4.5 Sample size estimation

This study was powered to detect a clinically minimal important difference between groups of 100s in the exercise capacity assessment (endurance time) (Casaburi, 2009, Laviolette et al., 2008). To detect this difference with a probability of $\alpha = .05$ and power = .8 using a bilateral hypothesis and estimating a 10% of dropouts 11 patients per arm were required. The standard deviation of the whole sample was taken from a recent study conducted in patients with NSCLC awaiting lung resection surgery (Coats V, 2013). Sample size calculation was performed using the Epidat® v3.1 Xunta de Galicia, 2005.

6.4.6 Randomization

Randomization was undertaken using a random-based computer programme (Epidat® v3.1 Xunta de Galicia, 2005) with an allocation ratio of 1:1. 22 patients were initially randomized and individual allocations were placed in consecutively numbered and sealed opaque envelopes by a third person not involved in the study. Once the first 22 patients were randomized, if the targeted sample size was not achieved, subsequent randomization was performed in blocks of six patients until the desirable sample was achieved.

6.4.7 Blinding/Masking

Participants were not blinded to group allocation since they knew if they were training or not. The physiotherapist responsible for the PPRP was also aware of the group allocation since she knew which participants were involved in the training. The baseline assessment was conducted by the same physiotherapist who supervised the training programme; however, group allocation was only revealed after the evaluations were completed, this way the investigator was also blinded when performing the initial assessments. All of the post-operative evaluations were performed by two blinded therapists who were unaware of the allocation of the patients.

6.4.8 Statistical analysis

Quantitative data are presented as mean and standard deviation (SD) while qualitative data are described in absolute numbers and percentage of the total. Normality was assessed using the Kolmogorov – Smirnov Test for each variable in each group. Initially, a comparative analysis of the participants regarding the main demographic and clinical variables was undertaken using an independent *t-test* or a *Mann Whitney Test* and the *Chi Square* Test. Changes in the primary and secondary variables (exercise capacity, functional capacity, muscle strength and HRQoL) for each group were evaluated using a general linear model of repeated measures. Inter-group comparisons were performed using independent *t-tests* for the primary and secondary outcomes including post-operative length of stay. Comparison of the incidence of post-operative complications was done using a *Chi Square* Test. Univariate correlations were analysed to identify factors influencing exercise performance in the early and late post-operative period. A multivariate regression was then performed to further confirm the results of the univariate analysis.

All statistical analyses were calculated using the SPSS® package for Windows® (Version 22, IBM Corporation, Chicago IL, USA) and a *p* value of <.05 was considered statistically significant.

6.5 RESULTS

This randomized single-blind controlled trial took place from October 2013 to October 2015 at the University Hospital of A Coruña. The recruitment period went on for 18 months, starting in October 2013 and finishing in April 2015. During that period, 319 patients joined the waiting list for lung resection surgery at the Thoracic Department. 68 eligible patients (21.3%) were contacted and 46 (67.6%) signed the informed consent. Six patients (13%) withdrew before randomization therefore 40 patients were randomized during the recruitment period; of those, 22 (55%) completed at least one of the post-operative evaluations and were analysed. A flow diagram of the study selection process is shown in Figure 6.5. Baseline characteristics of both groups are shown in Table 6.7.

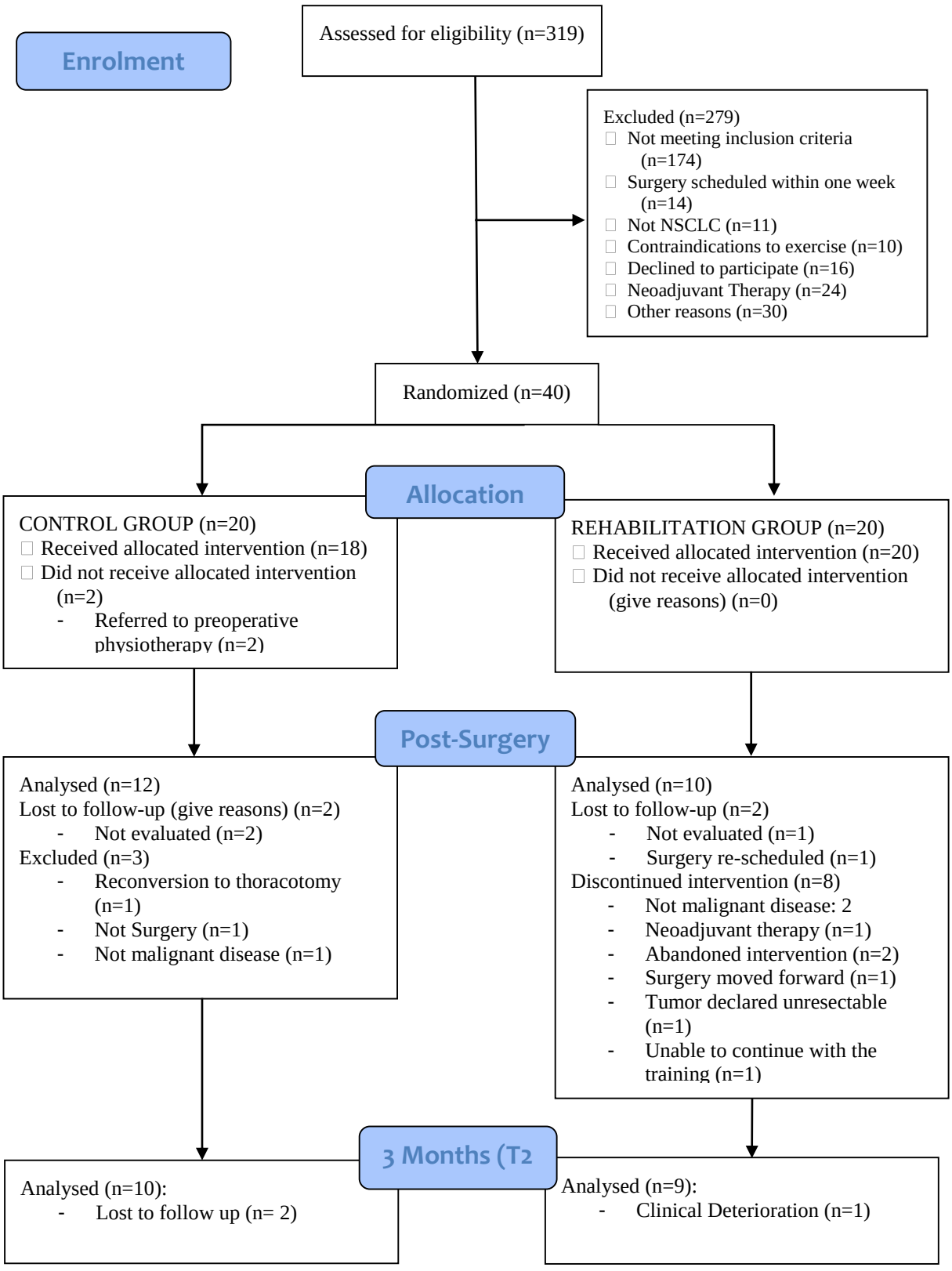


Figure 6.5: Flow diagram of the study.

Table 6.7: Baseline characteristics of the patients included in the study

VARIABLE	GROUP	
	CONTROL (n=12)	REHABILITATION (n=10)
Age (years)	69.4±9.4	70.9±6.1
Sex (M/F)	9/2	11/1
BMI	25.7±2.8	29.4±4.3
History of Smoking (n, %)		
No	2 (16.7%)	2 (20%)
Former	7 (58.3%)	8 (80%)
Current	3 (25%)	0
Package/Year	39.5±32.1	50.7±34.8
CCS	8.7±4.2	9.3±4.9
Respiratory Disease (n, %)	4 (33.3%)	7 (70%)
Cardiovascular Disease (n, %)	9 (75%)	8 (80%)
Renal Impairment (n, %)	0	0
Diabetes Mellitus (n, %)	3 (25%)	1 (10%)
Alcoholism (n, %)	0	0
PHx Cancer (n, %)	6 (50%)	4 (40%)
Symptomatology (n, %)	8 (66.7%)	10 (100%)
Cough	3 (25%)	3 (30%)
Dyspnoea	3 (25%)	7 (70%)
Expectoration	7 (58.3%)	4 (40%)
Other	4 (33.3%)	2 (20%)
SBP	15.12±2.7	13±1.7
DBP	7.1±0.9	7.7±1.2
FEV_1 (%)	87.6±26.1	69.2±15.1
FVC (%)	80.1±18	71.2±15
FEV_1/FVC	68.8±6	61.2±9.4
6MWT (m)	507.7±9	420.2±116.3
6MWT (%)	79.8±11.4	70.1±18.2
Maximal Workload (W) (median, IQR)	75 (67.5 – 84.4)	67.5 (50 – 75)
Maximal Workload (% predicted)	55.4±16.7	51.35±15.18
CCET (s)	366.83±205	322.40±96
Curl Arm (no. repetitions)	17.3±3.5	13.4±3
Sit To Stand (no. repetitions)	12.7±2.5	11.5±3.7

*BMI=Body Mass Index; CCS=Colinet Co-morbidity Score; PHx=Past History; SBP=Systolic Blood Pressure; DBP=Diastolic Blood Pressure; FEV_1=Forced Expiratory Volume in 1 second; FVC=Forced Vital Capacity; 6MWT=Six Minute Walk Test; IQR=interquartile range CCET=Constant-load Cycle Endurance Test

The mean preoperative period was 53.9±17.7 days. There was no significant difference in the therapeutic delay between groups (p =.89). Patients in the rehabilitation group attended a median of 16 sessions (range eight – 25) achieving a mean adherence of 100.2±32.6 %. Three patients reached less than 80% of the adherence. No adverse events were recorded during the training.

All patients underwent VATS through one or two ports performed by highly experienced surgeons. There was only one reconversion to thoracotomy (control group) and the patient was excluded from the analysis. Ten patients in the control group and six in the rehabilitation group underwent a lobectomy while the others received a sublobar resection. No significant differences were found between groups in the type of resection (p =.229). The pathologic diagnosis confirmed eight NSCLC and four lung metastases in the control group and eight cases of NSCLC, one carcinoid and one lung metastasis in the rehabilitation group (p =.89). One patient in the control group was diagnosed with benign disease and was also excluded from the analysis. The majority of the patients were diagnosed with an early stage of the disease and only two patients were stage IIIA. A registered specialized physiotherapist performed conventional chest physiotherapy in those patients requiring assistance to improve their respiratory status (three vs four patients in the control and rehabilitation groups respectively; p =.452).

Median time from surgery to T1 was 24.5 days (IQR: 10.7 – 34.2) or 3.5 weeks (IQR: 1.5 – 4.9). Median time from surgery to T2 was 98 days (IQR: 92 – 110) or 14 weeks (IQR: 13.1 – 15.7). No significant differences were found between groups (p =.093 and p =.842 respectively).

All 22 patients completed the early post-operative (T1) evaluation. However, from T1 to T2 two patients were lost to follow-up in the control group (one patient refused and the other was

out of town) and one in the rehabilitation group (the participant had severely deteriorated from T1 to T2), leaving 19 patients for analysis at T2.

6.5.1 Intra-group comparison

Rehabilitation group

Results for the main variables in the intervention group are shown in Table 6.8 and Figures 6.6 to 6.14. In brief, pre to post-intervention, patients in the rehabilitation group experienced a significant increase in the three main variables studied: endurance time, muscle strength and HRQoL (role physical and PCS). Exercise capacity (endurance time) experienced both a statistical and a clinically meaningful improvement from baseline to pre-surgery, with patients increasing 123% their baseline time (p <.001) (Figure 6.6). Upper and lower body strength also improved significantly (p =.002 and .041 respectively) (Figure 6.7 and Table 6.8).

Table 6.8: Changes in main outcomes pre to post intervention in the rehabilitation group

VARIABLE	N	BASELINE	PRE-Surgery	P value
CCET (s)	10	322.4±96.2	719±211.2	**<.001**
Arm Curl (no.)	10	13.40±3	16.30±2.9	**.002**
Chair to Stand (no.)	10	11.5±3.7	12.40±4.5	**.041**
Physical Functioning	10	63.5±20.8	71±14.9	.110
Role Physical	10	48±30.6	65.9±12.8	**.038**
Bodily Pain	10	64.5±26.3	69.2±23.8	.518
General Health	10	41.9±20.2	52.2±14.3	.072
Vitality	10	52±16.5	55±15.6	.526
Social Functioning	10	87.5±22	97.5±5.3	.223
Role Emotional	10	60.6±19.2	72.7±12.3	.098
Mental Health	10	63.2±13.6	64.4±19.2	.771
PCS	10	40.77±8	45.2±6.8	**0.08**
MCS	10	45.7±8.3	47.4±7.4	.511

*CCET= Constant-load Cycle Endurance Test; PCS= Physical Component Summary; MCS= Mental Component Summary

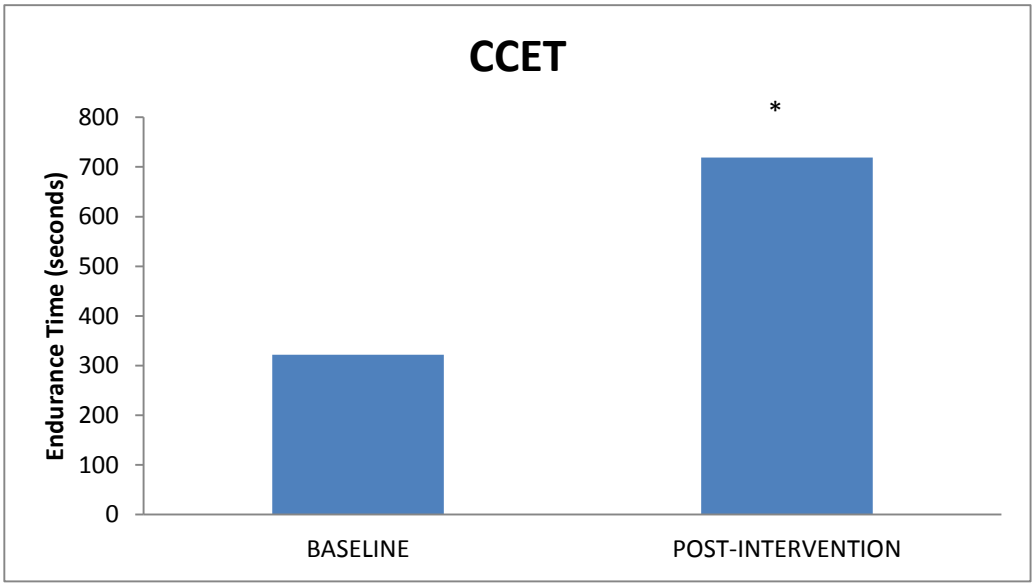


Figure 6.6: Changes in endurance time pre- to post-intervention in the rehabilitation group.

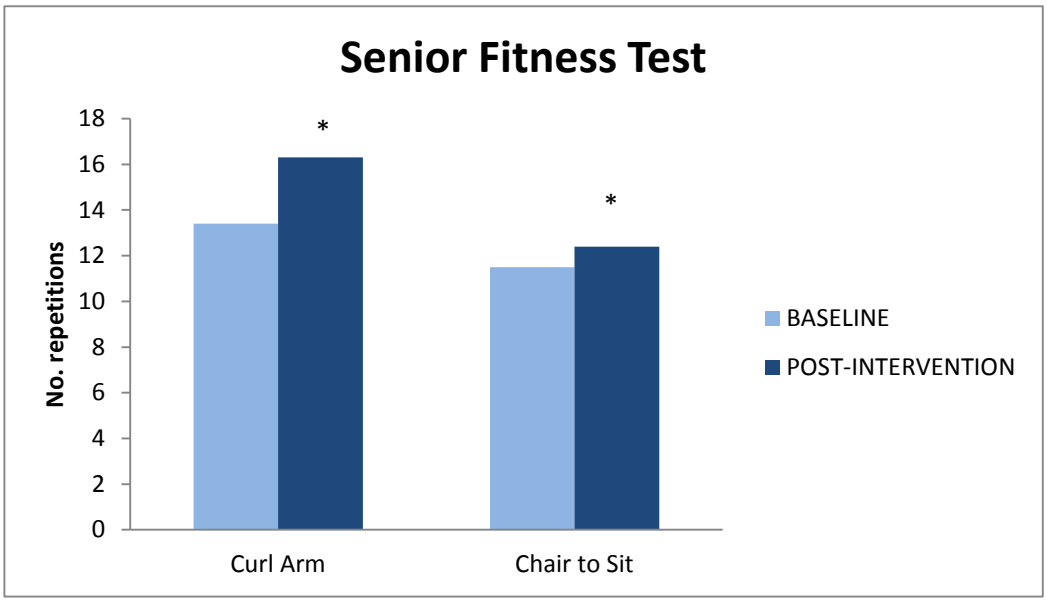


Figure 6.7: Changes in the SFT pre- to post-intervention in the rehabilitation group.

At baseline, HRQoL was below normative data across all health dimensions. After the training, all items increased but only significantly for the role physical and the PCS (p =.038 and .008 respectively). However, except for the social functioning, all of the items were still below normative data (<50).

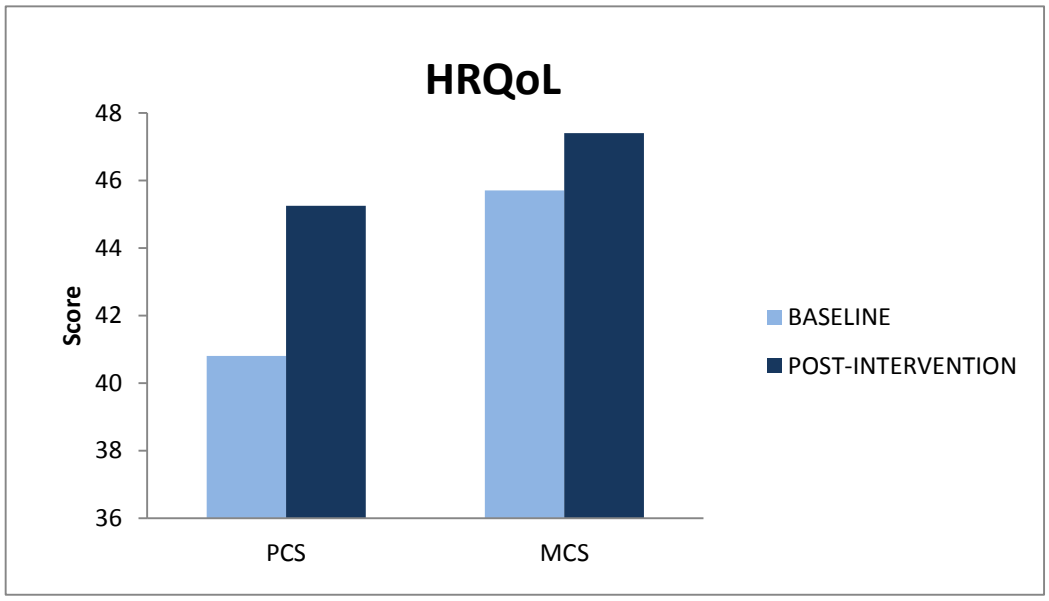


Figure 6.8: Changes in PCS and MCS pre- to post-intervention in the rehabilitation group.

At T1, exercise capacity decreased comparing to pre-surgery but continued over the baseline values (+137.3±268.2; p =.14). At T2, there was a recovery in the endurance time comparing to T1 (p =.16) (Figure 6.9). *Curl Arm* remained over the baseline values in almost 2 repetitions at T1 while the *30's Chair-to-Sit* Test slightly decreased (MD: -0.55±3.5). None of the parameters were significantly decreased comparing to baseline and were fully recovered at T2 (Figure 6.10 and 6.11). Functional capacity measured with the 6MWT slightly decreased at T1 and recovered at T2 (Figure 6.12). The HRQoL changes are shown in Table 6.9 and Figures 6.13 and 6.14.

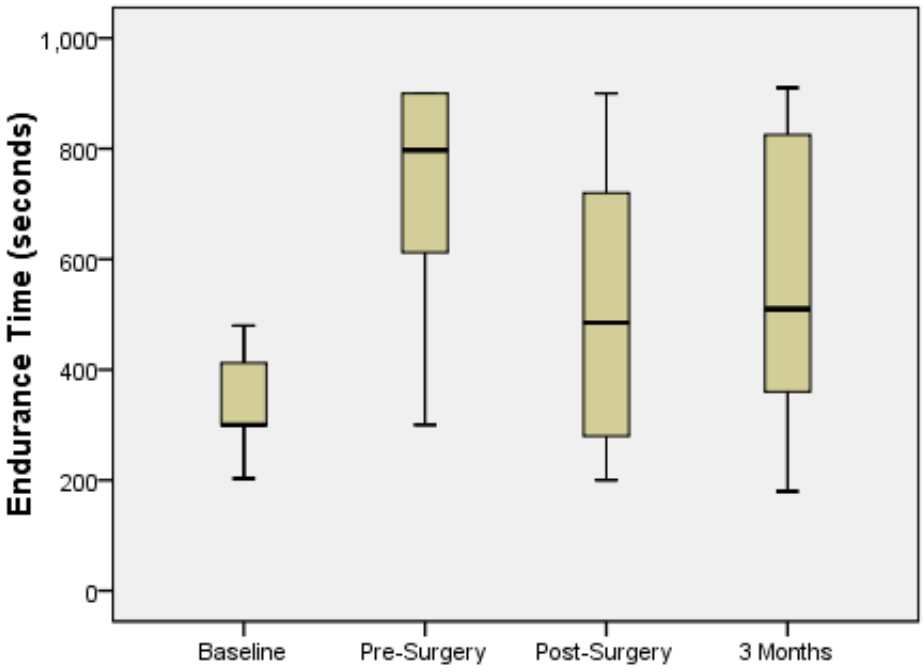


Figure 6.9: Changes in CCET during the study period in the rehabilitation group.

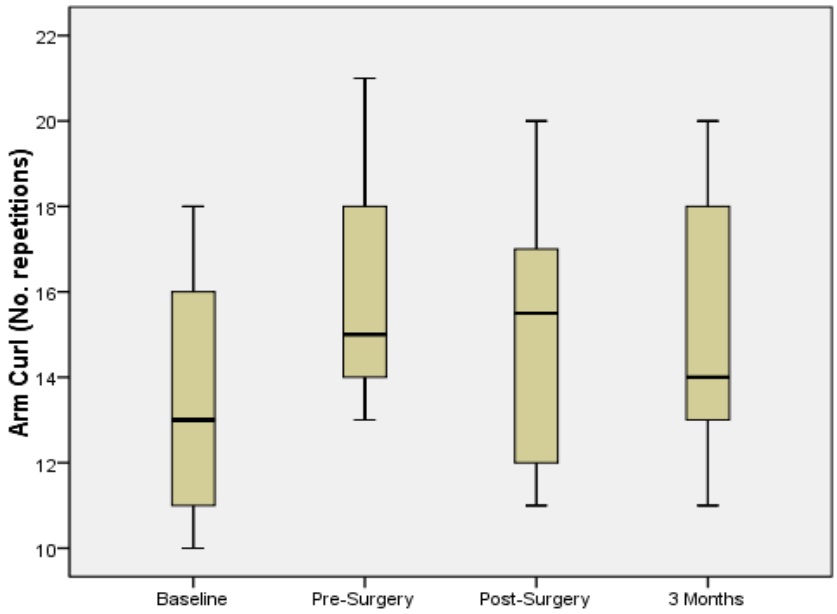


Figure 6.10: Changes in the *Arm Curl Test* during the study period in the rehabilitation group.

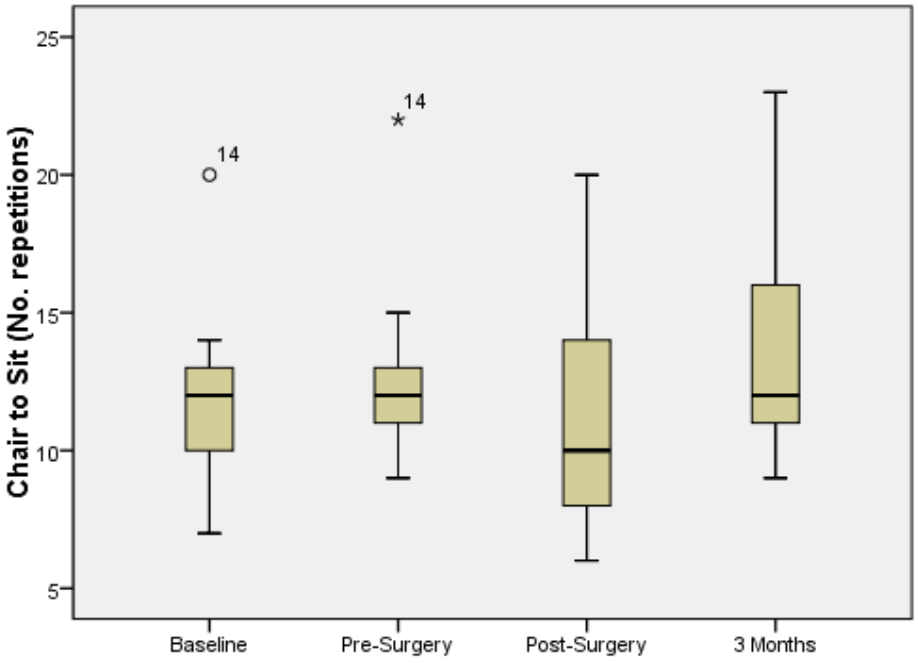


Figure 6.11: Changes in the *Chair to Stand Test* during the study period in the rehabilitation group.

Table 2.9: Changes in HRQoL across time in the rehabilitation group

HRQoL Domain	Baseline	Post-Surgery (T1)	95% Confident Interval		3 Months (T2)	95% Confident Interval	
			Lower Limit	Upper Limit		Lower Limit	Upper Limit
Physical Functioning	63.5±20.8	-10±17.3	-22.4	+2.4	-2.2±9.4	-9.4	+5
Role Physical	48±30.6	**-19.5±26.3***	-38.3	-0.7	+6.1±40.2	-24.8	+37
Bodily Pain	64.5±26.3	+3.2	-13.2	+19.4	**+26.3±26.6***	+5.9	+46.8
General Health	41.9±20.2	-12.4±23.5	-29.2	+4.4	-3.1±17.3	-16.4	+10.3
Vitality	52±16.5	**-12±12.9***	-21.3	-2.7	-1.7±15.6	-13.7	+10.3
Social Functioning	87.5±22	-16.2±30.6	-38.2	+5.7	-8.3±24.2	-26.9	+10.3
Role Emotional	60.7±19.2	+8±21.3	-7.2	+23.2	+8.1±28.6	-13.9	+30.2
Mental Health	63.2±13.6	0±10.1	-7.9	+7.9	-2.2±16	-14.5	+10.1
PCS	40.8±7.8	-2.8±5.8	-6.9	+1.3	**+4.3±4***	+1.3	+7.4
MCS	45.7±8.3	-0.6±8.9	-6.9	+5.8	-2.1±6.4	-7.1	+2.9

*p <.05

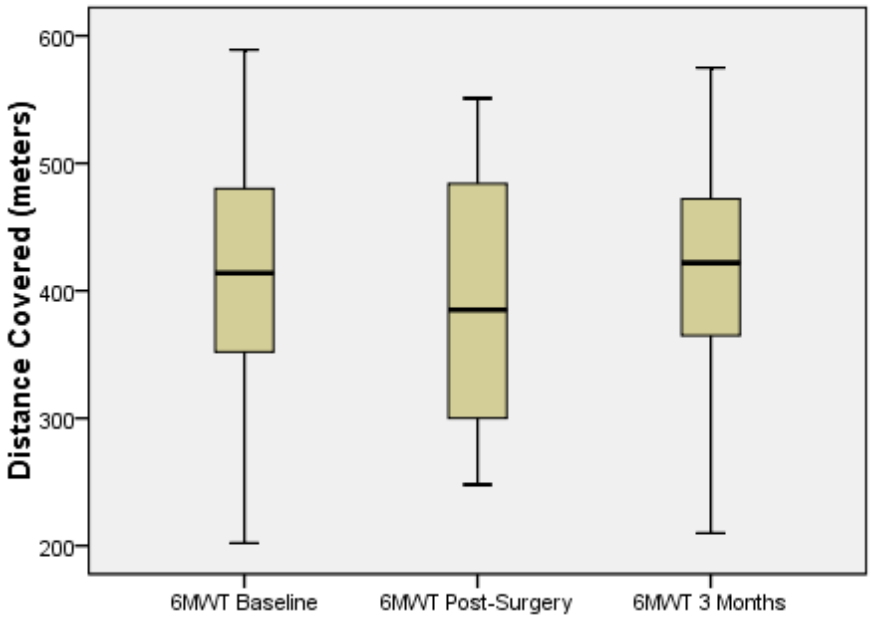


Figure 6.12: Changes in the 6MWT during the study period in the rehabilitation group.

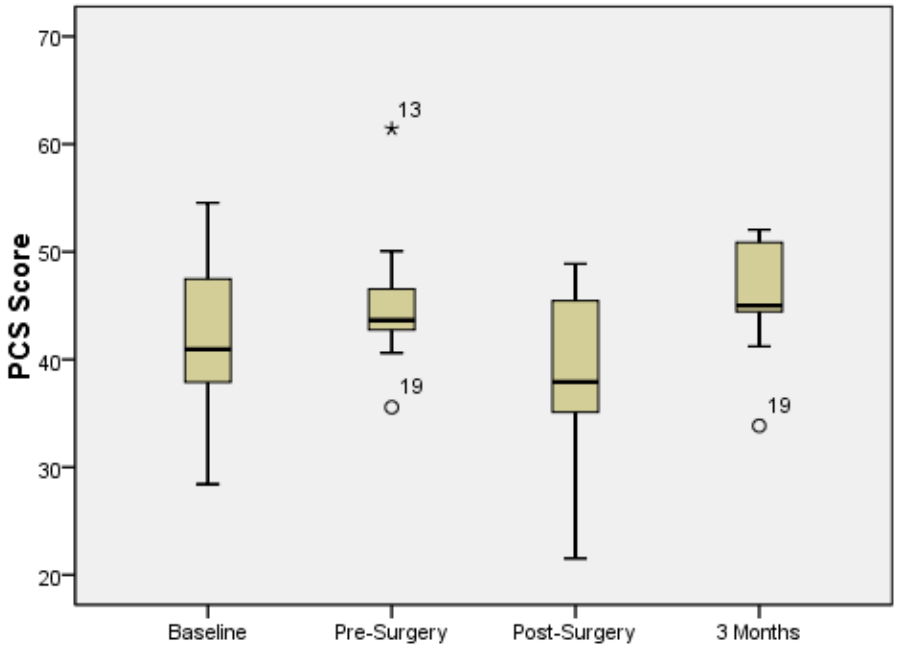


Figure 6.13: Changes in PCS during the study period in the rehabilitation group.

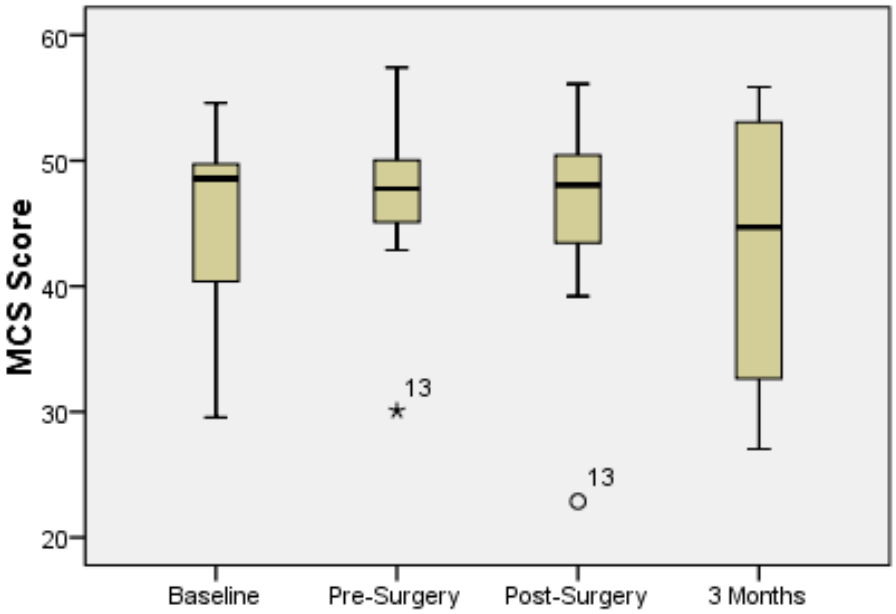


Figure 6.14: Changes in MCS during the study period in the rehabilitation group.

Control Group

The results of the intra-group comparison for the control group are presented in Table 6.10 and Figures 6.15 and 6.16. Exercise tolerance decreased slightly in the early post-operative period but continue to decline at T2 (MD = 137.8±221.7 seconds) which was statistically and clinically significant (Figure 6.13). The same tendency although less pronounced was seen in the functional capacity measured with the 6MWT (Figure 6.14). The decrease in the post-operative functional capacity at T1 was also clinically and statistically significant comparing to baseline (p =.016). There were no significant changes in neither of the SFT items included in the study.

HRQoL in the control group was also below normative data except for the Bodily Pain and the Vitality dimensions. At T1, patients significantly decreased their Physical Functioning, Role Physical, Bodily Pain and PCS (p <.05). Furthermore, the decline was clinically meaningful (>10 points) in the physical functioning, role physical, bodily Pain, vitality and social functioning (Table 6.10).

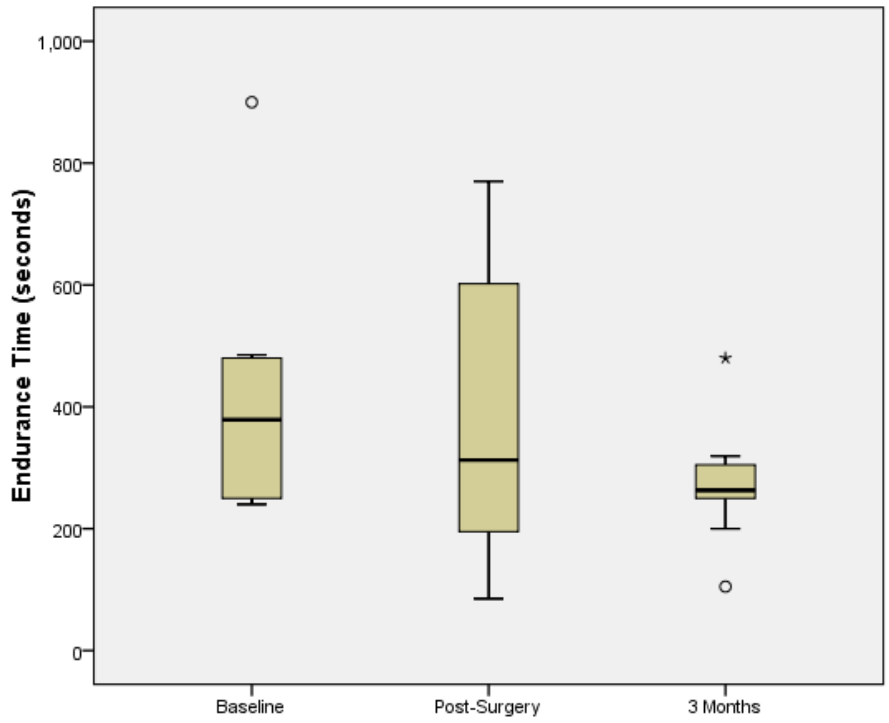


Figure 6.15: Changes in endurance time during the study period in the control group.

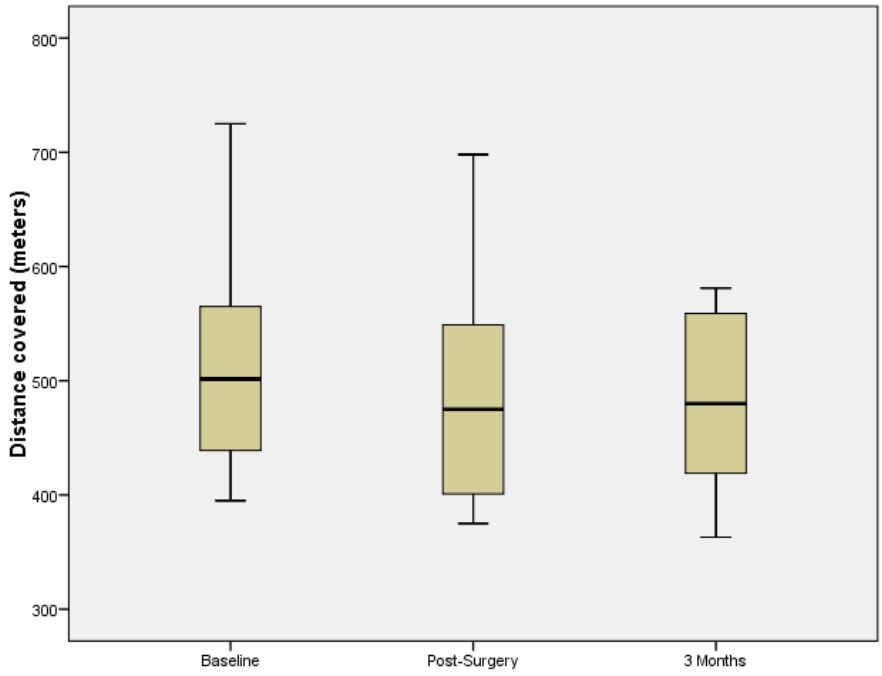


Figure 6.16: Changes in the 6MWT during the study period in the control group.

Table 6.10: Changes in HRQoL across time in the control group

SF-36 Domain	Baseline	T1	95% Confident Interval		T2	95% Confident Interval	
			Lower Limit	Upper Limit		Lower Limit	Upper Limit
Physical Functioning	79.6±16.6	**-13.3±17.7***	-2	-24.6	-12±19.9	-26.2	+2.2
Role Physical	64.6±20	**-13.7±15.8***	-3.7	-23.8	-11±22.3	-27	+5
Bodily Pain	89.7±13.9	**-24.4±32.7***	-5.7	-47.2	-15.7±30.8	-37.7	+6.3
General Health	53.8±28.5	+.3±24.2	+15.7	-15.1	+4.4±14.1	-5.7	+14.5
Vitality	68.3±18.5	-11.7±18.4	+.01	-23.3	-11.5±18.1	-24.5	+1.5
Social Functioning	83.3±30.3	-14.6±24.3	+.9	-30	-5±27.1	-24.4	+14.4
Role Emotional	60.6±18.7	+7.8±19.2	+20	-4.4	+1.3±11.7	-7	+9.7
Mental Health	67.3±19.3	-.37±14.4	+5.5	-12.8	-2.8±15.1	-13.6	+8
PCS	49.5±5.5	**-7.4±5.3***	-4	-10.8	**-4.8±5.8***	-8.9	-0.7
MCS	44.2±9.9	+.5±8.4	+5.8	4.8	-.04±8	-5.8	+5.7

*p <.05

6.5.2 Inter-group comparison

Results of the inter-group comparison for the primary and secondary study endpoints are shown in Table 6.11 and 6.12.

Results for the main outcomes

There were no statistically significant differences in exercise capacity, functional capacity or the SFT between groups in the early post-operative period (p >.05) (Table 6.11). Mean 6MWT in both groups was 95±10.2 % of the preoperative values. Only one patient in the rehabilitation group was below 80% of his baseline distance. This patient was a complex case under the effects of psychiatric medication that could most likely interfered with the recovery. In the HRQoL assessment, the only difference was found in bodily pain, with patients in the rehabilitation group exhibiting an improvement in three points while the control group had a mean reduction of 26 points (p =.026) (Table 6.12 and Figure 6.17).

In contrast, three months after surgery (T2), results showed a statistically significant difference between groups in endurance time (MD = 288.9±91.8; p =.006) and in the mean change for the *Curl Arm Test* (p =.045) and the number of *Chair-to-Sit* repetitions (p =.004) (Table 6.11). Patients in the rehabilitation group also showed an improvement in the 6MWT comparing to baseline (mean difference 8.14%) while the control group remained stable, but the differences were not statistically significant (p >.05). In the HRQoL assessment mean change in Bodily Pain and PCS also showed statistically significant differences between groups (p =.006 and .001 respectively). In particular, the control group had a mean decrease in PCS of almost five points comparing to baseline while participants in the rehabilitation group improved by four points (p =.001) (Table 6.12 and Figure 6.18). Both groups improved their bodily pain from T1 to T2, but the improvement was larger for the rehabilitation group and the differences were still significant (p =.006).

Table 6.11: Changes in exercise capacity, functional capacity and SFT across time in the rehabilitation and control groups

VARIABLE	GROUP	Baseline	Post-Surgery (mean difference)	P value	3 Months (mean difference)	*p* value
CCET (s)	Rehabilitation	322.4±96.2	+137.7±268.2	.097	**+226±269.4***	**.005**
	Control	366.8±205	-25.8±16.71		-137.8±221.7	
6MWT (m)	Rehabilitation	420.11±116.3	-15.55±47.731	.500	1.88±34.7	.186
	Control	514.5±100.9	**-27.7±33.7***		-31.5±64.6	
Arm - Curl (n)	Rehabilitation	13.4±3	+1.9±3	.105	+1.8±3.3	**.045**
	Control	17.3±3.5	-0.25±2.9		-1.8±3.5	
Chair-to-Stand (n)	Rehabilitation	11.5±3.7	-0.55±3.5	.531	**+2±2.2***	**.002**
	Control	12.7±2.5	+0.5±3.9		**-1.3±1.8***	

*Intra-group statistically significant difference (p <.05)

Table 6.12: Changes in HRQoL across time in the rehabilitation and control groups

HRQoL Domain	GROUP	Baseline	Post-Surgery (mean difference)	*p* value	3 Months (mean difference)	*p* value
Physical Functioning	Control	79.6±16.6	-13.3±17.7*	.662	-12±19.9	.197
	Rehabilitation	63.5±20.8	-10±17.3		-2.2±9.4	
Role Physical	Control	64.6±22.	-13.7±15.8*	.533	-11±22.3	.261
	Rehabilitation	48±30.6	-19.5±26.3*		+6.1±40.2	
Bodily Pain	Control	89.7±13.9	-26.4±32.7*	**.026**	-15.7±30.8	**.006**
	Rehabilitation	64.5±26.3	+3.2±23		+26.3±26.6*	
General Health	Control	53.8±28.5	+0.3±24.2	.252	+2±21.2	.328
	Rehabilitation	41.9±20.2	+12.4±23.5		+11.2±18.4	
Vitality	Control	68.3±18.5	-11.7±18.4	.962	-11.5±18.1	.225
	Rehabilitation	52±16.5	-12±12.9*		-1.7±15.6	
Social Functioning	Control	83.3±30.3	-14.6±24.3	.888	-5±27.1	.782
	Rehabilitation	87.5±22	-16.2±30.6		-8.3±24.2	
Role Emotional	Control	60.5±18.7	+7.8±19.2	.980	+1.33±11.7	.520
	Rehabilitation	60.6±19.2	+8±21.3		+8.1±28.6	
Mental Health	Control	67.3±19.3	-3.7±14.4	.517	-2.8±15.1	.936
	Rehabilitation	63.2±13.6	+0±11		-2.2±16	
PCS	Control	49.48±5.5	-7.4±5.3*	.067	-4.8±5.8*	**.001**
	Rehabilitation	40.77±8	-2.8±5.8		+4.3±4*	
MCS	Control	44.2±9.9	-0.5±8.4	.782	-.04±8	.555
	Rehabilitation	45.7±8.3	+0.6±8.9		-2.1±6.4	

*Intra-group statistically significant difference (p <.05)

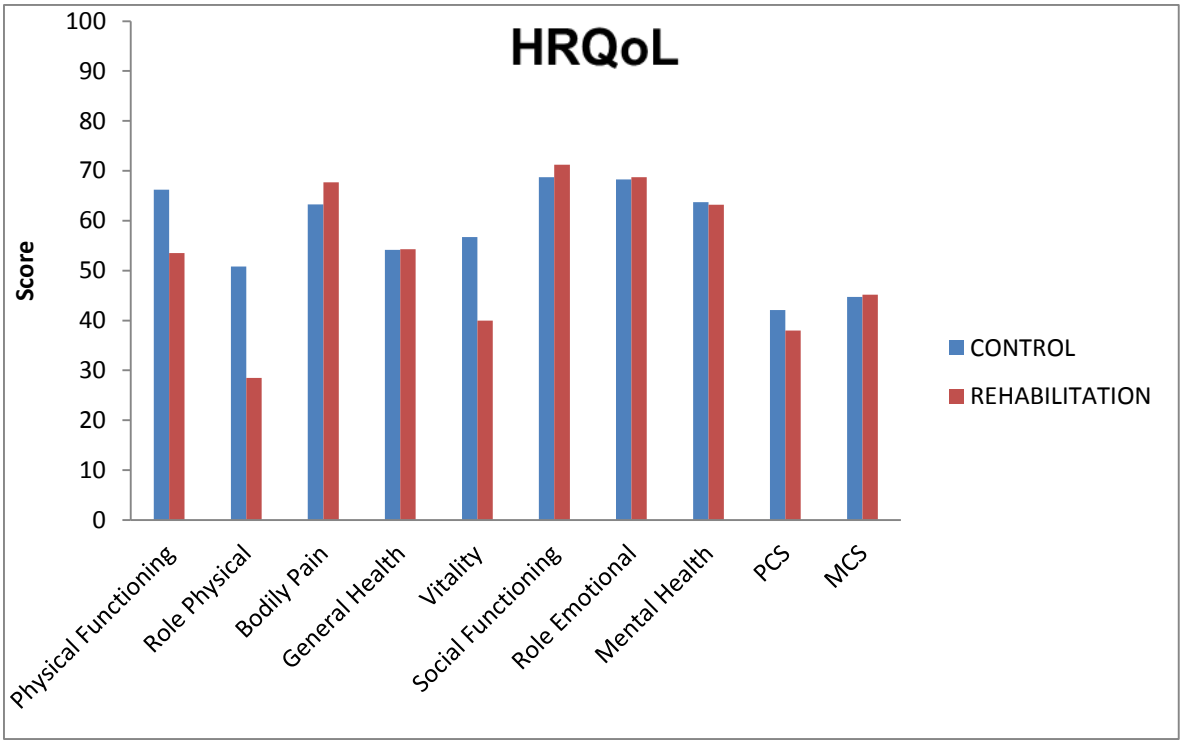


Figure 6.17: Inter-group comparison of HRQoL domains at T1.

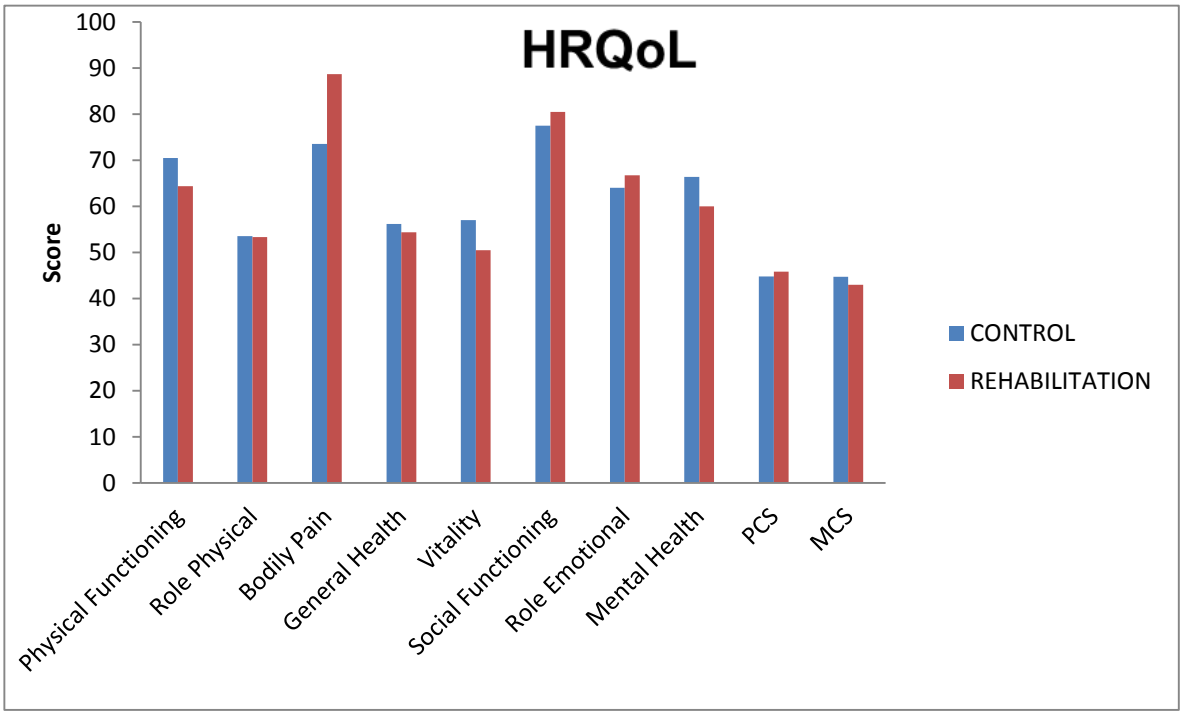


Figure 6.18: Inter-group comparison of HRQoL domains at T2.

Post-operative outcomes: hospital stay and incidence of complications

Comparison of the post-operative hospital stay and rate of post-operative complications are shown in Figures 6.19 and 6.20. Post-operative length of stay (LOS) was similar between groups and the difference was not statistically significant (three vs. two median days in the rehabilitation and control group respectively; p =.539).

There were no significant differences in any of the post-operative complications recorded although we observed more cases of prolonged air leak, pneumothorax, chest infection and desaturation in the rehabilitation group than in the control group (Figure 6.9). Nevertheless, any patient achieved a score of four in the MGS indicating a positive diagnosis of PPC.

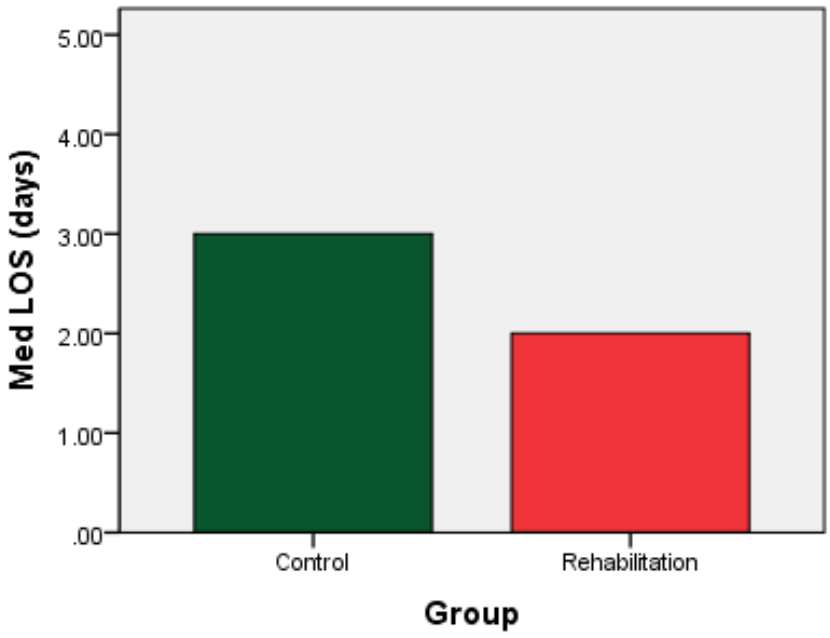


Figure 6.19: Comparison of LOS in the rehabilitation and control groups.

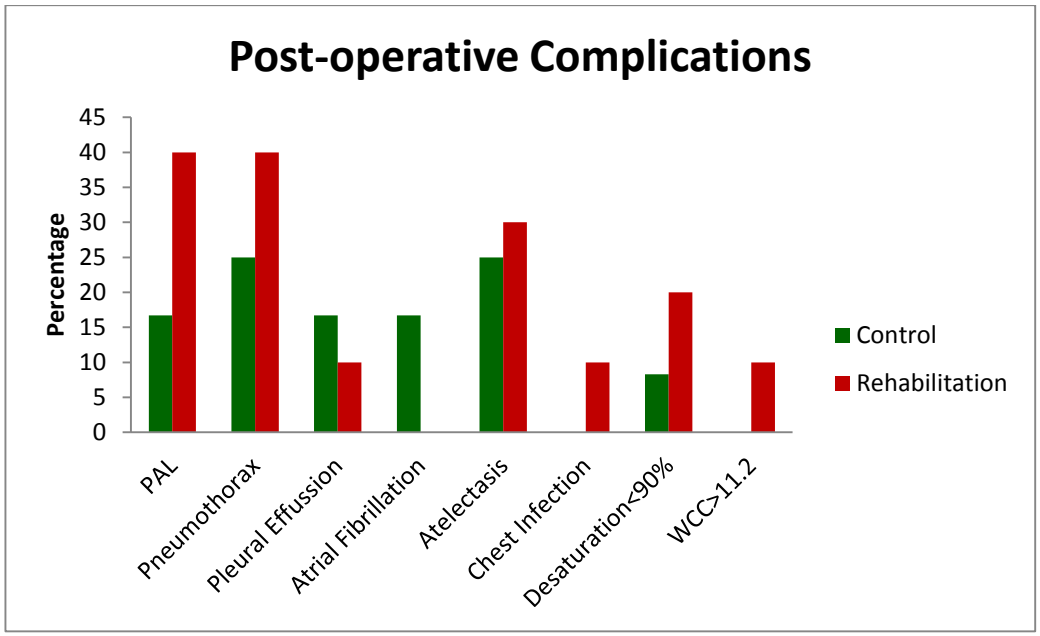


Figure 6.20: Comparison of PPCs in rehabilitation and control groups.

In the univariate analysis, the endurance time measured in the late post-operative period (T2) was correlated with the BMI, baseline FEV_1 (L and % of predicted), baseline FVC (L), endurance time pre-surgery, the Peak Workload and the number of PPRP sessions attended. In the multivariate analysis, FEV_1 (L) and the endurance time achieved pre-surgery were the only two independent factors associated with the endurance time achieved at three months, explaining up to 76% of the variation (Table 6.13 and 6.14). On the other hand, the three-month PCS was correlated with the PCS pre-surgery, the PCS post-surgery, the presence of cough, dyspnoea and other symptomatology at baseline, the occurrence of post-operative pneumothorax and the role physical of the SF-36. In the multivariate analysis, the two factors independently associate with PCS were the PCS pre-surgery and the presence of dyspnoea at baseline, accounting for 87% of the variation (Table 6.14).

Table 6.13: Correlation Coefficients for CCET and PCS measured three months post-surgery

	Variable	Coefficient	P value
CCET	BMI	.555	.017
	FEV1 (L)	-.576	.012
	FEV1 (%)	-.485	.041
	FVC(L)	-.593	.010
	FEV1 (l) post-surgery	-.601	.018
	No. Sessions	.616	.007
	CCET Pre-Surgery	.757	.018
PCS	PCS Pre-Surgery	.707	.033
	PCS Post-Surgery	.633	.004
	Role Physical Baseline	.430	.066
	Cough	-.364	.66
	Dyspnoea	-.381	.041
	Other symptomatology	-.329	.096
	Pneumothorax	-.474	.016

Table 6.14: Multivariate analysis for the endurance time (CCET) measured three months post-surgery

Model		Unstandardized Coefficients		Sig.	95.0% Confidence Interval for B	
		B	Std. Error		Lower Bound	Upper Bound
1	(Constant)	-44.416	250.318	.864	-636.326	547.493
	CCET Pre-Surgery	.841	.334	.040	.051	1.631
2	(Constant)	502.380	226.026	.068	-50.685	1055.445
	CCET Pre-Surgery	.970	.215	.004	.445	1.496
	FEV1 (L) Baseline	-352.930	104.104	.015	-607.664	-98.196

Table 6.15: Multivariate analysis for the PCS at T2 (3 months post-surgery)

Model		Unstandardized Coefficients		Sig.	95.0% Confidence Interval for B	
		B	Std. Error		Lower Bound	Upper Bound
1	(Constant)	50.512	1.767	.000	46.333	54.692
	Dyspnoea	-4.744	1.286	.008	-7.785	-1.703
2	(Constant)	30.563	5.090	.001	18.110	43.017
	Dyspnoea	-3.885	.757	.002	-5.737	-2.033
	PCS PRE	.420	.105	.007	.163	.677

6.6 DISCUSSION

This study was designed to evaluate the effects of a preoperative pulmonary rehabilitation programme on exercise capacity before VATS and to investigate whether or not the intervention would help to preserve post-surgical exercise and functional capacity to a greater extent than the standard care. Our results demonstrate that a PPRP in patients awaiting lung resection effectively improve exercise capacity, muscle strength and the physical component of the HRQoL which most likely minimize the functional decline observed after surgery and hasten post-operative recovery during the first three months after VATS.

Exercise training is considered the cornerstone of PR. The reported benefits of exercise training in chronic respiratory adults include an improvement in exercise tolerance, functional capacity, symptom control, mood and HRQoL (Holland et al., 2013). To optimize the results obtained, the instruments used to measure changes after the intervention must be sensitive to the exercise prescribed and responsive to change. There are three major categories of instruments to measure changes in exercise capacity in patients with chronic diseases: questionnaires, activity monitors and exercise testing (Casaburi, 2009). Within the latter, the constant-load protocols have demonstrated its superiority to detect such changes (Casaburi, 2009) but there is little consensus in the literature in terms of which particular exercise testing is better for patients with lung cancer. Granger et al., in a systematic review of the most common instruments used to measure functional capacity in patients with NSCLC concluded that the 6MWT was the most frequently used in this population (Granger et al., 2013a). However, the sensitivity and responsiveness of the test to quantify changes after a given intervention has been questioned and other submaximal exercise tests have been proposed instead (Borel et al., 2013, Granger et al., 2015a). In particular, the Constant-load Cycle Endurance Test (CCET) has gained popularity in patients with chronic obstructive pulmonary disease to monitor the effectiveness of several pharmacological and non-

pharmacological interventions. For instance, Ong et al. in a comparison of three exercise-testing protocols to measure intervention-related improvements after a pulmonary rehabilitation programme, found a 16% increase in the 6MWT, a 53% in VO_{2peak}, a 30% in the W_{peak} and a 144% improvement in the CCET (Ong et al., 2004). Porszasz et al. also reported a statistically significant increase in endurance time of 11.6±8.1 minutes after seven weeks of high-intensity endurance training in patients with COPD (Porszasz et al., 2005). Interestingly, the authors did not find any improvement in the VO_{2peak}. In a similar study, Laviolette et al. also found an improvement of 198 seconds in the endurance time measured with the CCET at 80% of the W_{peak} (Laviolette et al., 2008) and more importantly, the observed that the effects were maintained up to one year after the rehabilitation. Finally, the study by Coats et al. in patients awaiting lung cancer surgery found no change in VO_{2peak} after a four-week home-based exercise programme but a significant improvement in endurance time of 60% (Coats V, 2013). In our study, we found a significant increase in endurance time of 369.6±197 seconds measured at 80% of the W_{peak} which corresponds to an increment of 123% comparing to baseline. Notably, the improvement was sustained after the surgery although to a lesser extent (+137.3±268.2 seconds at T1 and +226±269.4 seconds at T2). One limitation of the test is that the magnitude of the improvement is strongly influenced by the power/duration relationship properties which dictates that the increments seen in endurance time are influenced by the baseline pre-treatment value (Borel et al., 2013, Whipp and Ward, 2009). In our study, patients in the rehabilitation group performed the CCET at a median workload of 54W while patients in the control group did the same at 60W (p =.021). This finding can explain why patients in the rehabilitation group experienced such a dramatic improvement in endurance time but it cannot justify the tendency observed in both groups, with the control group showing a progressive functional decline contrary to the rehabilitation group who improved their exercise capacity and sustained it for the total duration of the follow-up.

Resistance training has become an essential component of pulmonary rehabilitation given that aerobic training is less effective to improve muscle mass, muscle strength and muscle endurance than strength training. In cancer patients, resistance training can help to prevent cancer-cachexia and maintain patient's autonomy and self-care. The results drawn by a systematic review and meta-analysis in cancer survivors demonstrated that resistance training effectively increases lower and upper limb muscle strength (SMD = 14.57; 95% CI: 4.78-9.03, p <.001) and reduces fatigue (SMD: 1.86; 95% CI: -0.03 to -3.75; p =0.05) (Strasser et al., 2013). In the prehabilitation studies conducted in lung cancer patients, strength training was associated with improvements in functional capacity (6MWT) and HRQoL (Li et al., 2013, Mujovic et al., 2014). Although resistance training is more commonly delivered using free weights or weight machines, the use of less expensive and sophisticated equipment is gaining popularity. New evidence has arisen supporting the effectiveness of low-equipment pulmonary rehabilitation programmes for people with chronic respiratory diseases in the absence of traditional high-tech equipment (Alison and McKeough, 2014). One example of low-tech equipment is elastic bands, which are an affordable, practical and versatile way of improving muscle strength in sedentary population (Colado and Triplett, 2008, Colado et al., 2009). They have also demonstrated to be safe and effective to improve muscle strength, functional fitness and functional capacity in older frail people (Fahlman et al., 2011, Oesen et al., 2015). In patients with chronic respiratory diseases, the use of elastic bands is also expanding. In COPD, a minimally supervised training programme using elastic bands three times per week for 12 weeks significantly improved knee extensor strength by 4.9kg (95% CI: 1.1 – 8.7) (O'Shea et al., 2007). In another study comparing elastic tubing resistance training versus conventional training the authors found significant improvements in the distance covered with the 6MWT in both groups but to a larger extent in the elastic tubing group (p <.05). Muscle strength and HRQoL also improved in both groups but the differences were not statistically

significant (Ramos et al., 2014). In the same line, Nyberg et al. demonstrated that a low-load, high-repetition resistance training using elastic bands in COPD patients significantly improved 6MWT by 34 meters in comparison to a control group (Nyberg et al., 2014). In the lung cancer setting, Mujovic et al. also found a significant improvement in functional capacity (6MWT increased 53 meters by average) after a short, intense preoperative pulmonary rehabilitation programme including breathing exercises plus resistance training with elastic bands (Mujovic et al., 2015). Importantly, the improvement in the 6MWT was also statistically significant in comparison to a control group who did not exercise. In our study, both the *Arm Curl Test* and the *30's Chair to Sit Test* were significantly improved after the training. Although the improvements were small in magnitude specially if compared to longer interventions (Peddle-McIntyre et al., 2012), they were sustained over the three-month follow-up period. Altogether, these findings support the use of elastic bands as an effective alternative to traditional weight machines and free weights to improve muscle strength and functional capacity both in healthy people and in frail individuals with chronic respiratory diseases.

As discussed in previous chapters, HRQoL is becoming more relevant in the interdisciplinary management of individuals with lung cancer given its role in predicting long-term outcomes in this population. In an observational longitudinal study, Pompili et al. found that the physical component of the HRQoL was strongly associated with overall and cancer-specific survival in patients with stage I NSCLC (Pompili et al., 2013). Particularly, a PCS < 50 was associated with a hazard ratio of 2.3 for overall survival (95% CI: 1.1-4.4; p =.01). This finding is of great interest since the PCS is another modifiable factor in the perioperative period of lung resection surgery. However, several systematic reviews have highlighted the lack of consistency across studies when assessing the effectiveness of exercise-based interventions to improve HRQoL (Granger et al., 2011, Rodriguez-Larrad et al., 2014, Singh et al., 2013, Pouwels et al., 2015). In

contrast, our results demonstrate that a PPRP focused on endurance and strength training can significantly improve the PCS prior to lung resection surgery which was sustained at three months postoperatively. Similar results were also reported in another randomized controlled trial conducted in 249 patients undergoing CABG (Arthur et al., 2000). After 10 weeks of PR, patients in the rehabilitation group improved their PCS from baseline to pre-surgery in +1.55±7.48 points. Furthermore, the improvement was sustained throughout the first six post-operative months. In our investigation, we observed a significant increase of almost five points in the PCS which was also maintained at three months postoperatively. These results are proof of principle that prehabilitation can effectively improve PCS in a lung cancer population.

This study is, to our knowledge, the first to examine the effects of a PPRP on the post-operative outcomes after VATS for lung cancer. Only one previous study has evaluated a preoperative exercise-based intervention in patients undergoing VATS (Coats V, 2013) but this was a single-arm study and the patients were not followed up after the surgery thus the effects of the intervention in the post-operative period remain unknown in this surgical context. It is well-known that functional capacity is reduced after lung resection surgery but it appears to return to baseline during the first weeks. As seen in chapter three, the type of surgery performed including the extent of resection and the surgical approach can notably influence the pattern of recovery. For instance, Nomori et al. found that immediately after thoracotomy, the 6MWT was significantly reduced the first week but substantially improved by the second week reaching 93% of the baseline value (Nomori et al., 2004). In another study, however, the same authors found that patients undergoing VATS experienced only a 7% decrease in the 6MWT comparing to a 35% decrease in those undergoing thoracotomy (Nomori et al., 2003). Ueda et al. observed that in patients undergoing VATS, the 6MWT was ≥80% of the preoperative value only three days after the surgery (Ueda et al., 2006). These results are consistent with our investigation, since we observed that three

weeks after surgery the 6MWT was recovered by 94.6% and 97.6% of the baseline values in the control and rehabilitation group respectively. Interestingly, at three months, only patients in the rehabilitation group had improved their 6MWT and were slightly over the baseline, but the change was not statistically significant.

In addition to better preserve functional capacity after surgery, VATS has demonstrated to significantly reduce post-operative length of stay and post-operative pulmonary complications in several cohort studies and meta-analyses (Park et al., 2007, Cattaneo et al., 2008, Flores et al., 2009, Scott et al., 2010, Ilonen et al., 2011, Paul et al., 2013, Zhang et al., 2013, Cheng et al., 2007). In chapter four, we concluded that a preoperative exercise-based programme reduced post-operative length of stay (MD = -4.83; 95% CI: -5.9 to -3.76) and the risk for post-operative complications (RR = 0.45; 95% CI: 0.28, 0.74). However, the majority of the patients in those studies were operated using an open approach so it is not known whether such interventions could yield the same results in patients undergoing VATS. In our study, we could not find any significant differences in post-operative LOS or post-operative complications between groups. The median LOS was very low (two and three days in the rehabilitation and control groups respectively) even when comparing to other series (Nwogu et al., 2015, Cai et al., 2015, Kuritzky et al., 2015). In addition, any patient was diagnosed with a PPC according to the MGS, although up to 60% of the patients presented at least one isolated complication. The most common were persistent air leak with or without associated pneumothorax and atelectasis but none of the cases required further treatment and they were managed conservatively. Contrary to what we could have expected, patients in the rehabilitation group were more likely to be diagnosed with persistent air leak, pneumothorax, desaturation or chest infection. However, if we consider the baseline status of the patients, those in the rehabilitation group had worse pulmonary function and higher BMI which

can explain these findings to some extent. Also, both persistent air leak and pneumothoraxes are not particularly preventable from a physiotherapy point of view.

6.7 LIMITATIONS

Our study has important limitations that need to be discussed. First of all, we included patients with suspected or confirmed NSCLC, which resulted in some patients being diagnosed of lung metastases instead of lung cancer. Even though, any tumour found in the lungs can affect the oxygen cascade irrespectively of the origin of the tumour, so from a functional point of view those patients with lung metastases who undergo lung resection surgery can equally experience functional and psychological declines after surgery and thus could benefit from a perioperative rehabilitation intervention. Second of all, in order to guarantee an optimal recruitment rate, the inclusion criteria was broad resulting in a heterogeneous sample, especially in terms of pulmonary function (FEV_1 at baseline range from 41 to 131% of predicted). Also, despite the randomization, patients in the rehabilitation group had lower pulmonary function and a higher BMI. This resulted in more patients in the rehabilitation group undergoing a sublobar resection than those in the control group, which can obviously determine the pattern of recovery after the surgery. However, the differences were not statistically significant and a univariate general linear model showed no interaction with the extent of the resection thus we don't believe that this factor have had a major impact in the results obtained. Finally, we need to consider the number of dropouts during the investigation and the potential implications of this. Of the 20 patients randomized to the intervention group only 50% completed the study. However, this low completion rate had little to do with the PPRP and more with other perioperative features (changes in surgery, tumour found unresectable at the time of surgery or further testing showing no malignancy). In fact, adherence rate to the protocol was very good and only two participants discontinued the intervention by choice therefore we consider that the programme was well-accepted and tolerated by the patients.

6.7 CONCLUSIONS

The results of this randomized single-blind controlled trial show that a preoperative, supervised pulmonary rehabilitation programme consisted of endurance and resistance training plus breathing exercises effectively improved exercise capacity, muscle strength and the physical component of HRQoL in patients awaiting VATS. Furthermore, the results found both at three weeks postoperatively but especially at three months suggest that the preoperative intervention enhanced post-operative recovery by preserving functional and exercise capacity and HRQoL to a greater extent than the standard care. We encourage researchers to undertake future randomized controlled trials to evaluate the effects of such interventions on the post-operative outcomes in high-risk surgical patients undergoing VATS.

CHAPTER SEVEN: CONCLUSIONS AND FUTURE DIRECTIONS

7.1 SUMMARY OF THE THESIS

The studies included in this thesis were designed to assess whether a prehabilitation exercise-based intervention for patients undergoing VATS for lung cancer was feasible, safe, well-tolerated and effective to enhance physical functioning and prevent deterioration after surgery. As a whole, or findings suggest that:

- ✓ There is enough evidence to asseverate that patients after lung cancer surgery exhibit significant deterioration in exercise capacity and exercise which affects self-care and HRQoL.
- ✓ Prehabilitation of patients undergoing thoracic surgery by means of thoracotomy enhances pulmonary function and accelerates post-operative recovery. Furthermore, it is possible that a preoperative exercise-based intervention is more effective than conventional post-operative physiotherapy alone to reduce post-operative pulmonary complications.
- ✓ A pulmonary rehabilitation programme in the preoperative period of video-assisted thoracic surgery for lung cancer is feasible, well-tolerated and can be achieved without any further delay in the therapeutic management. Furthermore, the intervention can enhance the preoperative status by improving exercise capacity, functional capacity, muscle strength and the physical component of HRQoL
- ✓ In comparison to the standard care, a preoperative pulmonary rehabilitation programme can prevent functional deterioration after surgery and even increase physical performance comparing to baseline.

7.2 FUTURE DIRECTIONS

There have been numerous advances in the treatment of patients with lung cancer in recent years. For example, low-dose CT screening has increased the number of patients diagnosed with early disease; chemo- and radiotherapy regimes have been significantly optimized and the surgical management has experienced an outstanding improvement thanks to the development of minimally invasive approaches such as video-assisted surgery and robotic-assisted surgery. However, comparing with other cancer types, the evidence regarding exercise and physical activity in the context of lung cancer is scarce and somehow inconsistent. Exercise intolerance is a reality in cancer patients and profoundly affects their functional capacity and quality of life. There is a large body of knowledge on the limitations in exercise performance in healthy individuals and people with chronic obstructive respiratory diseases. However, as we have established throughout this thesis, the underlying mechanisms for the limitation of exercise capacity in patients with cancer is barely known and should be addressed in further investigations (Jones et al., 2009b). Exercise and physical activity both pre and post-diagnosis have shown to decrease the risk of cancer and improve disease-free survival and overall survival in several cancer types (Meyerhardt et al., 2006, Chen et al., 2011b, Tardon et al., 2005, Sun et al., 2012, Je et al., 2013). Yet, there is insufficient data to allow for formal recommendations in this population. According to a recent Cochrane systematic review, it appears that moderate and vigorous exercise during cancer treatment provides greater improvements in HRQoL, physical functioning, anxiety, fatigue and sleep disturbances than light exercise (Cavalheri et al., 2014). It has also been reported in another meta-analysis that an inverse non-linear dose-response exists between physical activity and cancer mortality (Li et al., 2015). In cancer survivors, engaging in 15 Metabolic Equivalents of Task (METs) per week can reduce the risk of cancer death by 27% (Li et al., 2015). The best modality of exercise in this population is also not established. In a retrospective study including 2,863 cancer survivors, physical activity

was not associated with a lower risk of all-cause mortality but those engaging in resistance training lowered their risk of mortality by 33% (95% CI: 0.45-0.99) even after adjusting for physical activity levels and other confounders (Hardee et al., 2014).

In the perioperative context of lung cancer, we have shown that preoperative exercise training can reduce post-operative complications and accelerate post-operative recovery after thoracotomy. However, there is no evidence at the moment that similar results would be achieved in patients undergoing minimally invasive procedures. Given the remarkable results obtained with this technique in the post-operative outcomes, it seems unlikely that improving the preoperative status of the patients would provide any further benefit in this population. Notwithstanding, with the progressive ageing of the lung cancer patient and the clinical and co-morbid diseases associated with smoking, the role of preoperative exercise training could be justified to enhance post-operative recovery and prevent functional decline especially in high-risk surgical patients.

In light of this, the future of exercise in the context of lung cancer is linked to uncover the underlying mechanisms of exercise limitation to determine the optimal modality, frequency, intensity and timing as well as analysing its role in increasing disease-free and overall survival.

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SUPPLEMENTAL FILE no.1 – ETHICAL COMMITTEE APPROVAL

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE
Secretaría Xeral

Comité Autonómico de Ética de la Investigación de Galicia
Edificio Administrativo de San Lázaro
15781 SANTIAGO DE COMPOSTELA
Tlf: 881 54 64 [illegible] Fax: 881 54 [illegible]
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galicia

DICTAMEN DEL COMITÉ AUTONÓMICO DE ÉTICA DE LA INVESTIGACIÓN DE GALICIA

Paula M. López Vázquez, Secretaria del Comité Autonómico de Ética de la Investigación de Galicia,

CERTIFICA:

Que este Comité evaluó en su reunión del día 26/09/2013, la enmienda del estudio:

Título: Efectividad de un programa de Rehabilitación Pulmonar Preoperatorio sobre la tolerancia al esfuerzo y la calidad de vida en pacientes sometidos a resección pulmonar por videocirugía
Versión Enmienda: enmienda nº1 de 01 de agosto de 2013
Promotor: Esther Giménez Moolhyzen
Código del Promotor: RSG-RPC-2011
Código de Registro CEIC de Galicia: 2011/395

Y que este Comité acepta de conformidad con sus procedimientos normalizados de trabajo y tomando en cuenta los requisitos éticos, metodológicos y legales exigibles a los estudios de investigación con seres humanos, sus muestras o registros, que dicha enmienda sea incorporada al estudio de investigación que se está realizando en los centros aprobados.

Centros	Investigadores principales
C.H. Universitario de A Coruña	Esther Giménez Moolhyzen

En Santiago de Compostela a 03 de octubre de 2013
La Secretaria

Paula M. López Vázquez

SUPPLEMENTAL FILE NO.2 – SERGAS APPROVAL TO ACCESS THE ELECTRONIC MEDICAL RECORDS

XUNTA DE GALICIA
CONSELLERÍA DE SANIDADE

SERVIZO GALEGO de SAÚDE | **Xerencia do Servizo Galego de Saúde**

A/A D. ALFREDO GARCÍA IGLESIAS
Gerente
Gerencia de Gestión Integrada de A Coruña

Santiago de Compostela, a 6 de febrero de 2013

En el contexto de las especificaciones 1.3, 6.1 y 8ª del Concierto entre la Universidad de A Coruña y el Servicio Gallego de Salud, y en virtud del artículo 11.2 del Decreto 29/2009, de 5 de febrero, por el que se regula el uso y acceso a la historia clínica electrónica, en lo que se refiere al acceso para fines estadísticos o epidemiológicos, de investigación y docencia, publicaciones científicas y estudios, como órgano de la Consellería de Sanidad competente en materia de investigación, **se autoriza** la propuesta de la Gerencia de Gestión Integrada de A Coruña de acceso a datos de la historia clínica electrónica (IANUS) para el estudio e investigadora a continuación referenciados:

Título: "**Rehabilitación pulmonar en el preoperatorio de cirugía torácica mínimamente invasiva para resección pulmonar en pacientes diagnosticados de cáncer de pulmón**"
Investigadora Principal: **ESTHER GIMÉNEZ MOOLHYZEN**
Investigadora autorizada: **RAQUEL SEBIO GARCÍA**, DNI 45849027-E

Se recuerda tanto a la investigadora como al centro la necesidad de cumplir los aspectos adicionales recogidos en la Ley 41/2002, básica reguladora de la autonomía del paciente y de derechos y deberes en materia de información y documentación clínica, así como la Ley 16/2003, de cohesión y calidad en lo que se refiere al sistema de información sanitaria. Asimismo, en lo relativo a la confidencialidad de los datos, es preciso tener en cuenta a Ley 15/1999, de 13 de diciembre, que regula la protección de datos de carácter personal y su reglamento, Real decreto 1720/2007, de 21 de diciembre. En el ámbito de Galicia, también la Ley 3/2001, de 28 de marzo, reguladora del consentimiento informado y de la historia clínica de los pacientes, modificada por la Ley 3/2005, de 7 de marzo.

Sin otro particular, quedamos a su disposición.

Javier Paz Esquete
S. G. de Investigación, Docencia e Innovación
Xerencia do SERGAS

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SUPPLEMENTAL FILE NO.3 – INFORMATION SHEET AND INFORMED CONSENT

HOJA DE INFORMACIÓN AL PARTICIPANTE EN UN ENSAYO CLÍNICO SIN MEDICAMENTOS NI PRODUCTOS SANITARIOS

TÍTULO:

Efectividad de un programa de rehabilitación pulmonar preoperatorio sobre la tolerancia al esfuerzo y la calidad de vida en pacientes sometidos a videocirugía.

CÓDIGO: RSG-RPC-2011

INVESTIGADOR/A PRINCIPAL:

Esther Giménez Moolhyzen
Diplomada en Fisioterapia. Experta en Fisioterapia Respiratoria por la UDC
Servicio de Cirugía Torácica. Hospital Universitario de A Coruña. As Xubias, nº 84 - 15006 A Coruña
Teléfono de contacto: 981178286
E-mail: emoolhui@hotmail.com

Este documento tiene por objetivo ofrecerle información sobre un estudio de investigación de tipo experimental (ensayo clínico) en el que se le invita a participar. Este estudio se realizará en el Hospital Clínico Universitario de A Coruña (CHUAC) y ha sido aprobado por el Comité Ético de Investigación Clínica de Galicia.

Si decide participar en el mismo, debe recibir información personalizada del investigador, leer antes este documento y realizar todas las preguntas que necesite para comprender los detalles sobre el mismo. Si lo desea, puede llevarse consigo el documento, consultarlo con otras personas y tomarse el tiempo necesario para decidir si participa o no.

La participación en este estudio es completamente voluntaria. Usted puede decidir no participar o, si acepta, cambiar de parecer retirando su consentimiento en cualquier momento sin que sea necesario dar ningún tipo de explicación. Le aseguramos que su decisión no afectará a la relación con su clínico ni a la asistencia sanitaria a la que usted tiene derecho.

¿Cuál es el propósito del estudio?

Este estudio se propone evaluar la efectividad de una intervención de fisioterapia en cuanto a mejorar la condición física y funcional así como la calidad de vida percibida en los pacientes que

se encuentran en lista de espera para resección pulmonar. El objetivo final es conocer si esta mejoría alcanzada durante el preoperatorio se traduce en una mejor recuperación postoperatoria, incrementando la tolerancia al esfuerzo y su capacidad para realizar las tareas básicas diarias de forma independiente.

¿Cómo se llevará a cabo la investigación?

Durante el periodo que dure el estudio, todos los pacientes que cumplan los criterios de inclusión y presten su consentimiento serán distribuidos aleatoriamente en dos grupos: un grupo experimental que acudirá a las sesiones de rehabilitación pulmonar en el CHUAC, y un grupo control que cumplirá con las instrucciones facilitadas por su facultativo.

Este es un estudio unicéntrico, que se llevará a cabo en la Sala de Rehabilitación Pulmonar del Hospital Clínico Universitario de A Coruña a lo largo de 18 meses.

El programa de Rehabilitación Pulmonar será dirigido por una de las investigadoras, mientras que las mediciones y las pruebas funcionales serán realizadas por una persona diferente ajena al grupo asignado al paciente, para que evitar que puedan influir en la interpretación de los resultados posibles expectativas previas de los investigadores.

¿Por qué me ofrecen participar?

La selección de las personas invitadas a participar en este estudio depende de unos criterios que están descritos en el protocolo de investigación. Estos criterios sirven para seleccionar a la población en la que se responderá al interrogante planteado en la investigación. Se le invita a participar en el estudio porque usted cumple con esos criterios.

En este estudio se espera una participación de un total de 22 personas, 11 por cada grupo que se forma.

¿En qué consiste la participación?

Los pacientes serán asignados al azar a uno de los dos grupos que se formarán para el estudio, teniendo un 50% de posibilidades de ser incluidos en uno o en otro. El grupo experimental, acudirá a la sala de Rehabilitación Pulmonar del CHUAC entre dos y cuatro días a la semana (según disponibilidad y lista de espera), durante las semanas previas a la cirugía. La duración aproximada de cada sesión de tratamiento es de 1 hora y en ella el paciente deberá realizar una serie de ejercicios de fuerza y de resistencia así como técnicas de fisioterapia respiratoria en caso de ser necesario. Así mismo, debe saber que se le solicitará información de carácter personal sobre sus datos antropométricos y clínicos y deberá completar algunos test físicos para evaluar sus valores de resistencia, función pulmonar, capacidad funcional y calidad de vida.

El grupo control continuará con las instrucciones facilitadas por su facultativo y solamente deberá facilitarnos sus datos demográficos y clínicos así como completar las mediciones sobre los aspectos a evaluar con el estudio.

Tras la cirugía, todos los pacientes deberán acudir a la sala de Rehabilitación Pulmonar para poder repetir las mediciones indicadas anteriormente. Finalmente, serán contactados para una última valoración a los tres meses de recibir el alta hospitalaria.

La investigadora principal o alguno de los miembros del equipo podrán decidir finalizar el estudio antes de lo previsto o interrumpir su participación en el mismo por aparición de nueva información relevante, por motivos de seguridad, o por incumplimiento de los procedimientos del estudio.

Recuerde que toda la información que nos facilite se haya protegida por la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal, que todos los investigadores nos comprometemos a cumplir y respetar.

¿Tiene algún riesgo la participación?

Los riesgos asociados a un Prográmame de Rehabilitación Pulmonar son muy bajos. Estos programas han sido diseñados para ser aplicados específicamente en pacientes con patologías respiratorias crónicas, teniendo en cuenta sus características fisiopatológicas especiales y sin haberse desencadenado en ningún caso efectos adversos graves.

Debido a que el perfil de los pacientes participantes en el estudio puede incluir la presencia de enfermedades como hipertensión arterial, diabetes mellitus, Enfermedad Pulmonar Obstructiva Crónica o patologías cardiovasculares, durante la realización de los ejercicios, se monitorizará la frecuencia cardíaca, saturación de oxígeno y la tensión arterial, con el objetivo de prevenir cualquier tipo de episodio de mayor gravedad que pudiera producirse.

En cualquier caso, cualquier acontecimiento considerado de gravedad será notificado al Comité de Ética de Investigación Clínica de Galicia.

¿Obtendré algún beneficio por participar?

No podemos asegurarle que exista un beneficio directo por participar en el estudio, pero en base a los resultados obtenidos con estos programas en otras patologías respiratorias, consideramos que existe una gran posibilidad de lograr la mejoría de los aspectos señalados al inicio y por lo tanto, creemos que su estado físico y funcional mejorará tras las sesiones de rehabilitación recibidas.

¿Recibiré la información que se obtenga del estudio?

Si usted lo desea, se le facilitará un resumen de los resultados del estudio. También podrá recibir los resultados de las pruebas que se le practiquen si así lo solicita.

¿Se publicarán los resultados de este estudio?

Los resultados serán presentados en publicaciones científicas para su difusión, pero en ningún caso se transmitirá dato alguno que pueda llevar a la identificación de los participantes

¿Cómo se protegerá la confidencialidad de mis datos?

El tratamiento, comunicación y cesión de sus datos se hará conforme a lo dispuesto en la Ley Orgánica 15/1999, de 13 de diciembre, de protección de datos de carácter personal y por su regulación (RD 1720/2007). En todo momento, usted podrá acceder a sus datos, corregirlos o cancelarlos.

Sus datos llevarán un código que no permite identificarlos directamente. La relación entre los códigos y su identidad será custodiada por el investigador. Sólo el equipo investigador y las autoridades sanitarias que tienen el deber de guardar la confidencialidad, tendrán acceso a todos los datos recogidos por el estudio. En situaciones de urgencia médica o requerimiento legal, las personas indicadas podrán consultarlos. Se podrá transmitir a terceros información que no pueda ser identificada, exclusivamente para los fines del estudio. En el caso de que alguna información sea transmitida a otros países, se realizará con un nivel de protección de los datos equivalente, como mínimo, al exigido por la normativa de nuestro país.

Su médico especialista y médico de cabecera pueden, si lo desea, recibir información sobre su participación en este estudio

Si usted decide interrumpir la participación, puede ser importante seguir utilizando los datos recogidos hasta ese momento para disponer de mayor información posible sobre la seguridad y la efectividad de la técnica investigada. Llegada esta circunstancia, se le pedirá autorización para utilizar dichos datos.

¿Qué pasará con los datos obtenidos?

Los datos obtenidos serán guardados de forma codificada, que quiere decir que poseen un código que se puede relacionar, mediante una información con el donante. Esta información está a cargo del investigador principal y sólo pueden acceder a ella los miembros del equipo y las autoridades sanitarias en el ejercicio de sus funciones.

¿Qué ocurrirá si hay alguna consecuencia negativa de la participación?

Como ya se mencionó con anterioridad, los riesgos asociados a un programa de Rehabilitación Pulmonar son muy bajos y no se han descrito efectos adversos graves. Se trata por

lo tanto de una intervención segura, supervisada en todo caso por personal especializado y que cuentan con una monitorización continua para evitar posibles episodios adversos.

¿Quién me puede proporcionar más información?

Puede contactar con uno de los investigadores colaboradores del proyecto a través del correo electrónico (raquel.sebio@udc.es) o en el siguiente número de teléfono: 668860237. Muchas gracias por su participación.

DOCUMENTO DE CONSENTIMENTO INFORMADO PARA EL PARTICIPANTE EN UN ENSAYO CLÍNICO SIN MEDICAMENTOS NI PRODUCTOS SANITARIOS

TÍTULO:

Efectividad de un programmea de rehabilitación pulmonar preoperatorio sobre la tolerancia al esfuerzo y la calidad de vida en pacientes sometidos a videocirugía.

CÓDIGO: RSG-RPC-2011

Yo, (nombre y apellidos) ……

- He leído la hoja de información al participante del estudio que se me ha entregado anteriormente, he podido hablar con Raquel Sebio García del estudio y hacer todas las preguntas sobre el estudio necesarias para comprender las condiciones en las que se realiza y considero que he recibido suficiente información sobre el estudio.
- Comprendo que mi participación es voluntaria, y que puedo retirarme del estudio cuando lo desee, sin tener que dar explicaciones y sin que esto repercuta en mis cuidados médicos.
- Accedo a que se utilicen mis datos en las condiciones detalladas en la hoja de información al participante.
- Presto libremente mi conformidad para participar en el estudio.

En canto a los resultados de las pruebas realizadas, yo:

☐ DESEO conocer los resultados de mis pruebas

☐ NO DESEO conocer os resultados de mis pruebas

El/la participante, El/la investigador/a,

Fdo.: **Fdo.:**

Fecha: **Fecha:**

SUPPLEMENTAL FILE NO.4 – TRAINING LOG TEMPLATE

CODIGO:

SESIÓN:

FECHA:

A. ENTRENAMIENTO DE FUERZA – RESISTENCIA:

EJERCICIO	COLOR THERA BAND	NÚMERO DE REPETICIONES	NÚMERO DE SERIES
Abducción Hombro			
Flexión Hombro			
Flexión de codo			
Chest Press			
Remo			
Lateral Pull Down			
Empuje Pierna			
Sentadilla			
Set Up			
Gemelos			

B. PROGRAMMEA DE ENTRENAMIENTO AL ESFUERZO:

PMT (W):

INTENSIDAD BASE (W):

INTENSIDAD PICO (W):

FRECUENCIA CARDÍACA MÁX. TEÓRICA:

Nº DE PICOS: 7

TIEMPO	WATT	SATURACIÓN	FC
1- 5’	30% PMT		
5 –- 6’	80% PMT		
6 – 10’	50% PMT		
10 – 11’	80% PMT		
11 – 15’	50% PMT		
15 – 16’	80% PMT		
16 – 20’	50% PMT		
20 – 21’	80% PMT		
21 – 25’	50% PMT		
25 – 26’	80% PMT		
26 – 30’	50% PMT		
30 – 31’	80% PMT		
31 – 35’	50% PMT		
35 – 36’	80% PMT		
36 – 40’	30% PMT		

SENSACIÓN DE DISNEA AL INICIO (Escala Borg Modificada):

SENSACIÓN DE DISNEA MÁXIMA ALCANZADA:

SENSACIÓN DE FATIGA EN MMII (Escala Borg Modificada):

FATIGA ALCANZADA EN MIEMBROS INFERIORES:

SUPPLEMENTAL FILE no.5 – DATA COLLECTION SHEET

CODIGO DEL SUJETO:

SEXO:

EDAD:

PESO:

TALLA:

LUGAR DE RESIDENCIA:

ANTECEDENTES PERSONALES

HISTORIA DE TABAQUISMO	**SÍ**	**NO**	**EXFUMADOR**
Nº PAQUETES/AÑO			
ALCOHOLISMO	**SÍ**	**NO**	
OTRAS PATOLOGÍAS			
ENFERMEDAD CARDIOVAS	NO	SI	
EPOC	NO	SI	GRADO[1]
ENFERMEDAD RESPIRATORIA	NO	SÍ	
INSUFICIENCIA RENAL	NO	SI	
DIABETES	NO	SI	
CÁNCER	NO	SÍ	

COLINET CO-MORBIDITY SCORE:

DATOS CLÍNICOS

DIAGNÓSTICO PRE-OPERATORIO:

SÍNTOMAS ASOCIADOS

TOS	**SÍ**	**NO**	
DISNEA	**SÍ**	**NO**	**GRADO**[2]
ANOREXIA	**SÍ**	**NO**	
ASTENIA	**SÍ**	**NO**	
EXPECTORACIÓN	**SÍ**	**NO**	**ASPECTO**

[1] Según Escala GOLD 2011
[2] Según Medical Research Council

OTROS:

VALORACIÓN

ESPIROMETRÍA

	VFC	FEV_1	FEV_1/VFC
BASAL			
POST-QX			

TEST DE CALIDAD DE VIDA

	BASAL	PRE-QX	POST-QX	SEGUIMIENTO
FECHA DE CUMPLIMENTACIÓN				

PRUEBA DE RESISTENCIA MÁXIMA EN CICLOERGÓMETRO

Fecha:
Potencia Máxima Teórica: *Frecuencia Cardíaca Máxima Teórica:*

Tiempo	Potencia	Sat	FC	Borg Disnea	Borg Fatiga	TA
Basal						
1'						
2'						
3'						
4'						
5'						
6'						
7'						
8'						
9'						
10'						
11'						
12'						
Rec 1'						
Rec 2'						
Rec 3'						

Motivo de parada:

PRUEBA DE 6 MINUTOS MARCHA

	T_0(1) Fecha:	T_0(2) Fecha:	T_2 Fecha:	T_3 Fecha:
Sat O2 Basal				
Sat O2 Final				
FC Basal				
FC Final				
Disnea Basal				
Disnea Final				
Fatiga Muscular Basal				
Fatiga Muscular Final				
Distancia recorrida (m)				
Número de Paradas				
Tiempo de Recuperación				
Val Ref[3]				

TEST DE APTITUD FÍSICA

	Val Ref[4]	T_0	T_1	T_2	T_3
30's Arm Curl					
30's Chair to Sit					

[3] P.Enright, 1995 Reference Equations
[4] Rikli and Jones, 2001(Heyward 2008, pp. 135-6)

PRUEBA DE RESISTENCIA SUBMÁXIMA

	T_0 Fecha:	T_1 Fecha:	T_2 Fecha:	T_3 Fecha:
FC Basal				
FC Final				
Saturación de O_2 Basal				
Saturación de O_2 Final				
Potencia de Prueba (80% PMT)				
Tiempo Mantenido				
Disnea Final				
Fatiga MMII Final				

INFORME QUIRÚRGICO

FECHA INGRESO:

FECHA DE LA CIRUGÍA:

EQUIPO QUIRÚRGICO:

PROCEDIMIENTO:

COMPLICACIONES POSTOPERATORIAS

VENTILACIÓN MECÁCICA > 48H	SÍ	NO
DRENAJE TORÁCICO > 5 DÍAS	SI	NO
ATELECTASIA	SÍ	NO
NEUMONÍA	SÍ	NO
NEUMOTORAX	SI	NO
DERRAME PLEURAL	SI	NO
INFECCION RESPIRATORIA/ INFILTRADOS	SI	NO
CAMBIOS EN EL ESPUTO	SI	NO
ANALISIS DE ESPUTO	SI	NO
FIBRILACIÓN ATRIAL	SI	NO
READMISION REA	SI	NO
DESATURACIÓN	SI	NO
LEUCOCITOSIS	SI	NO

NUMERO DE SESIONES DE FTR:

ALTA HOSPITALARIA:

DIAGNOSTICO POSTOPERATORIO:

ADYUVANCIA: SI NO

SUPPLEMENTAL FILE no.6 – SHORT FORM 36 HEALTH SURVEY (Spanish version)

CODIGO DEL PACIENTE:
FECHA DE CUMPLIMENTACION:

Cuestionario de Salud SF-36

(versión 2)

Institut Municipal d´Investigació Mèdica (IMIM-IMAS)
Unidad de Investigación en Servicios Sanitarios
C/ Doctor Aiguader, 80 E-8003 Barcelona
Tel. (+34) 93 225 75 53, Fax (+34) 93 221 40 02
www.imim.es

Su Salud y Bienestar

Por favor conteste las siguientes preguntas. Algunas preguntas pueden parecerse a otras pero cada una es diferente.

Tómese el tiempo necesario para leer cada pregunta, y marque con una X la casilla que mejor describa su respuesta.

¡Gracias por contestar a estas preguntas!

1. En general, usted diría que su salud es:

1 ☐ Excelente

2 ☐ Muy buena

3 ☐ Buena

4 ☐ Regular

5 ☐ Mala

2. ¿Cómo diría que es su salud actual, comparada con la de hace un año?

1 ☐ Mucho mejor ahora que hace un año

2 ☐ Algo mejor ahora que hace un año

3 ☐ Más o menos igual que hace un año

4 ☐ Algo peor ahora que hace un año

5 ☐ Mucho peor ahora que hace un año

3. Las siguientes preguntas se refieren a actividades o cosas que usted podría hacer en un día normal. Su salud actual, ¿le limita para hacer esas actividades o cosas? Si es así, ¿cuánto?

a. Esfuerzos intensos, tales como correr, levantar objetos pesados, o participar en deportes agotadores.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

b. Esfuerzos moderados, como mover una mesa, pasar la aspiradora, jugar a los bolos o caminar más de 1 hora.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

c. Coger o llevar la bolsa de la compra.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

d. Subir varios pisos por la escalera.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

e. Subir un sólo piso por la escalera.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

f. Agacharse o arrodillarse.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

g. Caminar un kilómetro o más.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

h. Caminar varios centenares de metros.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

i. Caminar unos 100 metros.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

j. Bañarse o vestirse por sí mismo.

1 ☐ Sí, me limita mucho

2 ☐ Sí, me limita un poco

3 ☐ No, no me limita nada

4. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de su salud física?

a. ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

b. ¿Hizo menos de lo que hubiera querido hacer?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

c. ¿Tuvo que dejar de hacer algunas tareas en su trabajo o en sus actividades cotidianas?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

d. ¿Tuvo dificultad para hacer su trabajo o sus actividades cotidianas (por ejemplo, le costó más de lo normal)?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

5. Durante las 4 últimas semanas, ¿con qué frecuencia ha tenido alguno de los siguientes problemas en su trabajo o en sus actividades cotidianas, a causa de algún problema emocional (como estar triste, deprimido o nervioso?

a. ¿Tuvo que reducir el tiempo dedicado al trabajo o a sus actividades cotidianas por algún problema emocional?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

b. ¿Hizo menos de lo que hubiera querido hacer por algún problema emocional?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

c. ¿Hizo su trabajo o sus actividades cotidianas menos cuidadosamente que de costumbre, por algún problema emocional?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

6. Durante las 4 últimas semanas, ¿hasta qué punto su salud física o los problemas emocionales han dificultado sus actividades sociales habituales con la familia, los amigos, los vecinos u otras personas?

1 ☐ Nada

2 ☐ Un poco

3 ☐ Regular

4 ☐ Bastante

5 ☐ Mucho

7. ¿Tuvo dolor en alguna parte del cuerpo durante las 4 últimas semanas?

1 ☐ No, ninguno

2 ☐ Sí, muy poco

3 ☐ Sí, un poco

4 ☐ Sí, moderado

5 ☐ Sí, mucho

6 ☐ Sí, muchísimo

8. Durante las 4 últimas semanas, ¿hasta qué punto el dolor le ha dificultado su trabajo habitual (incluido el trabajo fuera de casa y las tareas domésticas)?

1 ☐ Nada

2 ☐ Un poco

3 ☐ Regular

4 ☐ Bastante

5 ☐ Mucho

9. Las preguntas que siguen se refieren a cómo se ha sentido y cómo le han ido las cosas durante las 4 últimas semanas. En cada pregunta responda lo que se parezca más a cómo se ha sentido usted. Durante las 4 últimas semanas ¿con qué frecuencia…

a. se sintió lleno de vitalidad?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

b. estuvo muy nervioso?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

c. se sintió tan bajo de moral que nada podía animarle?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

d. se sintió calmado y tranquilo?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

e. tuvo mucha energía?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

f. se sintió desanimado y deprimido?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5☐ Nunca

g. se sintió agotado?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

h. se sintió feliz?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

i. se sintió cansado?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

10. Durante las 4 últimas semanas, ¿con qué frecuencia la salud física o los problemas emocionales le han dificultado sus actividades sociales (como visitar a los amigos o familiares)?

1 ☐ Siempre

2 ☐ Casi siempre

3 ☐ Algunas veces

4 ☐ Sólo alguna vez

5 ☐ Nunca

11. Por favor diga si le parece CIERTA o FALSA cada una de las siguientes frases:

a. Creo que me pongo enfermo más fácilmente que otras personas.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

b. Estoy tan sano como cualquiera.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

c. Creo que mi salud va a empeorar.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

d. Mi salud es excelente.

1 ☐ Totalmente cierta

2 ☐ Bastante cierta

3 ☐ No lo sé

4 ☐ Bastante falsa

5 ☐ Totalmente falsa

Gracias por contestar a estas preguntas.

SUPPLEMENTAL FILE no.7 - RESISTANCE TRAINING EXERCISE BOOKLET

A) Upper Body and Back

1) <u>Thera-Band Shoulder Front Raise in Standing</u>: Stand on the middle of the band under your feet. Grasp the ends of the band. Lift upward, keeping your elbows straight and thumbs up. Stop at shoulder level. Hold and slowly return.

2) <u>Thera-Band Shoulder Lateral Raise in Standing</u>: Stand on the middle of the band. Grasp the ends of the band. Lift the band upward, keeping your elbows straight. Stop at shoulder level. Hold and slowly return.

3) Thera-Band Elbow Biceps Curl (Standing): Stand on the middle of the band. Grasp the ends of the band. Lift the band upward, bending your elbows and palms up. Keep your elbows by your side. Hold and slowly return.

4) Thera-Band Upright Row in Standing: Place middle of the band under both feet and grasp each end of the band with palms facing down. Pull the ends of the band upward toward your chin, lifting your elbows upward. Hold and slowly return to the starting position.

5) Thera-Band Chest Flies: Secure the middle of the band to a stationary object at shoulder level. Face away from the attachment. Use a staggered step with one leg slightly in front of the other. Grasp the bands at shoulder height with your elbows straight. Keep your elbows straight and pull bands inward with palms facing each other. Slowly return.

6) Thera-Band Shoulder Lat Pull Down (standing): Secure the middle of a long band or tubing to a stationary object above shoulder level, facing the attachment. Grasp the ends of the tubing above shoulder height with your elbows extended. Bend your elbows and bring your hands to your chest, pulling the bands down and back. Hold and slowly return.

B) Lower body

7) Thera-Band Knee Leg Press in Supine: Lay on your back with your knee bent and middle of band looped around the bottom of the foot. Grasp the ends of the band in each hand near your shoulders. Extend your hip and knee against the band until straight. Hold and slowly return.

8) Calf raise: Place your feet at shoulder width. Keep your hands by your side and go up onto your toes. Hold and slowly return

9) Exercise Ball Wall Squat: Begin with ball behind your back and stabilized on wall. Keep neck and pelvis in neutral. Perform a squat by bending knees, lowering pelvis and rolling ball downward. Hold and slowly return.

10) Step-Up: Step up onto stairs or steps facing forward. Use the railing or other sturdy object for balance if needed.

SUPPLEMENTAL FILE no. 8 – SUMMARY OF THE THESIS IN SPANISH

INTRODUCCIÓN

El cáncer de pulmón es la primera causa de muerte por cáncer en el mundo. En España, según el último informe publicado por el Instituto Nacional de Estadística, en el 2013 21.664 personas fallecieron a consecuencia de este tumor, situándose como la tercera causa de muerte tras las enfermedades cardiovasculares (Instituto Nacional de Estadistica, 2015). En los próximos años, se espera que el cáncer de pulmón supere a éstas últimas como la primera causa de muerte en el mundo.

Aproximadamente, el 85% de los casos de cáncer de pulmón corresponden a la estirpe de células no pequeñas (CPCNP) para el cual, el tratamiento quirúrgico es el más indicado y el que mayores posibilidades de supervivencia aporta (Howington et al., 2013). Sin embargo, únicamente el 20 – 25% de los pacientes con CPCNP se encuentran en un estadio operable en el momento del diagnóstico, de los cuales, muchos no podrán someterse a una cirugía de resección tumoral por ser considerados pacientes de alto riesgo quirúrgico debido a su edad avanzada, la presencia de comorbilidades cardíacas y/o respiratorias graves o a sub-óptima función física y/o pulmonar, lo que conlleva un peor pronóstico y disminuye su supervivencia a largo plazo. El concepto de pre-habilitación ha surgido recientemente en contraposición a la rehabilitación convencional como una manera de preparar a los pacientes ante una cirugía mayor, especialmente a aquellos que tienen mayor riesgo de padecer complicaciones postoperatorias y por lo tanto de experimentar una recuperación más larga y tórpida. Así mismo, la pre-habilitación podría incluso reconducir a pacientes con muy baja función pulmonar y/o tolerancia al ejercicio considerados como de alto riesgo quirúrgico a enfrentarse a la cirugía en óptimas condiciones. Lamentablemente, existe muy poca evidencia en relación a la eficacia de estos programas especialmente en el contexto de cirugía

torácica y la mayor parte de los estudios han sido llevados a cabo en pacientes sometidos a una toracotomía convencional (Jones et al., 2007, Cesario et al., 2007, Morano et al., 2013, Sekine et al., 2005). Con el auge de la cirugía mínimamente invasiva, nos encontramos en un momento de relajación de los criterios quirúrgicos lo que ha llevado a pacientes con un peor estado basal a ser operados, lo que en último caso podría conllevar un aumento de la morbimortalidad perioperatoria. En este nuevo contexto quirúrgico, se desconocen los efectos que la pre-habilitación podría tener sobre la tolerancia al esfuerzo de los pacientes así como a nivel postoperatorio sobre la incidencia de complicaciones postoperatorias y la recuperación física y funcional durante los primeros meses tras la cirugía.

OBJETIVOS

En vista del rápido incremento de la videocirugía así como de la falta de estudios sobre el papel de la rehabilitación pulmonar y en concreto de la pre-habilitación en este contexto quirúrgico, los objetivos principales de esta tesis son:

1. Identificar, sintetizar y analizar la evidencia científica actual sobre los programas de pre-habilitación en pacientes con cáncer de pulmón sometidos a cirugía de resección pulmonar.
2. Examinar la viabilidad, seguridad y eficacia preliminares de un programa de rehabilitación pulmonar preoperatorio en pacientes con sospecha clínica o diagnóstico confirmado de cáncer de pulmón sometidos a resección pulmonar por videocirugía.
3. Analizar la eficacia de un programa de rehabilitación pulmonar preoperatorio en esta población para incrementar la función física y la calidad de vida así como para mejorar la recuperación postoperatoria.

4. Proporcionar una base sólida de donde partan futuras investigaciones en el campo de la pre-habilitación de cirugía torácica y otras cirugías mayores para reducir la morbilidad postoperatoria y acelerar la recuperación funcional y psicológica.

MATERIAL Y MÉTODO

Esta tesis se encuentra estructurada en tres estudios, cada uno de los cuales cuenta con una metodología propia en función del tipo de investigación y los objetivos propuestos: una revisión sistemática y meta-análisis, un estudio piloto de viabilidad y un ensayo aleatorizado controlado a simple ciego. Los estudios fueron llevados a cabo en el periodo comprendido entre Febrero de 2013 y Noviembre de 2015. En el siguiente apartado se expone un breve resumen de cada uno de los estudios incluidos en esta tesis en cuanto a su objetivo, metodología y principales resultados.

RESULTADOS

ESTUDIO #1:

Diseño: revisión sistemática y meta-análisis acerca de los efectos de la rehabilitación pulmonar preoperatoria en pacientes con cáncer de pulmón sometidos a resección pulmonar.

Objetivo: el objetivo principal del estudio era examinar los efectos de la rehabilitación preoperatoria en pacientes con cáncer de pulmón en cuanto a tolerancia al esfuerzo, capacidad funcional, función pulmonar y calidad de vida relacionada con la salud (CVRS). Como objetivos secundarios se encontraban: 1) comparar la incidencia de complicaciones postoperatorias y la estancia hospitalaria en los pacientes sometidos a pre-habilitación en comparación con el tratamiento estándar (no pre-habilitación) y 2) llevar a cabo un meta-análisis con el fin de cuantificar el tamaño del efecto de la intervención en cada una de las variables de medición seleccionadas.

Material y método: esta revisión sistemática se llevó a cabo conforme a las recomendaciones de PRISMA (*the Preferred Reporting Items for Systematic Reviews and Meta-analisys*). Así mismo, el protocolo fue registrado en la base de datos de PROSPERO bajo el código de identificación CRD42015024283. Seis bases de datos (CINAHL, EMBASE, MEDLINE, PEDro, Pubmed y SCOPUS) fueron sistemáticamente revisadas dando lugar a 1,656 referencias. 12 artículos fueron también identificados a través de una búsqueda manual. La búsqueda inicial fue realizada por una de las investigadoras y una vez eliminados los duplicados y las referencias no relevantes, dos investigadoras analizaron de forma independiente las referencias restantes en función de los criterios de inclusión pre-establecidos. Los artículos fueron incluidos si: 1) incluían pacientes con cáncer de pulmón; 2) evaluaban algún tipo de intervención preoperatoria relacionada con el ejercicio aeróbico o de fuerza o una combinación de ambos; 3) medían los resultados del programa en alguna de las siguientes variables: tolerancia al esfuerzo, capacidad funcional, función pulmonar, calidad de vida y/o complicaciones postoperatorias y estancia hospitalaria. El análisis de calidad fue realizado de forma independiente por dos investigadoras utilizando la escala proporcionada por PEDro para ensayos clínicos y la Newcastle-Ottawa Scale (NOS) para estudios de cohortes y series de casos. Finalmente, en aquellas variables en las que se consideró oportuno, además de un análisis descriptivo de los resultados se llevó a cabo un meta-análisis para cuantificar el tamaño del efecto y generar los correspondientes intervalos de confianza al 95% (I.C 95%). El programa utilizado fue el Review Manager© (RevMan) versión 5.3 para Windows©.

Resultados: tras aplicar los criterios de inclusión y exclusión 21 estudios fueron finalmente incluidos en la revisión sistemática (ocho ensayos clínicos, cuatro estudios de cohortes y nueve series de casos) pero únicamente 14 entraron en el posterior meta-análisis. La modalidad de ejercicio predominante en los estudios fue el entrenamiento aeróbico seguido de una combinación entre el entrenamiento aeróbico y de fuerza. Sólo dos estudios centraron sus intervenciones en el

entrenamiento de fuerza muscular periférica. Otros componentes frecuentes en los programas fueron los ejercicios respiratorios con o sin incentivador, el entrenamiento de la musculatura respiratoria o las técnicas de relajación. El análisis de calidad mostró un nivel metodológico medio (5/10 para los ensayos clínicos según la escala PEDro y 6/9 para los estudios de cohortes y series de casos según la escala NOS).

En cuanto a las variables analizadas, la mayoría de los estudios mostraron un aumento significativo pre – post intervención en la tolerancia al esfuerzo (consumo máximo de oxígeno) y la capacidad funcional (test de 6 minutos marcha). Sin embargo, los estudios mostraron una alta heterogeneidad y por lo tanto se consideró inapropiado realizar un meta-análisis. Solo cuatro estudios incluyeron un análisis sobre la calidad de vida y los resultados fueron inconsistentes, por lo que debido a esto y a la variabilidad encontrada en los instrumentos de medición se consideró de nuevo inapropiado calcular el tamaño del efecto. Por otro lado, la función pulmonar experimentó un aumento significativo en los dos principales parámetros estudiados (Capacidad Vital Forzada (CVF) y Volumen Espirado Máximo en el primer segundo (VEMS)). En este caso, el meta-análisis mostró un aumento significativo pre – post intervención (diferencia de medias estandarizada = 0,38; I.C 95%: 0,14 - 0,63 y 0,27; I.C 95%: 0,11 – 0,42 respectivamente). De la misma manera, la duración de la estancia hospitalaria fue significativamente menor en los grupos de pre-habilitación en comparación con el tratamiento estándar (diferencia de medias = -4,83 días; C.I 95%: -3,76 - 5,9) así como la incidencia de complicaciones postoperatorias (riesgo relativo (RR) = 0,45; C.I 95%: 0,34 – 0,89). Sin embargo, en esta última variable el nivel de heterogeneidad fue sustancial (I^2 = 65%) por lo que se llevó a cabo posteriormente un sub-análisis para examinar las posibles causas. Así, encontramos que al clasificar las complicaciones postoperatorias según el origen (sólo respiratorio versus respiratorio y/u otros), los estudios que incluyeron sólo complicaciones postoperatorias respiratorias mostraron un tamaño del efecto similar (RR = 0,55; I.C 95%: 0,34 –

0,89) pero significativamente menos heterogeneidad (I^2 = 27%). También el tipo de diseño influyó en el nivel de heterogeneidad de forma que al separar los ensayos clínicos aleatorizados versus los no aleatorizados y los estudios de cohortes, de nuevo el tamaño del efecto se mantenía estable mientras que el nivel de heterogeneidad se reducía totalmente (RR = 0,46; I.C 95: 0,26 – 0,82; I^2 = 0%).

Conclusiones: en conjunto, los resultados de esta revisión sistemática y meta-análisis demuestran que la pre-habilitación en pacientes con cáncer de pulmón sometidos a resección pulmonar reduce de forma significativa la morbilidad postoperatoria así como la estancia hospitalaria. Así mismo, la realización de un programa basado en el ejercicio físico resulta efectiva para incrementar la función pulmonar y podría mejorar además la tolerancia al esfuerzo y la capacidad funcional aunque en estos casos los resultados no son concluyentes. Finalmente, se necesitan más estudios para analizar el papel de estos programas sobre la calidad de vida de los pacientes.

ESTUDIO #2:

Diseño: estudio piloto para evaluar la viabilidad, tolerancia y eficacia preliminares de un programa de rehabilitación pulmonar preoperatorio en pacientes con sospecha clínica o diagnóstico confirmado de cáncer de pulmón sometidos a resección pulmonar por videocirugía.

Objetivos: el principal objetivo de este estudio era testar la viabilidad del programa en cuanto a adherencia y grado de tolerancia en los pacientes así como el grado de seguridad de la intervención en relación a los potenciales efectos adversos encontrados. Como objetivos secundarios se encontraban: 1) evaluar la eficacia preliminar del programa en cuanto a aumentar la capacidad funcional, la fuerza muscular y la calidad de vida; 2) describir el deterioro funcional y psicológico observado tras videocirugía y 3) determinar si tres meses tras la intervención quirúrgica los

pacientes habían recuperado sus valores basales en cuanto a capacidad funcional, fuerza muscular y calidad de vida.

Material y método: este estudio fue aprobado por el Comité Autonómico de Ética da Investigación de Galicia en el seno de un ensayo clínico aleatorizado y todos los pacientes incluidos firmaron el consentimiento informado antes de ser evaluados. Desde Febrero a Junio de 2013 todos los pacientes incluidos en lista de espera para resección pulmonar por sospecha clínica o diagnóstico confirmado de cáncer de pulmón en el Servicio de Cirugía Torácica del Hospital Clínico Universitario de A Coruña (CHUAC) fueron evaluados para su inclusión en el estudio. Los pacientes debían de ser mayores de edad, pertenecer al área sanitaria de A Coruña y no haber recibido tratamiento neoadyuvante en los seis meses anteriores. Se excluyeron aquellos pacientes que presentaban alguna contraindicación médica al ejercicio así como aquellos que presentaban algún trastorno del sistema músculo-esquelético que impidiese la realización de los ejercicios.

El programa de rehabilitación estaba dirigido por una fisioterapeuta especializada en rehabilitación pulmonar y constaba de los siguientes elementos: 1) entrenamiento aeróbico en ciclo-ergómetro (Monark 818 E, Monark Exercise AB, Sweden) siguiendo un protocolo interválico combinando cuatro minutos a baja intensidad (45 – 50 % de la carga máxima tolerada) con un minuto de alta intensidad (al 80 – 85% de la carga máxima) durante 30 - 40 minutos; 2) entrenamiento de fuerza-resistencia que consistía en la realización de ejercicios para miembros superiores e inferiores con bandas elásticas (Thera-Band©, The Hygienic Corporation, Akron, Ohio, USA) y ejercicios auto-resistidos con ayuda del peso corporal; 3) ejercicios respiratorios con incentivador volumétrico (Coach 2 Espirómetro de incentivo 22-4000 HD, Smith Medicals, USA) a realizar en el domicilio en dos sesiones de unos 15 minutos de duración cada una aproximadamente. Los pacientes completaron de tres a cinco sesiones semanales de una hora y cuatro de duración durante todo el periodo preoperatorio.

Las variables de medición seleccionadas para este estudio fueron: 1) adherencia (número de pacientes que alcanza al menos un 80% de las sesiones inicialmente planteadas); 2) seguridad (número de eventos adversos que precisan atención médica urgente o no urgente; 3) tolerancia al esfuerzo (test de 6 minutos marcha); 4) fuerza muscular (*Senior Fitness Test*) y 5) CVRS (SF – 36). Los pacientes fueron evaluados al inicio de la intervención (T0), al finalizar la intervención, previamente a la cirugía (T1), una semana después del alta hospitalaria (T2) y a los tres meses de la cirugía (T3).

Pese a la distribución normal de las variables y debido al reducido tamaño de la muestra, el análisis estadístico se realizó mediante pruebas no paramétricas para muestras relacionadas en cada una de las variables de medición. El programa estadístico utilizado fue el SPSS para Windows versión 21 (IBM Corporation, Chicago, IL, USA) y un valor de p <.05 fue considerado como estadísticamente significativo.

Resultados: durante el periodo de estudio, 23 pacientes fueron evaluados de los cuales, 12 (52.2%) cumplieron los criterios de inclusión establecidos por los investigadores. De los 12 pacientes inicialmente incluidos, tres fueron excluidos a posteriori debido a problemas con el transporte al centro de rehabilitación (n = 2) o porque fueron sometidos a cirugía con carácter urgente (n = 1). Nueve pacientes completaron la intervención y fueron analizados. De media, los pacientes completaron un total de 21 sesiones de las 18 inicialmente propuestas (rango 11 – 27). Solo un paciente alcanzó menos del 80% de adherencia. Ningún efecto adverso fue registrado durante el periodo de entrenamiento. En cuanto a la eficacia preliminar del programa, tras la intervención los pacientes aumentaron en 22,5 metros la distancia recorrida con el test de 6 minutos marcha (T6MM). Aunque el resultado no alcanzó valores estadísticamente significativos por un margen muy estrecho (p = .050), el aumento sí se encuentra dentro del rango identificado como clínicamente significativo para pacientes con cáncer de pulmón (Granger et al., 2015). La función

muscular medida a través del *Senior Fitness Test* (SFT) sí experimentó un aumento significativo con respecto a los valores basales (Tabla 1). En cambio, los cambios en la calidad de vida según el SF-36 fueron mínimos y no alcanzaron valores estadísticamente significativos salvo en el caso de la dimensión de salud mental. En el postoperatorio inmediato, el T6MM experimentó una reducción significativa con respecto a los valores basales (67,9 ± 65,5 metros), lo que nos indica que incluso con el abordaje quirúrgico mínimamente invasivo existe una disminución en la capacidad funcional inmediatamente tras la cirugía. La fuerza de los miembros superiores medida con el Test de flexión de brazo del SFT también disminuyó significativamente mientras que la de miembros inferiores se mantuvo estable (Tabla 1). A los tres meses de la intervención, los pacientes se encontraban por encima de los valores basales en el T6MM (105,5 ± 6,8%) mientras que la fuerza de miembros superiores e inferiores se mantenían entre el 80 y el 88% de los valores basales respectivamente.

Tabla 3: Evolución de las principales variables analizadas a lo largo del estudio

VARIABLE	**T0**	**T1**	**T2**	**T3**
T6MM (m)	557,6±74,4	580,1±80,7	489,7±98,7**** †	529,63±83,2
Flexión de brazo (nº)	16,9±5,4	20,7±2,6*	20±3,3**	19,2±3,2† †
Levantarse y sentarse de la silla (nº)	14,6±5,9	15,9±3,9*	16,1±5	13,2±7

*p <.05 entre T_0 y T_1; **entre T_0 y T_2; †entre T_1 y T_2† †entre T_0 y T_3

Conclusiones: en vista de los resultados preliminares observados en este estudio piloto podemos concluir que la rehabilitación pulmonar preoperatoria en pacientes sometidos a videocirugía por neoplasia maligna pulmonar es factible, segura y muy probablemente eficaz a la hora de incrementar la tolerancia al esfuerzo y la fuerza muscular. Pese al uso de técnicas mínimamente invasivas, inmediatamente tras la cirugía existe una pérdida importante de la capacidad funcional que aparentemente queda restablecida en los tres primeros meses tras la cirugía. Sin embargo, se desconoce si esta recuperación se debe, al menos en parte, al entrenamiento preoperatorio o corresponde a la evolución natural de los pacientes, por lo que es necesario un ensayo clínico aleatorizado para conocer el impacto de la rehabilitación preoperatoria en la recuperación funcional de los pacientes operados por videocirugía.

ESTUDIO #3:

Diseño: ensayo clínico aleatorizado controlado a simple ciego para valorar los efectos de un programa de rehabilitación pulmonar preoperatorio sobre la tolerancia al esfuerzo, la fuerza muscular y la calidad de vida en pacientes con sospecha clínica o diagnóstico confirmado de cáncer de pulmón sometidos a videocirugía.

Objetivos: los objetivos principales de este estudio fueron:

1. Analizar la eficacia de un programa de rehabilitación pulmonar preoperatorio para incrementar la tolerancia al esfuerzo en pacientes con sospecha clínica o diagnóstico confirmado de cáncer de pulmón sometidos a videocirugía.
2. Conocer si un programa de rehabilitación pulmonar preoperatorio es capaz de prevenir o paliar el deterioro funcional observado tras la cirugía en comparación con el tratamiento estándar (grupo control).

Como objetivos secundarios se encontraban:

1. Examinar los efectos del entrenamiento en la fuerza muscular y la calidad de vida de los pacientes.
2. Comparar la fuerza muscular y la calidad de vida de los pacientes en el grupo de rehabilitación y el grupo control durante el postoperatorio inmediato y tardío.
3. Comparar la estancia hospitalaria y la incidencia de complicaciones postoperatorias en ambos grupos con el fin de determinar si la pre-habilitación influye en dichas variables.
4. Identificar factores de riesgo relacionados con el deterioro de la capacidad funcional en el postoperatorio tardío tras videocirugía.

Material y método: este ensayo clínico fue registrado en la base de datos clinicaltrials.gov con el número de identificación NCT01963923. El estudio fue aprobado por el Comité de Ética Autonómico de Galicia (número de registro 2011/395) y los pacientes firmaron el consentimiento informado antes de someterse a ninguna evaluación.

Entre Octubre de 2013 y Abril de 2015, todos los pacientes incluidos en lista de espera para resección pulmonar por sospecha clínica o diagnóstico confirmado de cáncer de pulmón y que cumplían los criterios establecidos por los investigadores fueron evaluados para su inclusión en el estudio. Dichos criterios fueron:

- Ser mayor de edad en el momento del iniciar el estudio.
- Pertenecer al área sanitaria de A Coruña y residir en un radio no superior a 80 km del centro hospitalario.
- Presentar una de las siguientes condiciones: tener una función respiratoria alterada (VEMS < 80%, y/o Índice de Masa Corporal (IMC) > 30 kg/m^{2}y/o edad ≥ 75 años o exhibir dos o más de las siguientes comorbilidades: enfermedad respiratoria crónica, diabetes, hipertensión arterial, enfermedad renal crónica, enfermedad cardiovascular o antecedentes personales de cáncer.

Se excluyeron a aquellos pacientes que habían recibido tratamiento neoadyuvante en los seis meses anteriores a ser evaluados así como aquellos con alguna contraindicación al ejercicio o con alteraciones cognitivas y/o músculo-esqueléticas graves.

Aquellos pacientes que cumplieron los criterios de inclusión y aceptaron participar en el estudio fueron aleatorizados bien al grupo de intervención o bien al grupo control. Los pacientes del grupo control no recibieron atención fisioterápica de ningún tipo mientras que el grupo de rehabilitación acudió al centro entre 3 y 5 veces a la semana durante el periodo preoperatorio para llevar a cabo el programa de entrenamiento diseñado y que consistía al igual que en el estudio anterior de 1) 30 minutos de entrenamiento aeróbico en cicloergómetro **(**Monark 818 E, Monark Exercise AB, Sweden) combinando 4 minutos a baja intensidad (50% potencia máxima tolerada) con 1 minuto a intensidad elevada (80% potencia máxima tolerada); 2) entrenamiento de fuerza-resistencia para miembros superiores e inferiores con bandas elásticas (Thera-Band©, The Hygienic Corporation, Akron, Ohio, USA) y ejercicios auto-resistidos con ayuda del peso corporal; 3) ejercicios respiratorios con incentivador volumétrico (Coach 2 Espirómetro de incentivo 22-4000 HD, Smith Medicals, USA) a realizar en el domicilio en dos sesiones de unos 15 minutos de duración cada una aproximadamente.

Las principales variables de medición en este estudio fueron: 1) tolerancia al esfuerzo (prueba de carga constante en cicloergómetro al 80% de la potencia máxima tolerada); 2) fuerza muscular (SFT); 3) CVRS (SF-36) y 4) estancia hospitalaria y complicaciones postoperatorias.

Todos los pacientes fueron evaluados al inicio del estudio (T0), a las tres semanas aproximadamente de la cirugía (T1) y a los 3 meses (T2). A mayores, los pacientes en el grupo de rehabilitación fueron re-evaluados al finalizar el programa de entrenamiento previamente a la intervención quirúrgica.

El análisis estadístico consistió en una prueba *t de student* para muestras independientes en cada una de las principales variables así como una prueba t de muestras relacionadas para evaluar los cambios pre-post intervención en el grupo de intervención. La incidencia de complicaciones postoperatorias se analizó mediante una prueba de X^2. Todas las pruebas fueron realizadas con el pack SPSS para Windows versión 22 (IBM Corporation, Chicago, IL, USA) y un valor de p <.05 fue considerado como estadísticamente significativo para todos los análisis.

Resultados: 319 pacientes entraron en lista de espera para resección pulmonar por sospecha o diagnóstico confirmado de cáncer de pulmón en el departamento de Cirugía Torácica del CHUAC durante el periodo de reclutamiento. 68 (21,3%) pacientes fueron inicialmente contactos de los cuales finalmente 40 fueron aleatorizados. 22 (55%) pacientes completaron con éxito el estudio y fueron analizados.

Los pacientes del grupo de rehabilitación registraron un aumento significativo en las tres variables principales de medición al finalizar el programa de rehabilitación: tolerancia al esfuerzo (test de resistencia submáxima en cicloergómetro), fuerza muscular así como el componente físico del test de CVRS (Tabla 2). Tras la intervención quirúrgica, no se encontraron diferencias significativas en los dos grupos salvo en la dimensión de dolor corporal del test de calidad de vida (Tabla 3). Tampoco se encontraron diferencias significativas ni en la estancia hospitalaria ni en la

incidencia de complicaciones postoperatorias. Sin embargo, a los tres meses de la cirugía, los pacientes del grupo de rehabilitación mostraron una recuperación completa en todas las variables incluso superando los valores basales mientras que el grupo control experimentó un deterioro continuo y progresivo tanto a nivel funcional como psicológico. Las diferencias resultaron estadísticamente significativas tanto en la tolerancia al esfuerzo (duración mantenida en el test de resistencia submáxima en cicloergómetro) como en la fuerza muscular de miembros superiores e inferiores y en el componente sumario físico del test de calidad de vida (Tabla 3).

VARIABLE	N	BASAL	PRE-Cirugía	P valor
Prueba de CCEG (s)	10	322,4±96,2	719±211,2	**<.001**
Test de flexión de brazos (nª)	10	13,40±3	16,3±2,9	**.002**
Test de levantarse de la silla (nª)	10	11,5±3,7	12,4±4,5	**.041**
Función física	10	63,5±20,8	71±14,9	.110
Rol físico	10	48±30,6	65,9±12,8	**.038**
Dolor corporal	10	64,5±26,3	69,2±23,8	.518
Salud General	10	41,9±20,2	52,2±14,3	.072
Vitalidad	10	52±16,5	55±15,6	.526
Función social	10	87,5±22	97,5±5,3	.223
Rol emocional	10	60,6±19,2	72.7±12,3	.098
Salud mental	10	63,2±13,6	64,4±19,2	.771
CSF	10	40,77±8	45,2±6,8	**0.08**
CSM	10	45,7±8,3	47,4±7,4	.511

*CCEG= Carga Constante en Ciclo-ergómetro; CSF=Componente Sumario Físico; CSM=Componente Sumario Mental

VARIABLE	GRUPO	Basal	Post-Cirugía (diferencia media)	*p* valor	3 meses (diferencia media)	*p* valor
CCEG (s)	Rehabilitación	322.4±96.2	+137.7±268.2	.097	**+226±269.4***	**.005**
	Control	366.8±205	-25.8±16.71		-137.8±221.7	
T6MM (m)	Rehabilitación	420.11±116.3	-15.55±47.731	.500	1.88±34.7	.186
	Control	514.5±100.9	**-27.7±33.7***		-31.5±64.6	
Flexión de brazos (nª)	Rehabilitación	13.4±3	+1.9±3	.105	+1.8±3.3	**.045**
	Control	17.3±3.5	-0.25±2.9		-1.8±3.5	
Levantamiento de la silla (n)	Rehabilitación	11.5±3.7	-0.55±3.5	.531	**+2±2.2***	**.002**
	Control	12.7±2.5	+0.5±3.9		**-1.3±1.8***	

*diferencia estadísticamente significativa intra-grupo (p <.05)

Conclusiones: en vista de los resultados obtenidos en este ensayo clínico aleatorizado a simple ciego podemos concluir que la rehabilitación pulmonar preoperatoria en pacientes con neoplasias malignas no sólo optimiza la condición física basal de los pacientes previo a la cirugía sino que además parece contribuir e forma significativa a prevenir el deterioro funcional observado durante los primeros meses del postoperatorio.

CONCLUSIONES

En general, los resultados obtenidos con los estudios incluidos en el marco de esta tesis doctoral indican que:

- Existe suficiente evidencia científica para aseverar que los pacientes con cáncer de pulmón sometidos a resección pulmonar experimentan un deterioro en su capacidad funcional, tolerancia al esfuerzo y calidad de vida durante los primeros meses tras la intervención.
- La pre-habilitación de pacientes con cáncer de pulmón que van a ser sometidos a cirugía de resección pulmonar es útil a la hora de optimizar el estado basal de los pacientes ya que

mejora la función pulmonar y muy posiblemente la tolerancia al esfuerzo y la capacidad funcional lo que se traduce en una disminución en la estancia hospitalaria y el número de complicaciones postoperatorias en aquellos pacientes sometidos a cirugía abierta convencional.

- En pacientes con sospecha clínica o diagnóstico confirmado de cáncer de pulmón operados por videocirugía, la rehabilitación pulmonar preoperatoria es viable, segura y fácilmente tolerable y puede llevarse a cabo en nuestro medio sin incurrir en un aumento de la demora terapéutica.
- Finalmente, la rehabilitación pulmonar preoperatoria resulta eficaz para aumentar la tolerancia al esfuerzo, la fuerza muscular y el componente físico relacionado con la calidad de vida; además, en función de las diferencias observadas con respecto al tratamiento estándar, la pre-habilitación podría acelerar la recuperación funcional postoperatoria y paliar el deterioro tradicionalmente asociado a la cirugía de resección pulmonar.

SUPPLEMENTAL FILE no. 9 – SUMMARY OF THE THESIS IN GALICIAN

INTRODUCCIÓN

O cancro de pulmón é a primeira causa de morte por cancro no mundo. En España, segundo o derradeiro informe publicado polo Instituto Nacional de Estadística, no ano 2013 21,664 persoas faleceron a consecuencia deste tumor, o que o sitúa como a terceira causa de morte despois das enfermidades cardiovasculares (Instituto Nacional de Estadistica, 2015). De feito, nos vindeiros anos, espérase que o cancro de pulmón supere a éstas últimas como a primera causa de morte no mundo.

Aproximadamente, o 85% dos casos de cancro de pulmón corresponden á denominada estirpe de células non pequenas (CPCNP) para o cal o tratamiento quirúrxico considérase o máis indicado e o que máis posibilidades de supervivencia aporta (Howington et al., 2013). Nembargantes, únicamente o 20 – 25% dos pacientes con CPCNP atópanse nun estadio operable no momento do diagnóstico, dos cales moitos non poderán someterse a cirurxía de resección do tumor por ser considerados pacientes de alto risco quirúrxico debido a súa idade avanzada, á presenza de comorbilidades cardíacas e/ou respiratorias graves ou a unha subóptima función física e/ou pulmonar, o que leva consigo un peor pronóstico afectando negativamente á supervivencia a longo prazo. O concepto de pre-habilitación emerxeu recientemente na literatura en contraposición á rehabilitación tradicional como unha maneira de preparar ós pacientes ante una ciruxía maior, especialmente a aqueles que teñen maior risco de padecer complicacións postoperatorias e polo tanto de experimentar unha recuperación máis longa e tórpida. Así mesmo, a pre-habilitación podería incluso reconducir a pacientes con unha moi baixa función pulmonar e/ou tolerancia ó esforzo considerados como de alto risco quirúrxico a enfrentarse á cirurxía en óptimas condicións. Lamentablemente, existe moi pouca evidencia en relación á eficacia deste tipo de programas especialmente no contexto de cirurxía torácica e a maior parte dos estudos levados a cabo foron en

pacientes sometidos a unha toracotomía convencional (Jones et al., 2007, Cesario et al., 2007, Morano et al., 2013, Sekine et al., 2005). Co actual auxe da cirurxía mínimamente invasiva, atopámonos nun momento de apertura dos criterios quirúrxicos provocando que pacientes con peor estado basal sexan intervidos o que podería traducirse nun aumento da morbimortalidade perioperatoria. Neste novo contexto quirúrxico, descoñécense os efectos que a pre-habilitación podría ter sobre a tolerancia ó esforzo dos pacientes así como a nivel postoperatorio sobre a incidencia de complicacións postoperatorias e a recuperación física e funcional durante os primeiros meses tras a cirurxía.

OBXECTIVOS

En vista do rápido incremento no uso da videocirurxía para a resección de neoplasias pulmonares así como da falta de estudos sobre o papel da rehabilitación pulmonar e máis concretamente da pre-habilitación neste contexto, os principáis obxectivos desta tese de doutoramento son:

5. Identificar, sintetizar e analizar a evidencia científica actual sobre os programas de pre-habilitación en pacientes con cancro de pulmón sometidos a cirurxía de resección pulmonar.
6. Examinar a viabilidade, seguridade i eficacia preliminares dun programa de rehabilitación pulmonar preoperatorio en pacientes baixo sospeita clínica ou diagnóstico confirmado de cancro de pulmón sometidos a resección pulmonar por videocirurxía.
7. Analizar a eficacia dun programa de rehabilitación pulmonar preoperatorio nesta población para incrementar a función física e a calidadee de vida así como para mellorar a recuperación postoperatoria.
8. Proporcionar unha base sólida para futuras investigacións no campo da pre-habilitación en cirurxía torácica e outras cirurxías maiores para reducir a morbilidade postoperatoria e acelerar a recuperación funcional e psicolóxica.

MATERIAL E MÉTODO

Esta tese de doutoramento encóntrase estructurada en tres estudos, cada un dos cales conta con unha metodoloxía propia en función do tipo de investigación e os obxectivos marcados: 1) unha revisión sistemática e meta-análise; 2) un estudo piloto de viabilidade e 3) un ensaio aleatorizado controlado a simple cego. Os estudos foron levados a cabo no periodo comprendido entre Febreiro de 2013 e Novembre de 2015. No seguinte apartado atópase un breve resumo de cada un dos estudos incluidos nesta tese en canto a obxectivos individuais, metodoloxía e principais resultados.

RESULTADOS

ESTUDO #1:

Deseño: revisión sistemática e meta-análise acerca dos efectos da rehabilitación pulmonar preoperatoria en pacientes con cancro de pulmón sometidos a resección pulmonar.

Obxectivo: o obxectivo principal do estudo foi examinar os efectos da rehabilitación preoperatoria en pacientes con cancro de pulmón en canto a incrementar a tolerancia ó esforzo, a capacidade funcional, a función pulmonar e a calidade de vida relacionada coa saúde (CVRS). Como obxectivos secundarios atopábanse: 1) comparar a incidencia de complicacións postoperatorias e a estadia hospitalaria nos pacientes sometidos a pre-habilitación en comparación co tratamiento estándar (sen pre-habilitación) e 2) llevar a cabo un meta-análise co fin de cuantificar o tamaño do efecto da intervención sobre cada unha das variables de medición seleccionadas.

Material e método: esta revisión sistemática foi levada a cabo conforme ás recomendacións de PRISMA (*the Preferred Reporting Items for Systematic Reviews and Meta-analisys*). Así mesmo, o protocolo foi rexistrado na base de datos de PROSPERO baixo o código de identificación CRD42015024283. Seis bases de datos (CINAHL, EMBASE, MEDLINE, PEDro, Pubmed y

SCOPUS) foron sistemáticamente revisadas dando lugar a 1.656 referencias. 12 artigos foron tamén identificados a través dunha pesquisa manual. A pesquisa inicial foi realizada por unha das investigadoras e unha vez eliminados os duplicados e as referencias non relevantes, dúas investigadoras analizaron de forma independiente as referencias restantes en base ós criterios de inclusión pre-establecidos. Os artigos foron incluidos si: 1) incluían pacientes con cancro de pulmón; 2) evaluaban algún tipo de intervención preoperatoria relacionada co exercicio aeróbico ou de forza o una combinación de ambos; 3) proporcionaban resultados para algunha das seguintes variables: tolerancia ó esforzo, capacidade funcional, función pulmonar, calidade de vida e/ou complicacións postoperatorias i estadia hospitalaria. O análise de calidade fue realizado de forma independiente por dúas investigadoras utilizando a escala proporcionada por PEDro para ensaios clínicos e a Newcastle-Ottawa Scale (NOS) para estudos de cohortes e series de casos. Finalmente, naquelas variables nas que se considerou oportuno, además dun análise descriptivo dos resultados, realizouse un meta-análise para medir o tamaño do efecto da intervención e xerar os correspondentes intervalos de confianza ó 95% (I.C 95%). O programa empregado foi o Review Manager© (RevMan) versión 5.3 para Windows©.

Resultados: tras aplicar os criterios de inclusión e exclusión 21 estudos foron finalmente incluidos na revisión sistemática (oito ensaios clínicos, catro estudos de cohortes e nove series de casos) pero únicamente 14 entraron no meta-análise. A modalidade de exercicio predominante nos estudos foi o adestramento aeróbico seguido dunha combinación entre adestramento aeróbico e de forza. Namáis que dous estudos centraron as súas intervencións no adestramento da forza muscular. Outros componentes frecuentes nos programas foron os exercicios respiratorios con ou sen incentivador, o adestramento da musculatura respiratoria ou as técnicas de relaxación. O análise de calidade mostróu un nivel metodolóxico medio (5/10 para os ensaios clínicos segundo a escala PEDro e 6/9 para os estudos de cohortes e series de casos segundo a escala NOS).

En canto ás variables analizadas, a maioría dos estudos mostraron un aumento significativo pre – post intervención no nivel de tolerancia ó esforzo (consumo de oxígeno máximo) e na capacidade funcional (test de 6 minutos marcha). Non obstante, os estudos mostraron unha alta heteroxeneidade polo que se considerou inapropiado levar a cabo un meta-análise. Unicamente catro estudos analizaron os efectos da intervención sobre a calidade de vida e os resultados foron inconsistentes, polo que debido a esto e á a variabilidade encontrada nos instrumentos de medición de novo considerouse inapropiado calcular o tamaño do efecto nesta variable. Por outro lado, a función pulmonar experimentou un aumento significativo nos dous principais parámetros estudados (Capacidade Vital Forzada (CVF) e Volumen Espirado Máximo no primeiro segundo (VEMS)). Neste caso, o meta-análise mostrou un aumento significativo pre – post intervención (diferencia de medias estandarizada = 0,38; I.C 95%: 0,14 -0,63 e 0,27; I.C 95%: 0,11 – 0,42 respectivamente). Da mesma maneira, a duración da estadia hospitalaria foi significativamente menor nos grupos de pre-habilitación en comparación co tratamiento estándar (diferencia de medias = -4,83 días; C.I 95%: -3,76 -5.9) así como a incidencia de complicacións postoperatorias (risco relativo (RR) = 0,45; C.I 95%: 0,34 – 0,89). Nembargantes, nesta última variable o nivel de heteroxeneidade alcanzou valores substanciales (I^2 = 65%) polo que se levou a cabo posteriormente un sub-análise para examinar as posibles causas. Deste xeito, encontramos que ó clasificar as complicacións postoperatorias segundo a orixe (sólo respiratorio versus respiratorio e/ou outros), os estudos que incluíron unicamente complicacións de orixe respiratorio mostraron un tamaño do efecto similar (RR = 0,55; I.C 95% 0,34 – 0,89) pero significativamente menos heteroxeneidade (I^2 = 27%). Tamén o tipo de estudo influiu no nivel de heteroxeneidade de forma que ó separar os ensaios clínicos aleatorizados versus os non aleatorizados y os estudos de cohortes, de nuevo o tamaño do efecto mantivose estabe mentras que o nivel de heteroxeneidade se reducía totalmente (RR = 0,46; I.C 95: 0,26 – 0,82; I^2 = 0%).

Conclusións: en conxunto, os resultados obtidos nesta revisión sistemática e meta-análise demostran que a pre-habilitación en pacientes con cancro de pulmón sometidos a resección pulmonar reduce de forma significativa a morbilidade postoperatoria así como a estadia hospitalaria. Así mesmo, a realización dun programa basado no exercicio físico resulta efectiva para incrementar a función pulmonar e moi probablemente mellorar a tolerancia ó esforzo e a capacidade funcional aínda que nestes casos os resultados non son concluíntes. Finalmente, son necesesarios máis estudos para analizar o papel destes programas sobre a calidade de vida dos pacientes.

ESTUDO #2:

Deseño: estudo piloto para evaluar a viabilidade, tolerancia e eficacia preliminares dun programa de rehabilitación pulmonar preoperatorio en pacientes con sospeita clínica ou diagnóstico confirmado de cancro de pulmón sometidos a resección pulmonar por videocirurxía.

Obxectivos: o principal obxectivo deste estudo era probar a viabilidade do programa en canto a adherencia e grado de tolerancia dos pacientes así como o grao de seguridade da intervención en relación ós potenciais efectos adversos encontrados. Como obxectivos secundarios atopábanse: 1) evaluar a eficacia preliminar do programa para aumentar a capacidade funcional, a forza muscular e a CVRS; 2) describir o deterioro funcional e psicolóxico observado tras videocirurxía e 3) determinar se ós tres meses da intervención quirúrxica os pacientes alcanzaban os seus valores basais en canto a capacidade funcional, forza muscular e CVRS.

Material e método: este estudo foi aprobado polo Comité Autonómico de Ética da Investigación (CEIC) de Galicia no seo dun ensaio clínico aleatorizado e todos os pacientes incluidos firmaron o consentimento informado antes de seren evaluados. Dende Febreiro a Xuño de 2013 todos os pacientes incluidos en lista de espera para resección pulmonar por sospeita clínica ou diagnóstico

confirmado de cancro de pulmón no Servizo de Cirurxía Torácica do Hospital Clínico Universitario da Coruña (CHUAC) foron evaluados para a súa inclusión no estudo. Os pacientes debían de ser maiores de idade, pertencer á área sanitaria da Coruña e non ter recibido tratamento neoadyuvante nos seis meses anteriores. Excluíronse aqueles pacientes que presentaban algunha contraindicación médica para ó exercicio así como aqueles que presentaban algún trastorno do sistema músculo-esquelético que lles impedise a realización dos exercicios.

O programa de rehabilitación estaba dirixido por unha fisioterapeuta especializada en rehabilitación pulmonar e constaba dos seguintes elementos: 1) adestramento aeróbico en cicloergómetro (Monark 818 E, Monark Exercise AB, Sweden) seguindo un protocolo interválico que combinaba catro minutos a baixa intensidade (45 – 50 % da carga máxima tolerada) cun minuto de alta intensidade (ó 80 – 85% da carga máxima) durante 30 - 40 minutos; 2) adestramento de forza-resistencia para membros superiores e inferiores que consistía na realización exercicios con bandas elásticas (Thera-Band©, The Hygienic Corporation, Akron, Ohio, USA) e exercicios auto-resistidos con axuda do peso corporal; 3) exercicios respiratorios con incentivador volumétrico (Coach 2 Espirómetro de incentivo 22-4000 HD, Smith Medicals, USA) a realizar no domicilio en dúas sesións duns 15 minutos de duración cada unha aproximadamente. Os pacientes completaron de 3 a 5 sesións semanais de unha hora e cuarto de duración durante o periodo preoperatorio.

As variables de medición seleccionadas para este estudo foron: 1) adherencia (número de pacientes que alcanza canto menos un 80% das sesións inicialmente plantexadas); 2) seguridade (número de eventos adversos que precisaron atención médica urxente ou non urxente; 3) tolerancia ó esforzo (test de 6 minutos marcha); 4) forza muscular (*Senior Fitness Test*) e 5) CVRS (SF – 36). Os pacientes foron evaluados ó inicio da intervención (T0), ó finalizar a intervención previamente á cirurxía (T1), unha semana despois de recibir a alta hospitalaria (T2) y ós tres meses da cirurxía (T3).

Pese á distribución normal das variables e debido o reducido tamaño da mostra, o análise estadístico foi realizado mediante probas non paramétricas para mostras relacionadas en cada unha das variables de medición. O programa estadístico empregado foi SPSS para Windows versión 21 (IBM Corporation, Chicago, IL, USA) e un valor de p <.05 considerouse como estadísticamente significativo.

Resultados: durante o periodo de estudo, 23 pacientes foron evaluados dos cales, 12 (52.2%) cumpliron os criterios de inclusión establecidos polos investigadores. Dos 12 pacientes inicialmente incluidos, tres foron excluidos posteriormente debido a problemas co transporte ó centro de rehabilitación (n = 2) ou porque foron sometidos a cirurxía con carácter urgente (n = 1). Nove pacientes completaron con éxito a intervención e foron analizados. De media, os pacientes completaron un total de 21 sesións das 18 inicialmente propostas (rango 11 – 27). Solo un paciente alcanzou menos do 80% de adherencia. Ningún efecto adverso foi rexistrado durante o periodo de adestramento. En cunto á eficacia preliminar do programa, tras a intervención os pacientes aumentaron en 22,5 metros a distancia percorrida co test de 6 minutos marcha (T6MM). Aínda que o resultado non alcanzou valores estadísticamente significativos por unha marxe moi estreita (p = .050), o aumento sí se encontra dentro do rango identificado como clínicamente significativo para pacientes con cancro de pulmón (Granger et al., 2015). A función muscular medida co *Senior Fitness Test* (SFT) sí experimentó un aumento significativo con respecto ós valores basais (Tabla 1). Pola contra, os cambios producidos na CVRS segundo o SF-36 foron mínimos e non alcanzaron valores estadísticamente significativos salvo no caso da dimensión de saúde mental. No postoperatorio inmediato, a capacidade funcional medida co T6MM experimentou unha reducción significativa con respecto ós valores basais (67,9 ± 65,5 metros) o que nos indica que pese á utilización dunha abordaxe quirúrxica mínimamente invasiva existe unha disminución na capacidade funcional inmediatamente tras cirurxía. A forza dos membros superiores medida co test

de flexión de brazo do SFT tamén disminueu significativamente mentras que a dos membros inferiores mantívose en valores similares (Tabla 1). Ós tres meses da intervención os pacientes atopábanse por riba dos valores basais na distancia percorrida co T6MM (105,5 ± 6,8%) mentras que a forza muscular de membros superiores e inferiores se atopaba entre o 80 - 88 % dos valores basáis respectivamente.

Tabla 4: Evolución de las principales variables analizadas a lo largo del estudo

VARIABLE	**T0**	**T1**	**T2**	**T3**
T6MM (m)	557,6±74,4	580,1±80,7	489,7±98,7**** †	529,63±83,2
Flexión de brazo (nº)	16,9±5,4	20,7±2,6*	20±3,3**	19,2±3,2† †
Levantarse y sentarse de la silla (nº)	14,6±5,9	15,9±3,9*	16,1±5	13,2±7

*p <.05 entre T_0 y T_1; **entre T_0 y T_2; †entre T_1 y T_2† †entre T_0 y T_3

Conclusións: en vista dos resultados preliminares observados neste estudo piloto podemos concluir que a rehabilitación pulmonar preoperatoria en pacientes sometidos a videocirurxía por neoplasia maligna pulmonar é factible, segura e moi probablemente eficaz á hora de incrementar a tolerancia ó esforzo e a forza muscular. Pese á utilización de técnicas mínimamente invasivas, inmediatamente tras a cirurxía existe unha pérdida importante da capacidade funcional que aparentemente retorna ós niveles basáis nos tres primeiros meses tras a intervención. Non obstante, descoñecemos se esta recuperación se debe, a lo menos en parte, ó adestramento preoperatorio ou se corresponde á evolución natural dos pacientes, por lo que é preciso un ensaio clínico aleatorizado para coñecer o impacto da rehabilitación preoperatoria na recuperación funcional doos pacientes operados por videocirurxía.

ESTUDO #3:

Deseño: ensaio clínico aleatorizado controlado a simple cego para valorar os efectos dun programa de rehabilitación pulmonar preoperatorio sobre a tolerancia ó esforzo, a forza muscular e a calidade de vida en pacientes con sospeita clínica ou diagnóstico confirmado de cancro de pulmón sometidos a videocirurxía.

Obxectivos: os obxectivos principais deste estudo foron:

1. Analizar a eficacia dun programa de rehabilitación pulmonar preoperatorio para incrementar a tolerancia ó esforzo en pacientes con sospeita clínica ou diagnóstico confirmado de cancro de pulmón sometidos a videocirurxía.
2. Coñecer se un programa de rehabilitación pulmonar preoperatorio é capaz de previr ou paliar o deterioro funcional observado tras cirurxía en comparación co tratamiento estándar (grupo control).

Como obxectivos secundarios atopábamos:

1. Examinar os efectos do adestramento sobre a forza muscular e a CVRS dos pacientes.
2. Comparar a forza muscular e a CVRS dos pacientes no grupo de rehabilitación co grupo control durante o postoperatorio inmediato e tardío.
3. Comparar a estadia hospitalaria e a incidencia de complicacións postoperatorias en ambos grupos co fin de determinar se a pre-habilitación inflúe sobre as devanditas variables.
4. Identificar factores de risco asociados co deterioro da capacidade funcional durante o postoperatorio tardío tras videocirurxía.

Material e método: este ensaio clínico foi rexistrado na base de datos de ensaios clínicos (*clinicaltrials.gov*) co número de identificación NCT01963923. O estudo foi aprobado polo CEIC de Galicia (número de rexistro 2011/395) e os pacientes firmaron o consentimento informado antes de someterse a ningunha evaluación.

Entre Outubro de 2013 e Abril de 2015 todos os pacientes incluidos en lista de espera para resección pulmonar por sospeita clínica ou diagnóstico confirmado de cancro de pulmón e que cumplían cos criterios establecidos polos investigadores foron evaluados para a súa inclusión no estudo. Ditos criterios eran:

- Ser maior de idade no momento de iniciar o estudo.

- Pertencer á área sanitaria da Coruña e residir nun radio non superior a 80 km do centro hospitalario.
- Presentar una de las seguintes condicións: ter unha función respiratoria alterada (VEMS < 80%, e/ou Índice de Masa Corporal (IMC) > 30 kg/m^2 e/ou idade ≥ 75 años ou padecer dúas ou máis das seguintes comorbilidades: enfermidade respiratoria crónica, diabetes, hipertensión arterial, enfermidade renal crónica, enfermidade cardiovascular ou antecedentes personales de cancro.

Foron excluidos aqueles pacientes que recibiran tratamento neoadyuvante nos seis meses previos así como aqueles con algunha contraindicación para realizar exercicio ou que presentaban alteraciones cognitivas e/ou músculo-esqueléticas graves.

Aqueles pacientes que cumpliron cos criterios de inclusión e aceptaron participar no estudo foron incluidos de forma aleatoria ben no grupo de intervención ou no grupo control. Os pacientes do grupo control non recibiron atención fisioterápica de ningún tipo mentras que o grupo de rehabilitación acudeu ó centro entre 3 e 5 veces á semana durante o periodo preoperatorio para realizar o programa de adestramento que consistía, ó igual que o estudo anterior, de 1) 30 minutos de adestramento aeróbico en cicloergómetro **(**Monark 818 E, Monark Exercise AB, Sweden) combinando 4 minutos a baixa intensidade (50% potencia máxima tolerada) con 1 minuto a intensidad elevada (80% potencia máxima tolerada); 2) adestramento de forza-resistencia para membros superiores e inferiores con bandas elásticas (Thera-Band©, The Hygienic Corporation, Akron, Ohio, USA) e exercicios auto-resistidos con axuda do peso corporal; 3) exercicios respiratorios con incentivador volumétrico (Coach 2 Espirómetro de incentivo 22-4000 HD, Smith Medicals, USA) a realizar no domicilio en dúas sesións duns 15 minutos de duración cada unha aproximadamente.

As principáis variables de medición neste estudo foron: 1) tolerancia ó esforzo (proba de carga constante en cicloergómetro ó 80% da potencia máxima tolerada); 2) forza muscular (SFT); 3) CVRS (SF-36) e 4) estancia hospitalaria e complicacións postoperatorias.

Todos os pacientes foron evaluados ó inicio do estudo (T0), ás tres semanas aproximadamente da cirurxía (T1) e ós 3 meses (T2). A maiores, os pacientes no grupo de rehabilitación foron re-evaluados ó finalizar o programa de adestramento previamente a la intervención quirúrxica.

O análise estadístico consistiu nunha prueba *t de student* para mostras independentes para cada una das principais variables de medición así como unha prueba t de mostras relacionadas para evaluar los cambios pre-post intervención no grupo de intervención. A incidencia de complicacións postoperatorias se analizó mediante una prueba de X^2. Todas as probas foron realizadas co programa estadístico SPSS para Windows versión 22 (IBM Corporation, Chicago, IL, USA) e un valor de p <.05 considerouse como estadísticamente significativo para todos os análises.

Resultados: 319 pacientes entraron en lista de espera para resección pulmonar por sospeita ou diagnóstico confirmado de cancro de pulmón no departamento de Cirurxía Torácica do CHUAC durante el periodo de reclutamiento. 68 (21.3%) pacientes foron inicialmente contactos dos cales finalmente 40 foron aleatorizados. 22 (55%) pacientes completaron con éxito o estudo e foron analizados.

Os pacientes do grupo de rehabilitación rexistraron un aumento significativo nas tres variables principales de medición ó rematar o programa de rehabilitación: tolerancia ó esforzó (proba de carga constante en cicloergómetro), forza muscular así como no componente físico da CVRS (Tabla 2). Non se atoparon diferencias significativas en ninguna das variables analizadas entre os dous grupos ás tres semanas da intervención quirúrxica excepto na dimensión de dor corporal do test de calidade de vida (Tabla 3). Tampouco se encontraron diferencias significativas

entre os grupos nin na estadia hospitalaria ni en la incidencia de complicacións postoperatorias. Nembargantes, ós tres meses da cirurxía, os pacientes do grupo de rehabilitación mostraron unha recuperación completa en todas las variables incluso por encima dos valores basáis mentras que os pacientes do grupo control experimentaron un deterioro continuo e progresivo a nivel funcional e psicolóxico. As diferenzas resultaron estadísticamente significativas tanto na tolerancia al esforzó (duración sostida na proba de resistencia submáxima en cicloergómetro) como na forza muscular de membros superiores e inferiores e no componente sumario físico do test de calidade de vida (Tabla 3).

VARIABLE	N	BASAL	PRE-Cirurxía	P valor
Proba de CCEG (s)	10	322,4±96,2	719±211,2	**<.001**
Test de flexión de brazos (nª)	10	13,40±3	16,3±2,9	**.002**
Test de levantarse da silla (nª)	10	11,5±3,7	12,4±4,5	**.041**
Función física	10	63,5±20,8	71±14,9	.110
Rol físico	10	48±30,6	65,9±12,8	**.038**
Dor corporal	10	64,5±26,3	69,2±23,8	.518
Saúde Xeral	10	41,9±20,2	52,2±14,3	.072
Vitalidade	10	52±16,5	55±15,6	.526
Función social	10	87,5±22	97,5±5,3	.223
Rol emocional	10	60,6±19,2	72.7±12,3	.098
Saúde mental	10	63,2±13,6	64,4±19,2	.771
CSF	10	40,77±8	45,2±6,8	**0.08**
CSM	10	45,7±8,3	47,4±7,4	.511

*CCEG= Carga Constante en Ciclo-ergómetro; CSF=Componente Sumario Físico; CSM=Componente Sumario Mental

VARIABLE	GRUPO	Basal	Post-Cirurxía (diferencia media)	*p* valor	3 meses (diferencia media)	*p* valor
CCEG (s)	Rehabilitación	322.4±96.2	+137.7±268.2	.097	**+226±269.4***	**.005**
	Control	366.8±205	-25.8±16.71		-137.8±221.7	
T6MM (m)	Rehabilitación	420.11±116.3	-15.55±47.731	.500	1.88±34.7	.186
	Control	514.5±100.9	**-27.7±33.7***		-31.5±64.6	
Flexión de brazos (nª)	Rehabilitación	13.4±3	+1.9±3	.105	+1.8±3.3	**.045**
	Control	17.3±3.5	-0.25±2.9		-1.8±3.5	
Levantamento de la silla (n)	Rehabilitación	11.5±3.7	-0.55±3.5	.531	**+2±2.2***	**.002**
	Control	12.7±2.5	+0.5±3.9		**-1.3±1.8***	

*diferencia estadísticamente significativa intra-grupo (p <.05)

Conclusións: en vista dos resultados obtidos neste ensaio clínico aleatorizado a simple cego podemos concluir que a rehabilitación pulmonar preoperatoria en pacientes con neoplasias malignas non só optimiza a condición física basal dos pacientes previo á cirurxía senón que además parece contribuir de forma significativa a previr o deterioro funcional observado durante os primeros meses do postoperatorio.

CONCLUSIÓNS

En xeral, os resultados obtidos nos estudos incluidos no marco desta tese de doutoramento indican que:

- Existe suficiente evidencia científica para aseverar que os pacientes con cancro de pulmón sometidos a resección pulmonar experimentan un deterioro importante na capacidade funcional, tolerancia ó esforzo e CVRS durante os primeiros meses tras a intervención quirúrxica.
- A pre-habilitación de pacientes con cancro de pulmón que van a ser sometidos a cirurxía de resección pulmonar resulta útil á hora de optimizar o estado basal dos pacientes dado que mellora a función pulmonar preoperatoria e moi posiblemente a tolerancia ó esforzo e a capacidade funcional, o que se traduce nunha disminución na duración da estadia hospitalaria así como no número de complicacións postoperatorias en aqueles pacientes sometidos a cirurxía aberta convencional.
- En pacientes con sospeita clínica ou diagnóstico confirmado de cancro de pulmón operados por videocirurxía a rehabilitación pulmonar preoperatoria resulta viable, segura e fácilmente tolerable e pode levarse a cabo no noso medio sen incurrir nun aumento da demora terapéutica.
- Finalmente, a rehabilitación pulmonar preoperatoria resulta eficaz para aumentar a tolerancia ó esforzo, a forza muscular e o compoñente físico relacionado coa calidade de vida; ademáis, en función das diferencias observadas con respecto ó tratamento estándar, a pre-habilitación parece acelerar a recuperación funcional postoperatoria e paliar o deterioro asociado á cirurxía de resección pulmonar.