NON-INVASIVE MEASURES OF REGIONAL LUNG FUNCTION AND THEIR CLINICAL APPLICATION IN THORACIC SURGERY

by

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A thesis submitted to the University of Birmingham for the degree of

DOCTOR OF PHILOSOPHY

Institute of Inflammation and Ageing

College of Medical and Dental Sciences

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September 2020

ABSTRACT

The decision to operate, or not operate, is a critical step in the care of patients with a thoracic condition that potentially requires surgery. Weighing the risks and benefits of a thoracic operation involves careful assessment of the patient's lung function and how this may be altered by surgery. This thesis will describe the application of multiple different methods to assess regional lung function in the context of assessing patients who may benefit from thoracic surgery. The patients are those with resectable Non-Small Cell Lung Cancer (NSCLC), interstitial lung disease (ILD), severe emphysema, and pleural thickening.

Prediction of postoperative lung function for NSCLC was reported to be most accurate and precise using CT based on a systematic review and meta-analysis but using density and volume changes was found to be unfeasible in a cohort study. The Lobar Segmentation and Parenchymal Analysis modules of the open access Chest Imaging Platform were found not to give reproducible results for lobar lung volume and density. Heterogeneity of specific volume of gas on CT in 2D did not help to discriminate between Usual Interstitial Pneumonia and other types of ILD, but heterogeneity was higher in ILD compared to reported values in health.

Measurement of chest wall movement did not show a clinically useful difference between patients with mesothelioma compared to benign pleural thickening. Chest wall motion did not have an association with prognosis in patients with mesothelioma; data provided external validation for the Brims decision tree prognostication. Early dynamic hyperinflation may be associated with symptomatic benefit from lung volume reduction but further study of this is required to confirm this. Key limitations exist in the available technologies; the lack of normal reference ranges is particularly important.

DEDICATION

This thesis is dedicated to my mother and father for their unwavering love and support.

ACKNOWLEDGEMENTS

I am grateful to my supervisors Mr Babu Naidu and Dr Alice Turner for their guidance during this work and for their important contributions towards my professional development throughout my studies.

I would like to thank the funders of the studies described herein, specifically the British Lung Foundation, MesoUK and Pat Stone Meso Support, and PneumRx. Thank you to Thirona for providing complementary CT analysis. I would like to thank Pneumacare for providing the Thora3Di device and Mr Shayan Motamedi for providing parameters from device recordings.

Teamwork has played a pivotal role in the delivery of this work and I am thankful to the entire Thoracic Surgery Research Team for their 'on the job' training, shared working, and boundless moral support. A special thanks to Amy Kerr, for everything.

I would like to acknowledge Prof Andrea Aliverti, Ms Antonella LoMauro, Dr Francesca Pennati, and Dr Catarina Salito from the Department of Electronics, Information and Bioengineering at Politecnico di Milano for their advice and training in the use of their custom processes in Matlab and the SMARTtracker system. Thank you to John Kipritidis for a short but constructive dialogue.

Dr Peter Nightingale and Mr James Hodson at the Institute of Translational Medicine supported me regarding statistical testing and interpretation, for this I am very grateful.

I would like to thank Dr James Halle-Smith and Dr Rana Mehdi for their roles as reviewers in the systematic review. I would like to thank Mrs Amanda Wood and Dr Tae Kyung Park for their assistance in reviewing Chinese and Korean language articles. I would like to thank Ms Rachel Piccus for her role as an additional rater for reproducibility testing in CT analysis.

Finally and most importantly I would like to thank all of the patients who have taken part in research at Heartlands Hospital, their selflessness in their own time of need has been moving to witness.

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LIST OF ABBREVIATIONS

μ	Attenuation coefficient
2D	Two dimensional
3D	Three dimensional
3He-MRI	Hyperpolarized helium MRI
ANOVA	Analysis of variance
AUC	Area under the curve
BMI	Body mass index
CE	European conformity
CI	Confidence interval
CIP	Chest imaging platform
CO	Carbon monoxide
CO_2	Carbon dioxide
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CT-VD	CT volume and density
deltaSVg	Change in specific gas volume
DH	Dynamic Hyperinflation
DICOM	Digital imaging and communications in medicine
EBC	Endobronchial coils
EBV	Endobronchial valve
EEV	End expiratory volume
EIV	End inspiratory volume
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FPR	False positive rate
FRC	Functional residual capacity
FVC	Functional vital capacity
GDPR	General Data Protection Regulation
GLI	Global Lung Initiative
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HP	Hypersensitivity pneumonitis

HR	Hazard Ratio
HU	Hounsfield units
ICC	Intra class correlation coefficient
IE50	Ratio of tidal inspiratory displacement at 50% displacement to tidal expiratory displacement at 50% displacement
ILD	Interstitial Lung Disease
ILD-GAP	Interstitial Lung Disease Gender Age Physiology model
IPF	Idiopathic pulmonary fibrosis
IQR	Inter quartile range
LOA	Limits of agreement
LTRC	Lung Tissue Research Consortium
LVR	Lung Volume Reduction
MDT	Multi Disciplinary Team
MRI	Magnetic resonance imaging
NETT	National Emphysema Treatment Trial
NIHR	National institute for health research
NOS	Not otherwise specified
NPV	Negative predictive value
NSCLC	Non-Small Cell Lung Cancer
NSIP	Non specific interstitial pneumonia
OEP	Optoelectronic plethysmography
PET	Positron emission tomography
Ppo	Predicted postoperative
PPV	Positive predictive value
PROBAST	Prediction study Risk Of Bias Assessment Tool
PROM	Patient reported outcome measure
RCT	Randomised Controlled Trial
REC	Research ethics committee
ROC	Receiver operator characteristics
RV	Residual Volume
SABR	Stereotactic ablative radiotherapy
SD	Standard deviation
SE	Standard error
SGRQ	St George's Respiratory Questionnaire

SLP	Structured Light Plethysmography
SPECT	Single Photon Emission Computed Tomography
SPECT-CT	Co-registered SPECT and CT
SV	Specific volume
SVg	Specific volume of gas
Te	Expiratory time
Ti	Inspiratory time
TLC	Total lung capacity
TLCO	Diffusion Capacity of the Lung for Carbon Monoxide
TPR	True positive rate
Ttot	Total breath time
UIP	Usual interstitial pneumonia
UK	United Kingdom
V	Volume
VATS	Video Assisted Thoracoscopic Surgery
VC	Vital capacity
VESPIR	VEntilation via Scripted Pulmonary Image Registration
VIF	Variance inflation factor
VO_2 max	Maximum rate of oxygen consumption
VRI	Vibration response imaging
Vt	Tidal volume

CHAPTER 1: INTRODUCTION

1.1 Thoracic surgery

Thoracic surgery is a highly specialised field with only 40 units in the United Kingdom (UK) performing close to 25,000 operations per year; subspecialisation has been promoted to improve outcomes.[1] Thoracic surgical practice in the UK encompasses care for patients undergoing operations on the trachea, bronchi, lungs, pleura, chest wall, diaphragm, pericardium, and mediastinum. Thoracic surgeons work within a multidisciplinary structure and there are close working relationships between the surgeons, radiologists, respiratory physicians, oncologists, physiotherapists, and specialist nurses. There are a number of conditions potentially managed by this group of professionals and the conditions frequently have multiple treatment options that are provided by different members of the team. Consequently, there is a decision making process to determine which treatments patients should be offered; the potential to optimise diagnostic and therapeutic pathways for patients with different treatment options forms the basis of this thesis. It is beneficial to further explore the clinical context thoracic surgeons work in before proceeding to define the aims of the thesis.

1.1.1 Lung cancer

Lung cancer is the second most common cancer in males and females in the UK and constitutes 13% of incident cancers; it is the leading cause of cancer related deaths at 21% of all cancers related deaths.[2]. The direct costs of lung cancer in the UK are £163 million per year, however much of the cost associated with the disease is born by the individual with intangible costs estimated at £45 billion.[3] Such costs include pain,

suffering and loss of life years. Optimising management of these patients should easily be recognised as important for both individuals and society.

Primary lung cancer is broadly divided into pathological categories of small cell lung cancer and non-small cell lung cancer (NSCLC); resection of early stage NSCLC constitutes a third of the thoracic surgical workload and is performed with curative intent.[1] Anatomical resection of a lung tumour is the gold standard operation and includes pneumonectomy, bilobectomy, lobectomy, and segmentectomy; these procedures involve lymphatic dissection with removal of an entire lung, two lobes, a single lobe, or a lung segment respectively (Figure 1).[4,5] The lungs are divided into five lobes containing a total of 19 anatomical segments, each lobe is made up of between two and five segments, thus anatomical resection removes a variable amount of functional lung tissue that does not contain tumour and dyspnoea significantly affects more than half of those who have undergone surgery for lung cancer.[6] There are now extended treatment options for small lung tumours, including non-operative management with stereotactic ablative radiotherapy (SABR) or a more limited operation in the form of a segmentectomy or wedge resection.

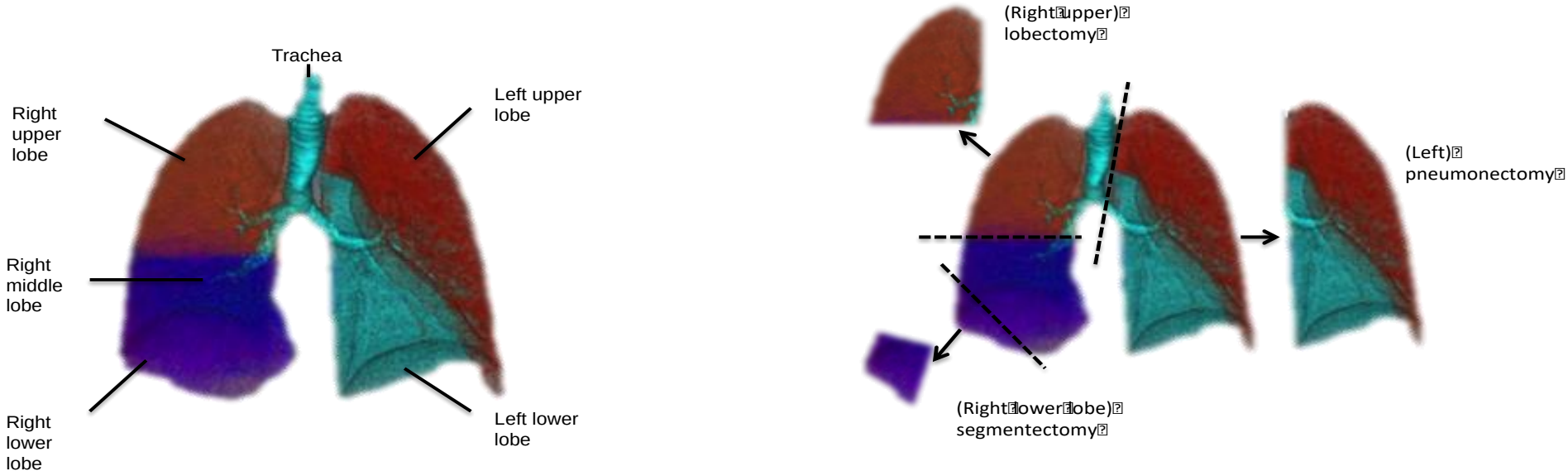


Figure 1 Overview of lung lobes (left) and types of resection (right)

1.1.1.1 Treatment options in early NSCLC

A randomised controlled trial (RCT) of SABR compared to surgery has not been successfully completed.[7] Meta-analyses of cohort studies of SABR and surgery showed SABR was associated with worse overall survival with hazard ratio (HR) 95% confidence intervals (CI) between 1.21 and 1.72, however lung cancer specific survival was found to be no different in the meta-analysis that reported this outcome, HR 1.17 and 95%CI 0.92 to 1.50.[8,9] SABR was found to have worse disease free survival, HR 1.84 95%CI 1.26 to 2.68 but local recurrence was found to be equivalent, HR 1.17 and 95%CI 0.68 to 1.98.[9] The critical confounding factor in the non-randomised data used in the meta-analyses is the patient selection bias in deciding which patients would undergo surgery, those considered fit enough for surgery would be likely to have a longer survival than those not considered fit enough for surgery. The results are not to be fully disregarded however because the longer disease free survival found in one of them highlights an additional potential benefit of surgery. Surgery provides an oncological staging advantage in terms of the ability to more accurately assess involvement of lymph nodes by metastases and thus determine which patients are likely to benefit from adjuvant chemotherapy. Secondary analysis within a meta-analysis revealed that 15.6% of patients undergoing surgery were upstaged by examination of lymph nodes retrieved intraoperatively and that subsequently 11.4% of patients received chemotherapy.[8]

The issue of whether lobectomy and segmentectomy are oncologically equivalent operations is still fiercely debated amongst surgeons.[10,11] Wedge resection, excision of a portion of lung smaller than a segmentectomy, does not follow anatomical routes of lymphatic drainage and confers a greater risk of local recurrence, thus it is only

performed if anatomical resection is not possible.[12] The only available RCT favoured overall survival, cancer specific survival, and risk of cancer recurrence in the patients treated with lobectomy, but much has changed in clinical practice since the trial was conducted.[13] Full results of two ongoing RCTs are eagerly awaited, particularly in light of changes in preoperative staging, use of minimally invasive surgery, and changes in perioperative care since the completion of the first RCT.[14,15] In the absence of these results a propensity matched analysis of a real life database of patients aged 70 and over found worse overall survival (HR 1.28, 95%CI 1.10 to 1.49) and cancer specific survival (HR 1.49, 95%CI 1.20 to 1.85) in those treated with segmentectomy compared to lobectomy.[16]

The implementation of available evidence in practice means that surgery is still considered the gold standard treatment for early NSCLC and lobectomy is preferred over sublobar resection for most tumours. Preoperative assessment underpins decision making about proceeding to surgery and the kind of resection to be offered.

1.1.1.2 Preoperative assessment in lung cancer

Thorough assessment of patients is essential prior to proceeding with any lung cancer surgery; the three key risk elements are mortality, postoperative cardiac event, and postoperative dyspnoea. The risk of postoperative dyspnoea is primarily assessed by performing spirometry to obtain the forced expiratory volume in one second (FEV1) and gas transfer to assess the transfer factor of the lung for carbon monoxide (TLCO). The predicted postoperative (ppo) value of these measures is calculated according to the location and size of the tumour and therefore the extent of lung resection required to

remove it. The prediction is most commonly done using the segment counting method, which involves counting the lung segments to be removed as a proportion of the 19 native lung segments and reducing the preoperative FEV1 or TLCO by this proportion. Patients are considered to be at low risk of dyspnoea if the ppoFEV1 and ppoTLCO are above 40% of the expected value for the patient. Further testing involving exercise is recommended for patients considered not to be low risk; these tests involve either calculating the maximum rate of oxygen consumption (VO_2max) or measuring the distance walked at an incrementally increasing speed until exhaustion or inability to achieve the required speed (shuttle walk). Preoperative lung function testing according to the British Thoracic Society guideline is summarised in Figure 2. [17] Guidelines also recommend considering the potential for a lung volume reduction (LVR) effect in patients affected by chronic obstructive pulmonary disease (COPD), this is highly relevant because COPD is found in at least 50% of individuals with lung cancer.[18]

1.1.2 Lung volume reduction for emphysema

There are reported to be 210 million people worldwide with a diagnosis of COPD and under diagnosis is common, with many sufferers being unaware they have the disease.[19,20] COPD is the fifth leading cause of mortality worldwide and this is projected to increase over three decades and account for 7.8% of all deaths and an increasing number of lost disability adjusted life years.[21] The direct costs of COPD in the UK exceed £1.8 billion per year, but this rises to over £48 billion if indirect and intangible costs, such as time off work and suffering respectively, are taken into account.[3] Having COPD is associated with an impairment in quality of life that is more pronounced in cases where patients are middle aged versus older patients, predominantly due to greater dyspnoea

amongst the younger patients.[22] Treatments for COPD that both improve prognosis and quality of life are clearly important to benefit both patients and society.

The American Thoracic Society/European Respiratory Society definition of COPD is:

'*a preventable and treatable disease state characterised by airflow limitation that is not fully reversible'* [23]

COPD includes emphysema, which is pathologically rather than clinically defined as:

'*abnormal permanent enlargement of airspaces distal to the terminal bronchioles*' and includes '*destruction of alveolar walls without obvious fibrosis'*[24]

It has been shown that the airflow limitation found in COPD can be attributed both to narrowing of the inflamed airways and also a dramatic reduction in the number of terminal bronchioles to between a tenth and a quarter of the healthy number in very severe COPD; representative images of tissue changes are shown in Figure 3. [25] Severe emphysema results in hyperinflation of the lung and hyperexpansion of the chest is believed to contribute to dyspnoea by disrupting normal respiratory mechanics of the lung tissue and chest wall, especially the diaphragm.[26]

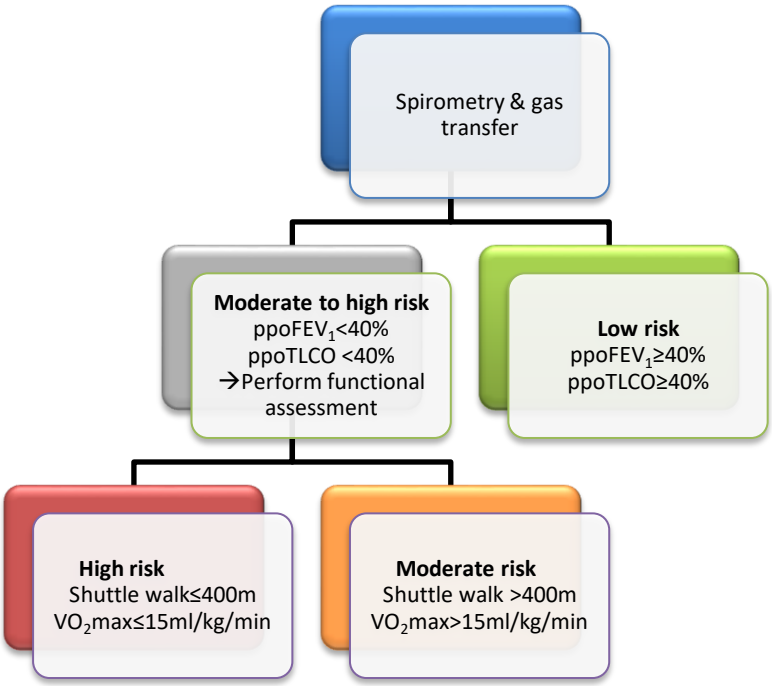


Figure 2 Summary of respiratory risk assessment prior to resection of lung cancer, ppo: predicted postoperative, VO_2max: maximum rate of oxygen consumption.

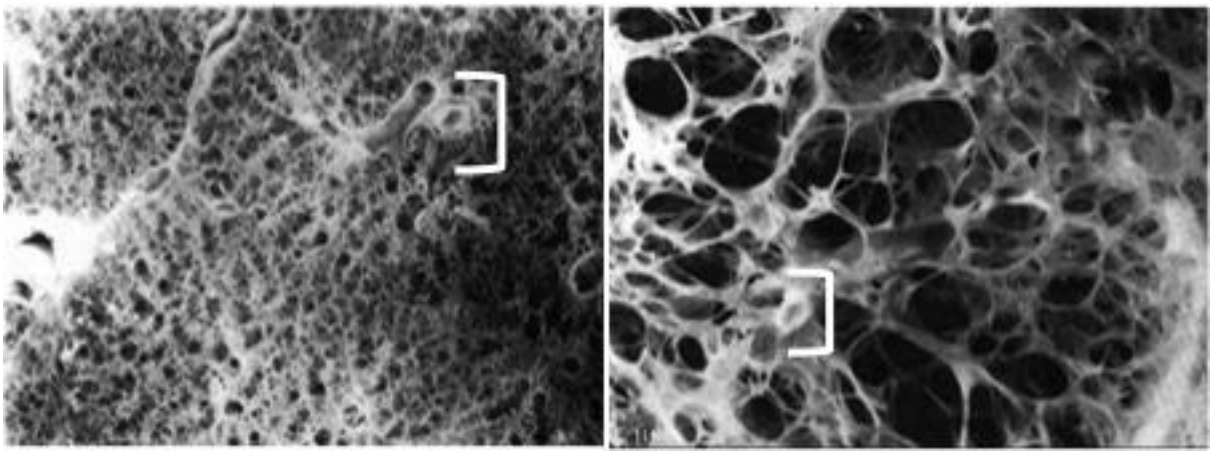


Figure 3 Normal lung tissue (left) and emphysematous lung tissue (right) structure viewed with electron microscopy [27] Brackets indicate terminal bronchioles.

The mechanism of action for all kinds of LVR is thought to be by improving the biomechanics of breathing.[28] Patients with severe emphysema have shortened diaphragms that generate lower transdiaphragmatic pressures compared to normal subjects.[29] LVR surgery has been shown to increase the length and strength of the diaphragm, and that the increase in length is associated with an increase in exercise capacity.[29,30] The role of the LVR is presently in the management of patients with established severe COPD, specifically patients with emphysema as the predominant aspect of their lung disease.

The mainstay of treatment for stable COPD is with medical therapy and lifestyle optimisation; the most important step is smoking cessation and continued absolute avoidance of tobacco. Further first line steps include vaccination against influenza and streptococcus pneumonia, optimisation of any comorbidities, and pulmonary rehabilitation.[31] The pulmonary rehabilitation regime is usually delivered in a group setting and involves exercise, education, nutritional advice, and psychological and behavioural management. Medical treatment commonly includes inhaled therapies, but may include oral medication and oxygen therapy. Only a highly select subset of patients with COPD are potentially suitable for LVR as part of their management and despite the large numbers of patients affected by COPD LVR constitutes less than 1% of the operative workload for thoracic surgeons.[1] However, LVR surgeries are performed on patients with a much higher risk profile than those undergoing other procedures. The risk of respiratory failure is the main concern and therefore the decision to operate at all is a complex one made with caution. [32]

The distribution of small airway and alveolar tissue loss within the lungs of some patients may be highly heterogeneous; this is of particular relevance in thoracic surgery because resection of disproportionately diseased lung tissue by way of surgical LVR can improve patients' quality of life and longevity with correct selection of surgical candidates.[33,34] Patients that are most likely to benefit from LVR surgery are those with heterogeneous emphysema that affects the upper lobes and who also have a low exercise tolerance. Surgical LVR at Heartlands Hospital is performed via sequential, bilateral Video Assisted Thoracoscopic Surgery (VATS) for patients judged to be fit enough by the Multidisciplinary Team (MDT) and less invasive LVR can be performed via bronchoscopy for placement of Endobronchial Valves (EBV) or Endobronchial Coils (EBC) for patients who meet the criteria for likely benefit from LVR, but are judged to be less able to withstand VATS. Criteria for referral to the LVR MDT with reference to percentage expected values are in Table 1.

Table 1 Local criteria for referral to for consideration of lung volume reduction

Criterion	**Standard required**
Smoking cessation	Abstinence >6 months
Pulmonary rehabilitation	Completed within last 12 months
FEV1	15-40%
Residual Volume	>180%
TLCO	20-45%
6 minute walk test distance	>140m
Capillary CO_2	<7.5kPa
Estimated pulmonary artery pressure	<40mmHg

1.1.3 Pleural effusion and pleural thickening

Both lungs and hemithoraces are lined by a pleural membrane with a thin lubricating layer of pleural fluid present in the potential space between the two layers of pleura; a build-up of fluid between the two layers is termed a pleural effusion and abnormal pleural thickening may occur with or without pleural effusion. This kind of pleural disease is associated with at least fifty conditions, the treatment of which is very different. One type of disease that causes pleural thickening and or pleural effusion is pleural mesothelioma, a malignancy that arises from the mesothelial cells that line the pleura and has a strong causal relationship with asbestos exposure.[35] The tumour encases the lung, forming a thick rind that follows the contours of the visceral and parietal pleurae (Figure 4). The prognosis after diagnosis is poor with a median survival of 8.9 months in a population based survey.[36] Metastatic malignancy, which can be

either from the lung or distant organs, can also cause pleural thickening and or effusion and is also associated with a dismal prognosis, median survival can be just 3.5 months depending on the primary origin of the malignancy.[37] Other causes of pleural disease, such as the presence of fibrosis after the resolution of pleural infection or haemothorax, are entirely benign and confer no adverse effects on the individual if they are asymptomatic. It is therefore critically important to diagnose the cause of the pleural abnormality accurately, and ideally rapidly, to reduce the psychological burden on those undergoing assessment. Although mesothelioma is considered a rare disease pleural effusions and mesothelioma are associated with over 300,000 hospital admissions in England per year.[38]

The presence of a unilateral pleural effusion or thickening in the absence of signs of infection is a typical scenario that leads to clinical concern for malignancy. Pleural aspiration is the first key investigation to diagnose the cause of the disease by obtaining cellular material for biochemical and cytological analysis, but the diagnostic yield is variable. The sensitivity of cytology is between 48.5% and 90.3%, and the specificity between 64.3% and 100% for diagnosing malignant pleural effusion.[39–43] Imaging is routinely performed, though malignant and benign pleural disease can appear almost identical on Computed Tomography (CT) scans despite this modality being very useful for indicating the presence or absence of other intra-thoracic disease processes (Figure 5). Image guided percutaneous biopsy can provide tissue for diagnosis but the gold standard is thoracocoscopy and biopsy, performed either by respiratory physicians or thoracic surgeons. Pleural biopsies constitute 10% of the operative workload for thoracic surgeons and they are performed primarily for diagnostic purposes; concurrent

palliative treatment is possible in the form of talc pleurodesis or insertion of an indwelling pleural catheter.[1,44] Both of these palliative procedures are used to manage effusions secondary to malignancy. Talc pleurodesis, which is performed by poudrage under general anaesthetic in theatre, can alternatively be performed by slurry through a chest drain under local anaesthetic outside of theatre and the approaches are equally effective.[44] The talc invokes inflammation of the pleurae, causing them to become adherent and thus obliterate the space between the two pleural layers and this prevents fluid accumulation. Talc is usually chosen if the lung re-inflates after drainage of an effusion; if the lung does not re-inflate and the two pleural surfaces remain separated talc pleurodesis is rendered ineffective and is known as a trapped lung. Management of fluid accumulation around a trapped lung can be achieved with placement of an indwelling pleural catheter, which allows repeated drainage of fluid in the community if and until the layers of pleura become opposed and inflamed secondary to the presence of the drain. Insertion of an indwelling pleural catheter can also be performed under local anaesthetic or during VATS under general anaesthetic. Management of benign pleural thickening is either to reassure and conservatively manage the asymptomatic patient or to offer decortication. Decortication would require a second operation under general anaesthetic to strip the fibrous rind away from the lung and the inner aspect of the ribcage, this is done to allow the lung to re-expand and allow the ribcage to move normally and in doing so restore pulmonary function.[45]

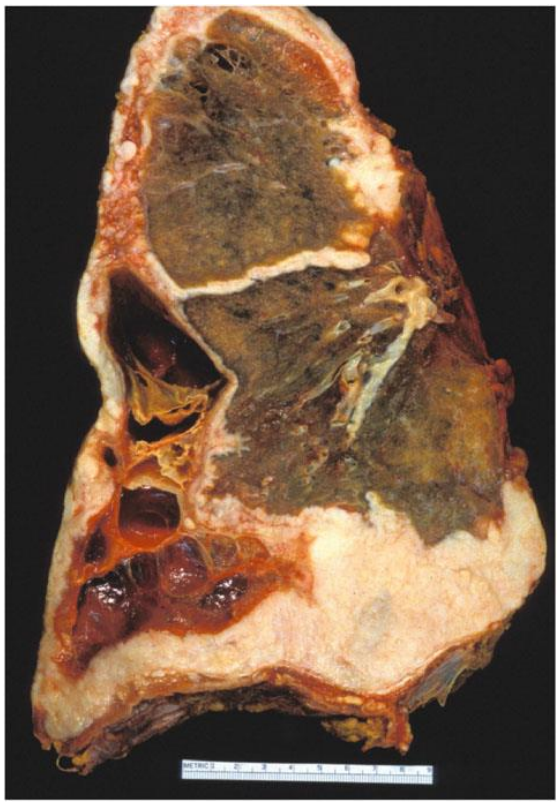


Figure 4 Mesothelioma encasing the lung [46]

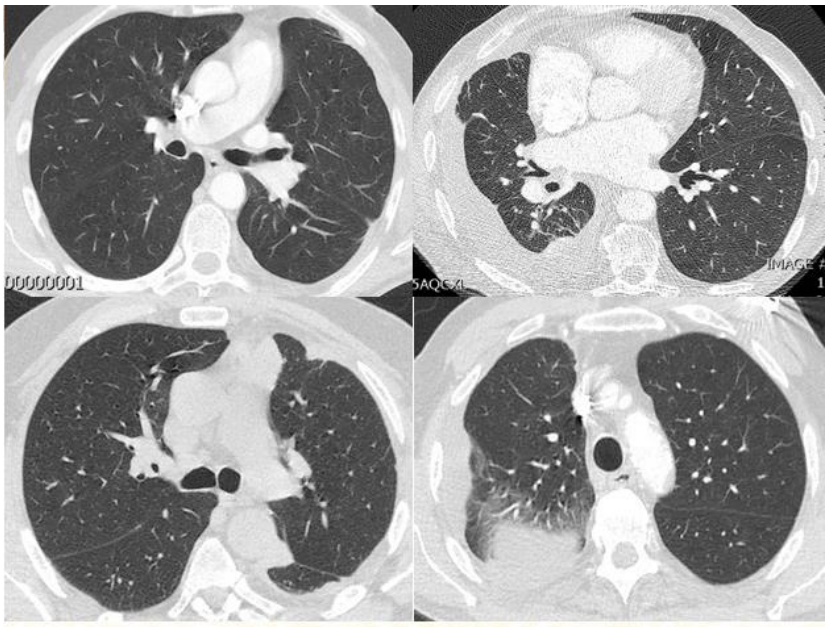


Figure 5 Thoracic CT scans of patients demonstrating the similar appearances of benign pleural disease (upper images) and mesothelioma (lower images).

1.1.4 Interstitial lung disease

Interstitial lung diseases (ILDs) are a heterogeneous group of conditions that are associated with alterations in the substances that support epithelial linings within the lung, ILDs are sufficiently rare to be classified as an orphan disease.[47,48] There are no economic analysis about the financial costs of ILD but the personal impact can be huge and extends to caregivers as well a the patient.[49]

Microscopic appearances of ILD can help illustrate the pathological process associated with these conditions, though the range of mechanisms that underpin morphological changes of fibrosis of the lungs are myriad and remain relatively poorly understood. The more consistent microscopic features of ILD are fibrosis, architectural change, inflammatory cell infiltrates, type II pneumocyte hyperplasia, and vessel intimal hyperplasia.[50] The inflammatory response distorts the normal alveolar structure as excessive fibrous tissue composed of collagen, elastin, and smooth muscle is laid down in the interstitium. Usual interstitial pneumonia (UIP) is a classical pattern of ILD and is the pattern seen in patients with idiopathic pulmonary fibrosis (IPF); it is thought to represent an on-going abnormal response to epithelial injury by an as yet unidentified insult or agent. In UIP the disease process is present at multiple stages of its evolution with a patchy distribution of normal alveoli, active deposition of fibrous tissue, and mature fibrous tissue; this is termed temporal heterogeneity and spatial heterogeneity (Figure 6).[51] In contrast, non-specific interstitial pneumonia (NSIP) shows an even distribution of inflammatory cells in cellular NSIP or diffuse fibrosis of the alveoli in fibrotic NSIP.[51]

Distortion of the normal lung architecture and altered compliance of lung tissue results in impairment of gas exchange and restriction of lung expansion. Classical clinical manifestations include dyspnoea, dry cough, and reduced exercise tolerance and examination reveals inspiratory auscultatory crackles; disease progression leads to hypoxaemia and clubbing of the digits with eventual cor pulmonale.[52] Testing typically reveals a restrictive pattern on spirometry, this is an FEV1 below the lower limit of normal and an FEV1/FVC ratio above the upper limit of normal, total lung capacity (TLC) and TLCO are also reduced.[53,54] Imaging may reveal reticular shadowing on chest radiograph however CT scanning is a routine part of assessment of ILD; CT findings are diverse but common features include volume loss, ground glass opacities, reticular shadowing, and traction bronchiectasis; fibrosis can be seen as a honeycomb pattern particularly in UIP.[55]

Diagnosis of the particular subtype of ILD is made by consensus at MDT meetings after input from respiratory physicians and radiologists, however sometimes the diagnosis remains uncertain and the input of histopathologists is needed to provide assessment of the microscopic changes in tissue obtained via surgical lung biopsy. Biopsy and tissue diagnosis was historically considered the gold standard diagnostic test but the requirement for biopsy has been challenged as the risks of surgery have been highlighted and the limitations of relying on one clinician to subtype the ILD have been recognised; the agreement between pathologists can be lower than is clinically desirable.[56] Diagnostic biopsies for interstitial lung disease constitute less than 4% of the thoracic surgical workload.[1] The surgery can at best only provide diagnostic and prognostic information, it has no prospect of symptomatic or prognostic benefit and the

30-day mortality rate is similar to that of lobectomy at around 2.4%.[57] The most serious complication of surgery is the development of an acute exacerbation of ILD, which results in acute lung injury in the postoperative period and is associated with a 50% mortality rate.[58] Ventilation during anaesthesia is thought to cause such exacerbations either from mechanical trauma or from chemical irritation secondary to the administration of oxygen and anaesthetic drugs.[58] Measures of lung function decline with progression of ILD and those with poor lung function are generally considered unfit for diagnostic biopsy due to the excessively high risks involved, a TLCO <40% is considered advanced disease.[56]

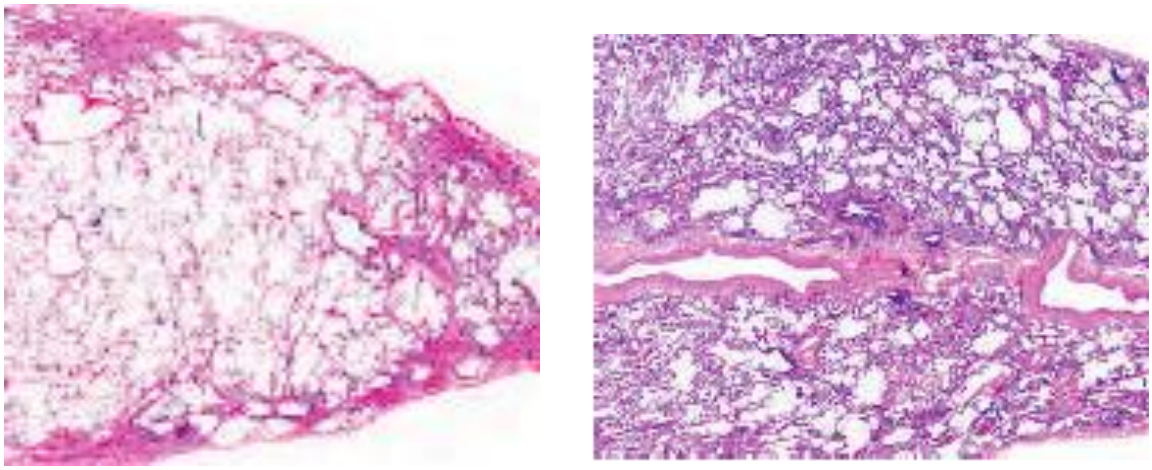


Figure 6 Microscopy of lung tissue showing patchy changes in UIP (left) and diffuse changes in NSIP (right) [51]

1.2 Measures of lung function in routine clinical use

A number of methods are currently available to assess lung function; those in common usage include measurement of spirometry, lung volumes, and gas transfer factor. Through widespread recording of these measurements in normal individuals from different populations it is possible to compare the value recorded for an individual patient to the expected value according to gender, height, age, and ethnicity, this allows the absolute value and the percentage predicted value to be available to the clinician for interpretation.[59] An understanding of the basic principles behind these routine tests is useful to appreciate how novel methods differ, and therefore where valuable clinical information can be added.

1.2.1 Spirometry

Spirometry measures the gas volume changes and passage of time during respiratory manoeuvres; patients have to co-operate to inhale fully, forcefully exhale, and then continue to fully exhale to perform spirometry. The volumes are recorded by the patient blowing into a tube with a good seal between the mouth and the tube and with a nose clip in place, thus the measures derived are all external to the patient. Two key measures produced from this process are the FVC and FEV1.[60]

1.2.2 Lung volumes

Lung volumes are commonly measured by helium dilution or body plethysmography; these techniques enable measurements of volumes including gas that is within the lungs without it passing through an external tube. [61] The helium dilution method is based upon the change between inhaled and exhaled helium concentrations when a known

volume of helium and gas mixture is connected to the patient. The simplified calculation of lung volumes using helium dilution is:

Concentration of helium prior to breathing x Volume in equipment circuit = Concentration of helium after breathing x Lung volume at which breathing commenced

Different lung volumes can be calculated by having the patient commence breathing in the circuit at different points in the respiratory cycle. For example, the first breath taken can start from the residual volume (RV) after forced exhalation or from Functional Residual Capacity (FRC) after relaxed exhalation. Lung volumes that are commonly referred to are illustrated in Figure 7.

Body plethysmography is based upon Boyle's Law and allows measurements to be made because of the relationship between gas volume and pressure; when a given volume of gas is under increased pressure then the volume will reduce (where temperature is kept constant). Patients are positioned in an enclosed chamber and changes in pressure, volume or airflow are measured as the patient breathes. Patients are required to try to make short shallow breaths (panting) whilst the breathing circuit is temporarily blocked with a shutter near the mouth in order to measure the unknown volume of gas within the lung after exhaling (Figure 8). Pressure and volume changes measured within the chamber and within the mouthpiece are used to calculate the volume of gas within the lung.

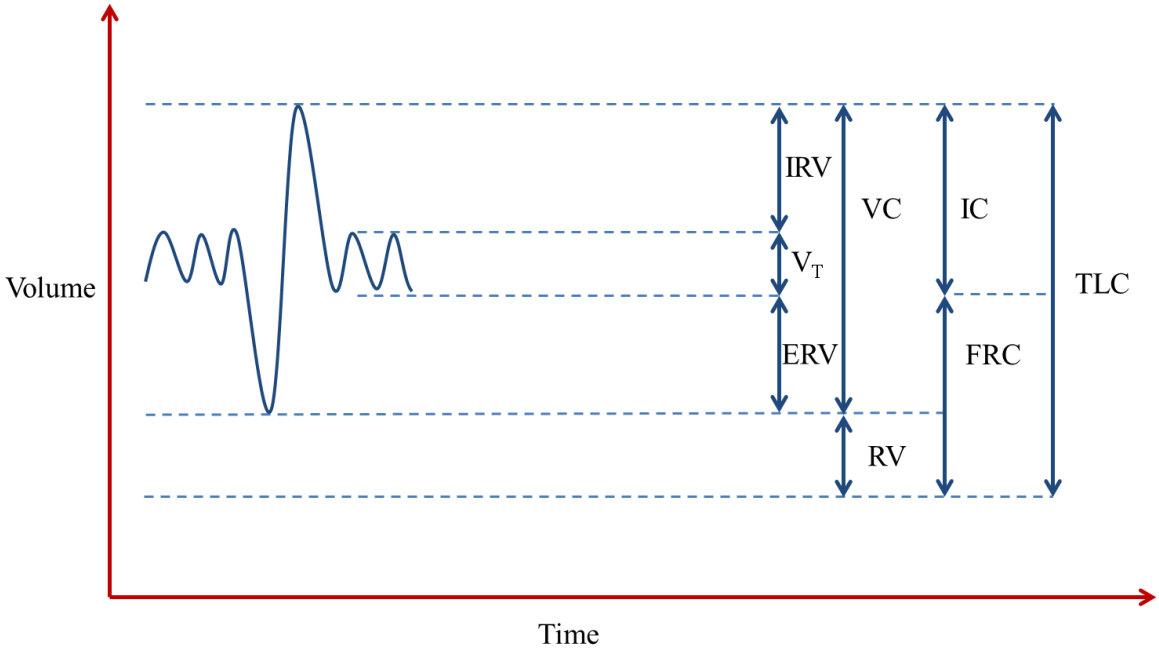


Figure 7 Parameters measured during assessment of lung volumes.

IRV: Inspiratory reserve volume, VT: Tidal volume, ERV: Expiratory reserve volume, VC: Vital capacity, RV: Residual volume, IC: Inspiratory capacity, FRC: Functional residual capacity, TLC: Total lung capacity

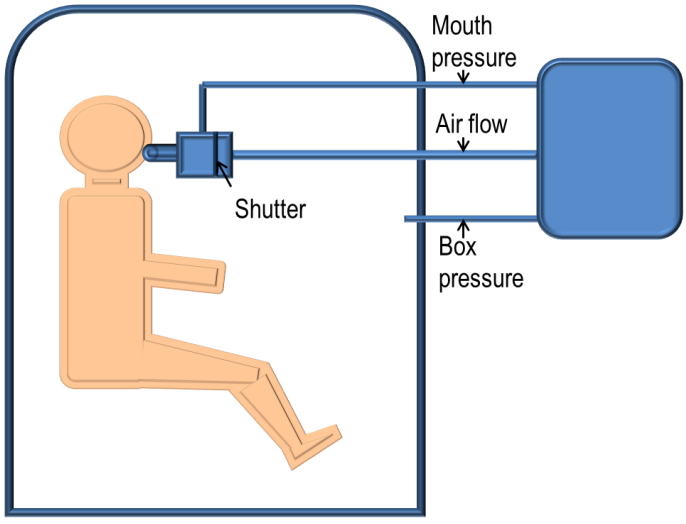


Figure 8 Equipment set up for body plethysmography

1.2.3 Gas transfer

TLCO measures the capacity for binding of carbon monoxide (CO) to erythrocyte haemoglobin following administration of inspired CO. The measure may also be referred to as DLCO, for the purposes of this thesis TLCO will be used throughout. TLCO is measured by administering a very low concentration of CO to a patient prior to a vital capacity (VC) manoeuvre; the patient then holds their breath for a set period of time and finally exhales. [62] The initial exhaled volume of gas, which resided within the dead space of the respiratory system, is discarded and then the remaining concentration of CO in air exhaled from the alveolar space is measured. The change in concentration of CO is used to determine the passage of CO into the bloodstream since this is limited by diffusion across the alveolar wall and into the red blood cells, as opposed to being limited by the delivery of blood to the alveolar bed. The inhaled CO is diluted initially by the presence of the residual volume (RV) gas; an inert gas, such as helium, needs to be added to the inhaled gas mixture to measure the initial dilution of inspired gases into the RV of the lung so the exhaled concentration of CO can be adjusted for this and also so the total lung capacity (TLC) can be calculated.[63]

It should now be clear that these tests provide information about function of the respiratory system as a whole, however pathological processes may be heterogeneously distributed throughout the lungs. As such, measures of regional lung function hold potential to provide useful information about lung diseases both for aiding in diagnosis and their potential responses to therapy.

1.3 Assessment of regional lung function

Regional ventilation is assessed clinically using radiological methods and the potential of different techniques continues to be explored. Regional respiratory movements can be assessed by analysis chest wall motion; this has been explored to a lesser extent but has a significant difference in that it can be measured during exercise.

1.3.1 Computed tomography scanning

CT scans produce cross sectional images by measuring the attenuation coefficients (μ) of X ray beams that are passed through the image subject from multiple angles. X ray photons are emitted, pass through the tissue and are subsequently detected as they leave the opposite side of the subject (Figure 9). The change in 'strength' of the X ray beam from emission to detection will be related to the interaction between X ray photons and the atoms of the tissue within the subject. More radiolucent structures will attenuate the X ray beam to a lesser degree and more radiopaque structure will attenuate it more. The attenuation coefficients are used to reconstruct a representation of the subject, depicting the interactions between the X ray photons and different tissues. Conventionally attenuation coefficients are reported in Hounsfield Units (HU) that include a linear transformation to give standardised values:

$$HU = 1000 \times ((\mu - \mu water) / (\mu water - \mu air))$$

The radiological densities of substances at standard temperature and pressure are -1000HU for air, 0HU for pure water, and 1000HU for compact bone. Radiological density in HU and the physical density of matter in mass per unit volume are related but calibration is required for comparison across different scanners or series over time. A

voxel is a three dimensional (3D) representation of the average attenuation of the structures below the resolution of the scan for its volume; a pixel is a two dimensional (2D) representation of the average attenuation of the structures below the resolution of the scan for a given voxel (Figure 10). As the amount of gas is increased relative to the amount of alveolar tissue the density of the corresponding voxel will be reduced.

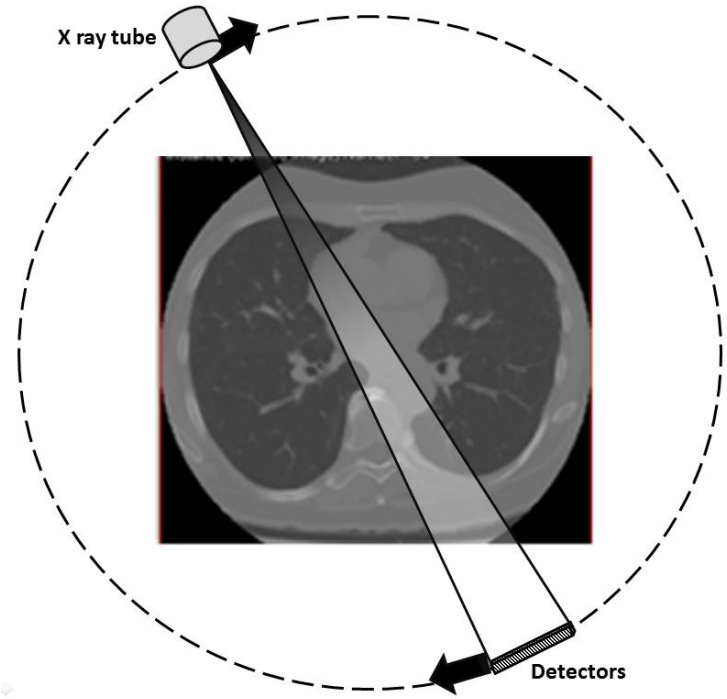


Figure 9 Illustration of how X rays are emitted and detected during CT scanning

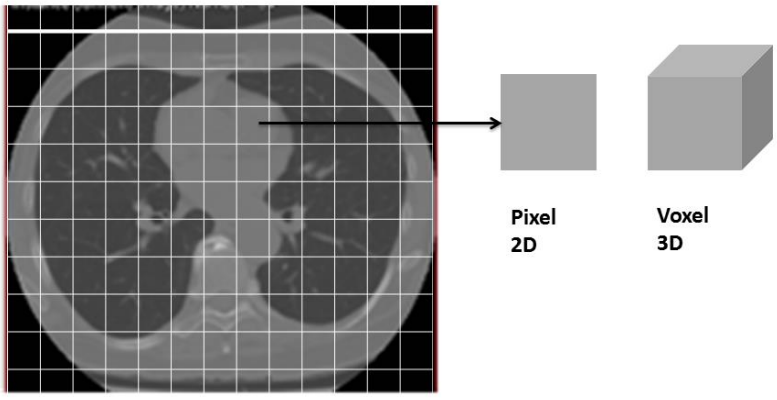


Figure 10 Representation of how pixels and voxels relate to CT images of the chest

Modern CT scanners have a resolution of less than a millimetre; the voxel size achieved from a High Resolution CT scan is approximately 0.5 x 0.5 x 1mm and as such these scans can visualise pulmonary structures down to the secondary pulmonary lobule.[64,65] Radiologists can assess lung parenchyma on CT in a qualitative manner and this is of immense diagnostic value but the assessment only provides nominal data based upon human judgement. Information about subtle variation or changes in tissues may be required and quantitative assessment that can provide the continuous data that is necessary for this purpose.

1.3.2 Computed Tomography ventilation imaging

CT ventilation imaging is the process of determining the regional ventilation of the lung using non-contrast images of the chest. This was developed using the end inspiratory and end expiratory phases of the scans that are routinely performed prior to radiotherapy treatment of thoracic structures. Each 3D voxel describes the density of a set volume of the body, which in the lungs includes both lung tissue and air. A voxel with a lower density contains a greater fraction of air and a voxel with a higher density contains a greater fraction of lung tissue. A region of interest contains multiple voxels and the densities of voxels within the volume occupied by region of interest can be used to determine how much air and tissue the region contains. The fraction of gas in the volume (V) of a region of interest within the lung can be calculated using the following formula:

$$V_{gas} / (V_{gas} + V_{tissue}) = \text{mean HU} / (HU_{gas} - HU_{water}) \quad [66]$$

The change in the fraction of gas within the lung between inspiratory and expiratory CT scans is thus a marker of ventilation; CT scans can produce a map of the regional ventilation if the change in fraction of gas is calculated for regions of the lung. This equation is limited in that it assumes lung tissue has the same density as water and further work has included the density of lung tissue. Ventilation alone does not produce oxygenated blood however, a perfused capillary bed is also required, with this in mind the measure of ventilation to a region of lung would be more clinically useful if it also accounted for how much lung tissue was present in the same region. The specific volume of gas per gram of lung tissue (SVg) can be used in an attempt to address this issue. The specific volume of a substance is the inverse of its density; i.e. how much volume it occupies for a given weight, reported in millilitres per gram. The specific volume of lung tissue (SVtissue) is reported as 1/1.065 or 0.939ml/g from histological study.[67] The specific volume of the whole lung as a unit (including the lung tissue and gas within the lung) can be estimated from CT scans:

$$SV_{tissue\ and\ gas} = 1000/(HU+1000) \quad [68]$$

Subtracting the tissue from the lung it is possible to calculate the SVg for a voxel:

$$SV_g = SV_{tissue\ and\ gas} - SV_{tissue} \quad [68]$$

Multiple studies have found the measure of lung expansion on CT and the gold standard histological measurement of lung expansion to correlate well. [69–71] SVg for inflated normal lung tissue is predominantly between 0.0 – 6.0ml/g with a quarter of the lung having a slightly higher SVg of 6.0-10.2ml/g and no regions with SVg over 10.2ml/g. Emphysematous lung has regions with SVg over 10.2ml/g and higher proportions of the

lung with 6.0-10.2ml/g. [71] Healthy lung tissue has a median change in SVg (deltaSVg) value of 4.7ml/g, interquartile range (IQR) 2.2 and skewness -0.2 whereas emphysematous lung has corresponding values of 1.3ml/g, IQR 4.1 and skewness 0.5.[68]

1.3.3 Measuring chest wall motion

Functional assessments of the lung so far assess the gases involved with respiratory movements (spirometry) and the lung itself (radiological imaging); comparatively little is understood about how these measures relate to the function of the chest wall, but the lungs cannot function spontaneously without the influence of the diaphragm, ribcage, intercostal muscles and abdominal muscles. Various techniques have been used in research settings to evaluate chest wall motion, each with their benefits and limitations.

Metal coils can be integrated into belts to be worn by patients to perform respiratory inductive plethysmography. [72,73] The coils are stretched or relaxed during inspiratory and expiratory movements respectively and the electrical current is altered by self inductance, this is measured and the change in length of the belt allows the volume of the trunk to be derived. Piezoelectric materials can also be integrated into a belt to be worn by patients.[74,75] These devices exploit the generation of electrical impulses in response to deformation of the piezoelectric material. The magnitudes of the electrical impulses are converted to the distance the material is deformed by (elongation of the belt during inspiration) and so the volume change in the trunk is derived. Both of these methods can measure volume changes over the trunk but cannot differentiate differences in motion between the left and right sides of the body. Additionally, the belts will only cover a small percentage of the trunk surface, so subtle variations may be missed (Figure 11).

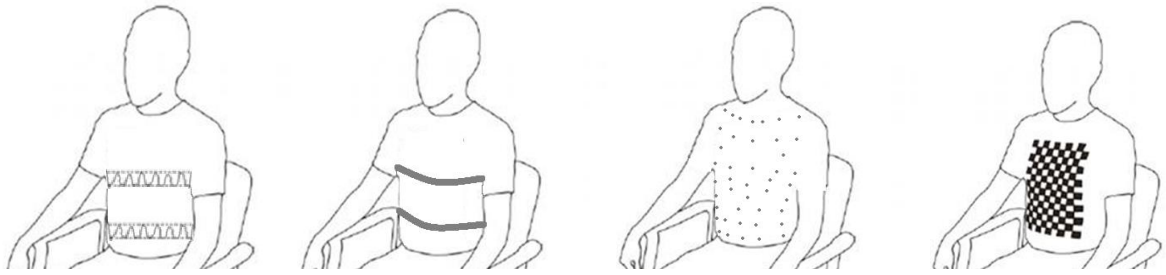


Figure 11 Illustration of how chest wall motion measuring devices are positioned on the trunk of patients. From left to right: inductive coil belt, piezoelectric belt, OEP markers, SLP grid

1.3.3.1 Optoelectronic Plethysmography

Optoelectronic plethysmography (OEP) can characterise the regional contribution of the trunk to respiratory volume changes at rest and during exercise or specific manoeuvres. Measurements are made using infrared reflective markers placed on the patient's trunk, both anteriorly and posteriorly, according to anatomical landmarks then infrared light is emitted and recorded by cameras positioned around the patient (Figure 12). The timing from emission to receipt of the infrared light beams enables the recording of the position of markers in three dimensional space.[76,77] Tracking the movement of the infrared markers allows reconstruction of the volumes and movements of the trunk at rest and during exercise. The trunk can be compartmentalised in to the pulmonary ribcage where the lung is apposed to the ribcage, the diaphragmatic ribcage where the diaphragm inserts or apposes, and the abdomen. The left and right sides can be analysed separately and thus the trunk can be analysed as between one and six compartments. OEP is highly accurate with a mean measurement discrepancy of just 0.017mm and although measurements tend to overestimate absolute volumes this is clinically insignificant, always being within 12ml of the true value. [78] The use of OEP so far has

been restricted to research because, although it is simple to perform, it is time consuming to perform and analyse. In addition, assessments are limited to intrapersonal or case-control comparisons because there is a lack of established normal values at population level.

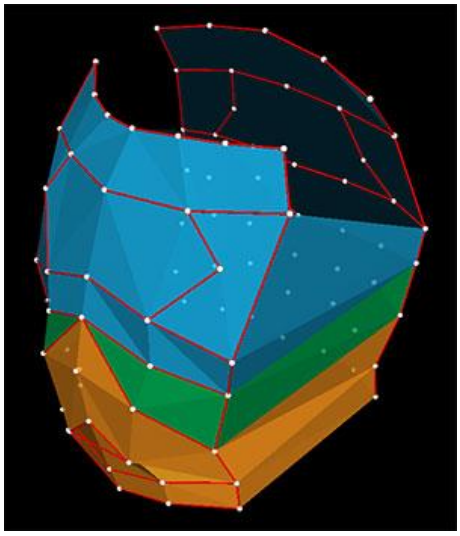


Figure 12 3D reconstruction of the thorax used in OEP analysis of chest wall motion. Blue: pulmonary ribcage, green: diaphragmatic ribcage, orange: abdomen.

1.3.3.2 Structured Light Plethysmography

Structured light plethysmography (SLP) can also record regional changes in the trunk position. SLP is performed using a projected grid of visible light onto the anterior surface of the patient's trunk. The deformation in the grid allows the change in distance from the projector and cameras to be measured and thus changes in the volume of the trunk are derived (Figure 13). [79] This technique does not require any contact with the patient, the system is portable and the process takes a timed five minutes with no specific manoeuvres required. SLP measures have been shown to have good correlation

with pneumotachography volumes and have also been validated against respiratory inductive plethysmography.[80,81] Again there is a lack of publically available normal values for SLP in populations.

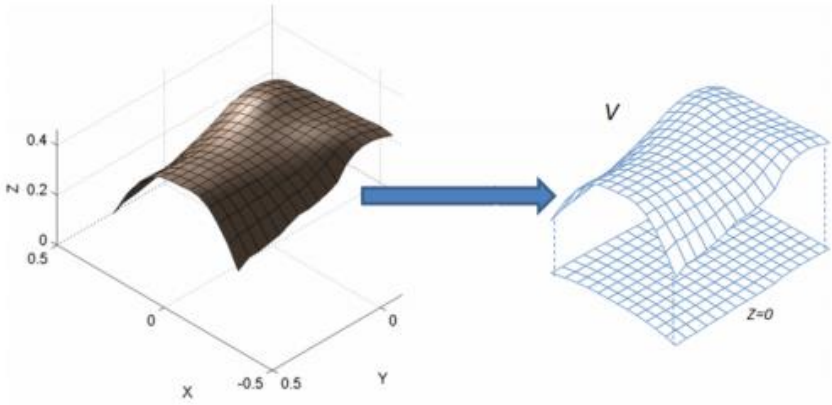


Figure 13 Illustration of the conversion from light grid to volumes using SLP.[79]

1.4 Aims of this thesis

Technology has been an important partner in the field of surgery and has lead to huge advancements in the range of possible procedures and benefitted many patients.[82] However, failure to properly evaluate new technology can be catastrophic; the field of thoracic surgery is regrettably familiar with how the excitement and hope surrounding new technology can be abused.[83] The aims of this thesis are to assess the potential for clinical application of technological solutions in assessing regional lung function, particularly how these may be used in the preoperative setting.

Chapter 2 is a systematic review and meta-analysis of the evidence base for predicting postoperative lung function in patients undergoing lung cancer resection.

Chapter 3 describes a feasibility study of using change in SVg (deltaSVg) as a refinement of CT based methods for predicting postoperative lung function in patients undergoing lung cancer resection.

EBCs have been marketed as a less invasive LVR procedure and potentially the only option as a procedure for those with homogenous emphysema.[84] The EBCs do not remove or entirely collapse a lobe of the lung, therefore the effects of the EBCs on the chest wall and diaphragm are uncertain. Chapter 4 aims to use OEP to advance understanding of the mechanism of action of EBCs as a method of LVR.

Preliminary data suggested chest wall motion differs significantly between patients with mesothelioma compared to benign pleural disease. [85] Chapter 5 reports a study assessing the utility of SLP as a diagnostic test to stratify patients undergoing diagnostic surgical pleural biopsy.

The structure of diseased lung tissue differs between subtypes of ILD with some having diffuse changes and others having heterogeneous regions of fibrosis. Chapter 6 reports a study using deltaSVg to assess heterogeneity of regional ventilation in relation to the diagnosed subtype of ILD in patients.

Chapter 7 concludes the thesis.

CHAPTER 2: PREDICTING POSTOPERATIVE LUNG FUNCTION FOLLOWING LUNG CANCER RESECTION: A SYSTEMATIC REVIEW AND META-ANALYSIS

This chapter has been published: Oswald NK, Halle-Smith J, Mehdi R, Nightingale P, Naidu B, Turner AM. Predicting Postoperative Lung Function Following Lung Cancer Resection: A Systematic Review and Meta-analysis. *EClinicalMedicine*. 2019;15:7-13. doi:10.1016/j.eclinm.2019.08.015

2.1 Introduction

There were 39,205 new cases of lung cancer in 2016 in England and Wales, 89% of which are NSCLC; survival remains low (37% at one year) and measures have been sought to improve survival in the UK, one such measure would be an increase in the surgical resection rate.[86,87] Surgical resection with curative intent is the standard of care for stage I and II NSCLC but whilst 27% of patients have cancer of these stages, only 17% undergo surgery. [86] Such invasive treatment requires careful preoperative assessment; the predicted postoperative FEV1 and TLCO (see Section 1.2) are used to stratify risk of mortality and postoperative dyspnoea, with an expected value of between 30% and 60% predicted being the cut off for requesting further investigations.[17,88,89]

A multitude of different techniques to predict postoperative lung function have been reported but there has not been a quantitative review of their accuracy or precision. Inaccuracies in prediction about respiratory fitness for lobectomy could contribute to explaining the variability of changes in lung function after cancer surgery if patients

were deemed to be fit for an extensive resection when in fact this resulted in significant impairment in function.[90] Predictions are used to inform important treatment decisions including whether to proceed with surgical resection or recommend other treatment modalities, such as radiotherapy or chemotherapy. Predictions of risk are relayed to patients during counseling for surgery and The National Lung Cancer Audit recently reported that patient preference is a significant reason that patients with resectable tumours do not undergo resection.[86] In addition, if a patient is judged to be in the high-risk category for operative mortality based upon predictions, treatment may be delayed to allow time for further investigations, such as cardiopulmonary exercise testing or ventilation and perfusion scintigraphy scanning.[91] There is a need for formal comparison of prediction methods to enable clinicians to choose the most accurate method and understand its limitations, in doing so they can interpret information for patients so they can choose to proceed with the most appropriate course of treatment with a minimum of delay.

2.2 Methods

A systematic review and meta-analysis of the techniques to predict postoperative lung function in patients undergoing lung cancer resection was conducted and reported in line with the standards set out by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[92] The aim of the review was to address the following questions:

- What methods have been used to predict postoperative lung function in patients undergoing lung cancer resection?

- How accurate and precise are the available methods in predicting postoperative lung function in patients undergoing lung cancer resection?

The review was registered on the International Prospective Register of Systematic Reviews (PROSPERO), record number [CRD42017058955].

2.2.1 Inclusion and exclusion criteria

The population for inclusion was adults with suspected or confirmed primary lung cancer. They must have undergone the intervention of lung resection with curative intent, which would be any of pneumonectomy, lobectomy, segmentectomy or wedge resection, and the patients must have had lung function measured before and after surgery. Surgeries for known benign conditions, palliation of lung cancer, purely diagnostic surgery, emergencies, and bronchoscopy without concomitant lung resection were excluded. Comparison between the predicted postoperative lung function and the actual measured postoperative lung function must have been performed with comparison of the accuracy and precision of the techniques being planned for meta-analysis. A technique for predicting postoperative lung function must have been applied and the results reported, the results of this prediction were considered the outcome for the purposes of framing the review question. All retrospective and prospective studies were eligible, but case reports and case series (fewer than eight participants) were excluded.

Studies reporting combined results of surgery for both benign and malignant pathology were eligible provided the majority of the study population had primary lung cancer as the indication for the procedure. This can and does occur in clinical practice for patients

without a confirmed preoperative tissue diagnosis of cancer who are scheduled to undergo a frozen section pathological diagnosis during surgery. These cases are relevant because clinical decision making is identical until the frozen section result is reported during the operation. Therefore, good quality research that followed up all patients fully would be likely to include some patients that were suspected of having lung cancer but eventually had an alternative benign diagnosis.

2.2.2 Search strategy and study selection

The following electronic bibliographic databases were searched: EMBASE, MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts of Reviews of Effects (DARE), NHS Economic Evaluation Database (NHS EED), Cochrane Database of Systematic Reviews (CDSR). The search strategy combined terms relating to lung surgery, terms relating to measuring lung function, terms relating to the postoperative period and terms relating to prediction or correlation between measures. No language, date or other restrictions were applied. The searches included all eligible studies published prior to 18th January 2018. Additional studies were sought through sources such as reference lists of included papers and contact with experts in the field.

The search terms entered into PubMed, primarily covering the MEDLINE database, were:

1. Lung cancer surgery
2. Lung surgery
3. Pulmonary surgery
4. Lung resection
5. Pulmonary resection
6. Sublobar resection

7. Anatomical resection
8. Pneumonectomy
9. Lobectomy
10. Wedge
11. Segmentectomy
12. Thoracic surgery
13. Predict*
14. Correlat*
15. Quanti*
16. Postoperati*
17. Post operati*
18. Post surg*
19. After surgery
20. After pneumonectomy
21. After lobectomy
22. After thoracotomy
23. After VATS
24. Respiratory function test
25. Respiratory function
26. Pulmonary function test
27. Pulmonary function
28. Lung function test
29. Lung function
30. Gas transfer
31. Diffus* capacity
32. Spiromet*
33. All surgical terms 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
34. All prediction terms 13 or 14 or 15
35. All postoperative terms 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
36. All lung function terms 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32
37. 33 and 34 and 35 and 36

The search terms entered into Ovid, covering the MEDLINE and EMBASE databases, were:

1. (lung cancer surgery or lung surgery or pulmonary surgery or lung resection or pulmonary resection or sublobar resection or anatomical resection or pneumonectomy or lobectomy or wedge or segmentectomy or thorax surgery).af.
2. (predict* or correlat* or quanti*).af.
3. (postoperati* or post operati* or post surg* or after surgery or after pneumonectomy or after lobectomy or after thoracotomy or after VATS).af.
4. (spiromet* or respiratory function test or respiratory function or pulmonary function test or pulmonary function or lung function test or lung function or gas transfer or diffus* capacity).af.
5. 1 and 2 and 3 and 4

The titles and abstracts of studies retrieved by the searches were screened independently by two reviewers to identify studies that potentially met the inclusion criteria, the full texts of potentially eligible studies were independently assessed for eligibility by two reviewers. Any disagreement about eligibility was resolved through consensus, with a third reviewer where necessary. Studies assessed as low risk of bias overall were included in the meta-analysis.

2.2.3 Data management

A pre-piloted electronic form (Microsoft Excel 2010) was used to record extracted data from eligible studies and record risk of bias assessments. The information extracted included: study population and participant demographics, prediction technique, funding, study methodology, recruitment rate, study completion rate, type of surgery performed, lung function at baseline, lung function postoperatively, predicted postoperative lung function, and the postoperative time that lung function was assessed. One reviewer

extracted data independently and a second reviewer checked the data, discrepancies were resolved through consensus, with a third author where necessary. Missing data from studies eligible for meta-analysis were requested from study authors via electronic mail.

2.2.4 Foreign languages

Final meta-analysis included full papers that were written in English and German (one paper). Full papers that were assessed but either excluded or were not judged low risk of bias overall were written in English, Japanese, Chinese, French, Italian, Russian, Korean, Spanish, and Turkish. The review team first reviewed papers written in English, which provided a basis of strong familiarity with the style of reporting of the subject matter and then reviewed papers in foreign languages; team members were familiar with German, French, Italian, and Spanish enabling translation with the aid of the Google Translate app (Google Commerce Ltd) for vocabulary. The Google Translate app 'camera' function was used to translate phrases in Japanese, Chinese, Russian, Korean, and Turkish. Native speakers provided the second review for papers in Korean, and (where necessary) sense checks were carried out via native speakers of the other included languages for which the Google Translate app was required.

2.2.5 Bias assessment

There are few bias tools specific to prediction studies. Quality in Prognosis Studies (QUIPS) is available for assessing studies about identifying predictors of outcome in a cohort of patients, this could have been used for the presented review but it is less suited to assess models performing predictions in a clinical setting for individual patients. Quality Assessment of diagnostic Accuracy Studies 2 (QUADAS-2) is available

for assessing tests relating to diagnosis; this tool could be applied in the context of this review but it more suited to tests that have a categorical outcome and the signaling questions are more intuitive for tests with a binary outcome.

A preliminary version of the Prediction study Risk Of Bias Assessment Tool (PROBAST) was sought from the authors of the tool and used to assess full papers that met eligibility criteria and a final version of the tool is now publically available.[93,94] A key element of risk of bias assessment for this review included the timing of measuring postoperative lung function; this is known to stabilise after around three months postoperatively and decline gradually with time, as such measurements before three months or after 12 months were considered a source of bias.[95,96] Additionally, exclusion of patients because of almost ubiquitous co-morbidities or postoperative complications were considered an important source of bias. The authors' intentions when excluding these patients are understandable, they were likely to want a homogenous group of patients whose lung function has not been influenced by complications, but co-morbidities and complications are so common in thoracic surgery that any prediction model should be able to perform well in spite of them to be of any use in clinical practice. Only one study reported using a multivariable model and as such the original PROBAST guidance was found to be less helpful during the pilot data extraction.[97] Studies usually reported very simple mathematical adjustments for a proportional loss of lung function and as such assessing for variable selection, multiple events per individual, and model calibration were not well suited to assessing risk of bias in this review. Clarity and completeness of data reporting were noted to be issues during the pilot extraction and hence were included in adjustments to PROBAST to assist risk of bias assessment in this section. The PROBAST

form was also personalised to aid reviewers in considering relevant factors such as timing and complications in their judgement of risk of bias; the tool as used is included in Appendix 1.

2.2.6 Data analysis

Statistical advice was sought from a senior statistician at The Institute of Translational Medicine, University Hospitals Birmingham NHS Foundation Trust prior to planning meta-analysis. The principal summary measures were the mean difference between measured and predicted postoperative lung function (accuracy) and the standard deviation (SD) of the mean difference (precision). Meta-analysis of mean difference was performed using the generic inverse variance method in Revman Version 5.3.[98] Multilevel meta-analysis of Variance Ratio, as described in detail by Senior et al, was used to analyse the SD of the mean difference in RStudio Version 1.1.463.[99,100] Patient level data was extracted from article scatter plots using online software WebPlotDigitizer Version 4.1, where necessary.[101] Meta-analysis was performed on absolute values; the corresponding authors of papers that provided percentage values only were contacted to provide additional data but no response to these enquiries was received. I^2 or Cochran's Q was calculated as a measure of consistency across studies, as provided by software packages Revman and RStudio respectively. Analysis of funnel plots was planned to assess risk of publication bias.

2.3 Results

2.3.1 Included studies

A total of 3816 papers were found using the search strategy and 135 full papers met criteria for inclusion, flow of studies through the selection process is shown in Figure 14. The most common reason for exclusion was that the article did not measure postoperative lung function, but compared two or more prediction techniques to each other without the true value being known, or did not perform prediction of postoperative lung function.

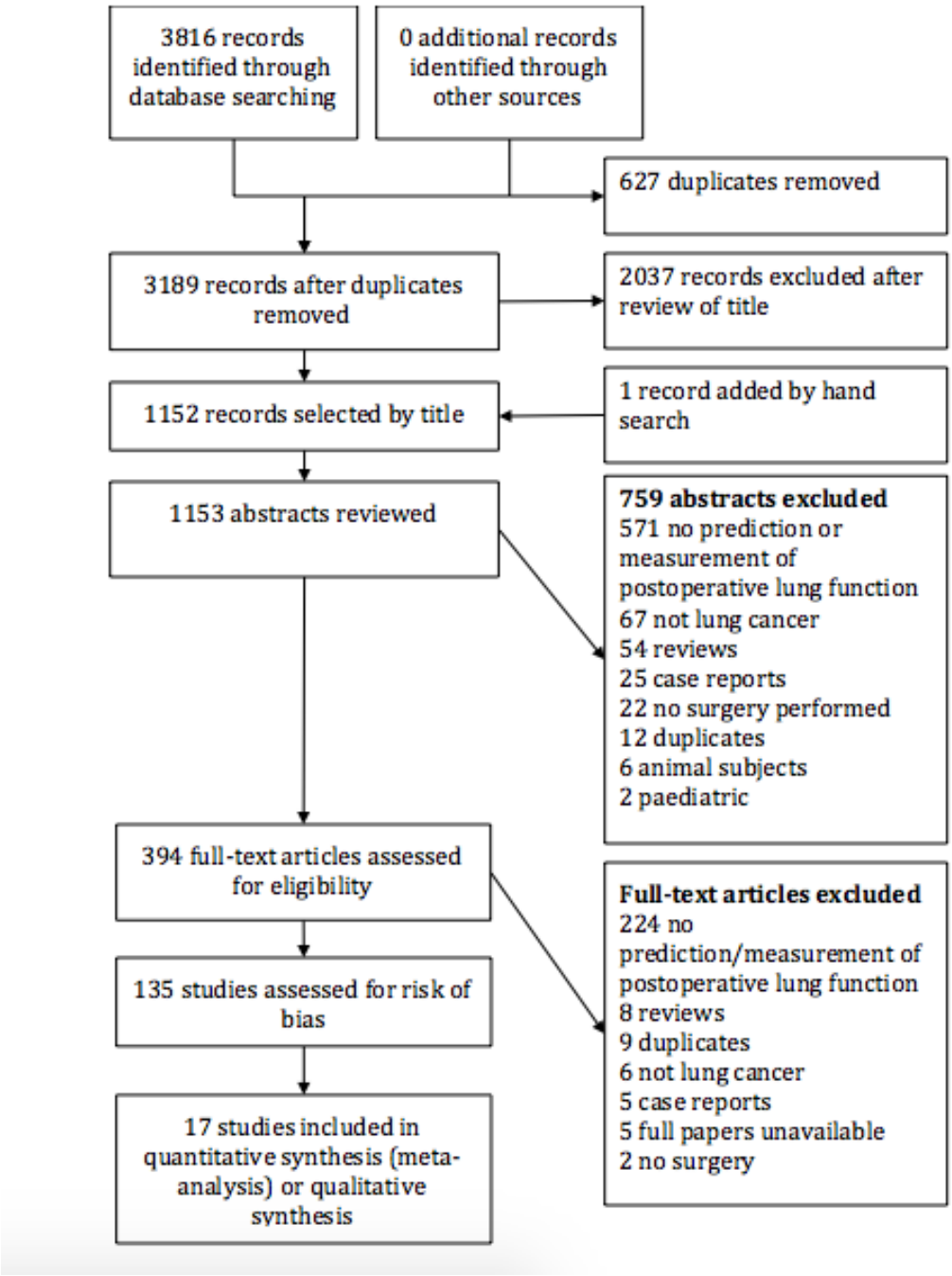


Figure 14 Study screening and selection flow diagram

Articles reported 16 different types of prediction tests, in order of frequency they reported:

- Perfusion scintigraphy
- Segment counting
- Ventilation scintigraphy
- Single Photon Emission Computed Tomography (SPECT)
- Computed Tomography volume and density (CT-VD)
- Vibration Response Imaging (VRI)
- Ventilation perfusion scintigraphy
- Subsegment counting
- Computed Tomography (CT) volume
- Co-registered SPECT-CT
- Perfusion Magnetic Resonance Imaging (MRI)
- Perfusion CT
- Newly derived regression equation
- Ventilation CT
- CT volumetry and partial densitometry
- Lateral position test

The tests broadly involve estimation of how much lung tissue was to be removed with or without estimation of the functionality of the lung tissue. Segment counting assumes that the 19 segments in the lungs are each of equal size and function, with a proportional reduction in lung function following resection as per the Juhl and Frost formula.[102] Sub-

segment counting assumes 42 sub-segments within the lung and reduction in lung function following resection as per the Nakahara formula.[103] VRI used the intensity of breath sounds recorded by external sensors placed across the chest as a proxy for regional lung ventilation.[104] CT volume tests used the volume of the lobe to be resected relative to the total lung volumes as measured on CT as the proportion of function expected to be lost. [105] CT-VD tests used the density of lung tissue in HU to define healthy lung tissue in combination with the volume resected, in doing so excluding diseased tissue from calculations. [105–109] The CT density mask to define functional lung tissue varied between -1024 and -910HU for the lower limit and -650 and -500HU for the upper limit.[105–108] The most commonly used limits were -910 for the lower and -500 for the upper. CT volumetry and partial densitometry used the volume of lung tissue but only defined a lower limit of Hounsfield Units below which the tissue was considered emphysematous; an upper limit was not defined and thus lung tissue that was non-functional due to fibrotic disease processes could still have been included as normally functioning tissue.[110]

2.3.2 Risk of bias and applicability

A total of 17 of the 135 full papers had sufficiently low risk of bias to warrant inclusion for meta-analysis. The risk of bias assessments for all studies are presented in Table 2 and Figure 15, the characteristics of studies that were judged as low risk of bias are presented in Table 3. There were too few studies reporting each method (n<10) to perform a valid funnel plot analysis of publication bias.[111] Study outcomes and predictors were found to be applicable to the review question in almost all cases.

The most frequent reason for concern about high risk of bias was the timing of postoperative lung function measurement because this had been performed within 3 months of surgery (i.e. before measurements plateau), or measurements had varied vastly in their timing, such as the one study that reported a range of measurement timing between 24 days and 5 years.[112–117] The method of patient selection was often unclear or appeared to be based upon convenience, for example in retrospective studies of patients who happened to have had postoperative lung function measured and also a particular preoperative test performed.[116,118–121] The patient cohort within a study is likely to be unrepresentative of the patient population presenting for potential lung resection if they had needed to undergo additional testing that is not part of usual care either before or after surgery. Exclusion of patients based upon postoperative factors, such as pneumonia, cancer recurrence or postoperative chemotherapy was also frequently described; these postoperative issues are common and exclusion of these patients potentially selects a subgroup of healthier, low risk individuals that are not representative of the patient population.[114,122–125]

Reporting of recruitment rate and follow up rate was frequently incomplete and therefore difficult to assess for risk of bias. Where rates were reported, follow up rates were often low, which is not unexpected since significant postoperative complications are common, but few studies fully described patients who were lost to follow up.[108,124–130] Blinding was rarely mentioned, however risk of bias introduced by the prediction method was not usually a considered to be high risk of bias because categorical judgments about disease groups was not a factor in the predictions, rather objective measurements and quantitative software formed the basis of the predictions.[106,108] The

predictor variables were generally reported in more detail, as they were the focus of the article being published, and this enabled assessment in almost all cases as opposed to the risk being unclear.

In nine cases the statistical analysis reported in the article was not adequate, such as only reporting r values for correlation and not information about agreement or mean difference. The studies were otherwise considered low risk of bias and had reported patient level data or summary data with sufficient clarity so as to allow the reviewers to perform agreement analysis independently and hence include the data in meta-analysis. Studies where independent analysis was performed are indicated in Table 2.

Table 2 Risk of bias assessments for eligible full papers by year of publication

Author, year	**Risk of bias**					**Applicability**		
	Participant selection	**Predictors**	**Outcome**	**Sample size and flow**	**Analysis**	**Participant selection**	**Predictors**	**Outcome**
Hara et al, 2017 [131]	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Low
Fourdrain et al, 2017 [110]	Low	Low	Low	Low	Low	Low	Low	Low
Suh et al, 2017 [128]	Low	Low	Unclear	High	High	High	Low	Low
Usuda et al, 2017 [132]	High	Low	Low	Unclear	High	Low	Low	Low
Yoo et al, 2016 [133]	Unclear	Low	Unclear	Unclear	High	Low	Low	Low
Nomori et al, 2016 [134]	Low	Unclear	Low	High	High	Low	Low	Low
Yabuuchi et al, 2016 [105]	Low	Low	Low	Low	Unclear[#]	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Ueda et al, 2015 [118]	High	Low	Low	High	Unclear	Low	Low	Low
Murakami et al, 2015 [123]	High	Low	Low	High	High	Unclear	Low	Low
Kovacevic-Kusmierek, et al 2015 [135]	Unclear	Low	Low	Unclear	Low	Low	Low	Low
Ohno et al, 2015 [106]	Low	Low	Low	Low	Low	Low	Low	Low
Hashimoto et al, 2015 [136]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Choi et al, 2015 [137]	Unclear	Low	Unclear	Unclear	Unclear	Low	Low	Low
Edvardsen et al 2015 [138]	Unclear	Low	High	Unclear	Low	Low	Low	Low
Rangarajan et al, 2015 [139]	Unclear	Unclear	Low	Unclear	Low	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Simsek Veske et al, 2014 [113]	Low	Low	High	Unclear	High	High	Low	Low
Saito et al, 2014 [140]	Low	Low	High	Low	Unclear	Low	Low	Low
Seok et al, 2014 [141]	High	Low	Low	Unclear	High	Low	Low	Low
Takahashi, 2014 [142]	Unclear	Low	High	Unclear	High	Low	Low	Low
Vos et al, 2014 [143]	Unclear	Low	Unclear	Low	Unclear	Low	Low	Low
Marinov et al, 2014 [144]	Low	Low	High	Unclear	Unclear	Low	Low	Low
Franchi et al, 2014 [145]	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low
Li et al, 2014 [146]	High	Low	Low	Low	High	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Mizobuchi et al, 2014 [122]	High	Low	Low	High	Unclear	Low	Low	Low
Yanagita et al, 2013[147]	Low	Low	Low	Low	Unclear[#]	Low	Low	Low
Detterbeck et al, 2013 [126]	High	Low	Low	High	High	High	Low	Low
Westhoff et al, 2013 [148]	Low	Low	High	Low	Low	Low	Low	Low
Chae et al, 2013[129]	Low	Low	Low	Low	Low	Low	Low	Low
Marinov et al, 2013 [149]	Unclear	Low	High	Unclear	Unclear	Low	Low	Low
Janssens et al, 2013 [150]	Unclear	Low	Unclear	Unclear	Low	Low	Low	Low
Cukic, 2012 [151]	High	Low	High	Unclear	High	High	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Kim et al, 2012 [152]	Low	Low	High	Unclear	High	High	Low	Low
Comce et al, 2011 [153]	Low	Low	High	Unclear	High	High	Low	Low
Comce et al, 2011 [112]	High	Unclear	High	Low	Low	Low	Low	Low
Zhu et al, 2011 [154]	Low	Low	High	Low	High	Low	Low	Low
Ohno et al, 2011 [155]	Unclear	Low	Low	Unclear	Low	Low	Low	Low
Holvoet et al, 2011 [156]	High	Low	Low	Unclear	Low	High	Low	Low
Papageorgiou et al, 2011 [157]	Unclear	Low	Low	Unclear	Unclear	Unclear	Low	Low
Kovacevic-Kusmierek et al,	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
2011 [158]								
Pancieri et al, 2010 [159]	Low	Low	Low	Unclear	Low	High	Low	Low
Morice et al, 2010 [160]	Low	Low	High	High	Low	Low	Low	Low
Jimenez et al, 2010 [161]	High	Low	High	Low	Low	Low	Low	Low
Caglar et al, 2010 [162]	Unclear	Low	High	Unclear	High	Low	Low	Low
Yamashita, 2010 [163]	Low	Low	Low	Low	Low	Low	Low	Low
Eberhardt et al, 2010 [164]	Unclear	Low	Low	Unclear	Unclear	Low	Low	Low
Lian et al, 2010 [165]	High	Low	Unclear	High	Low	High	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Ueda et al, 2009 [166]	Unclear	Low	Low	Unclear	High	Low	Low	Low
Yoshimoto, 2009[107]	Low	Low	Low	Low	Low	Low	Low	Low
Maestre et al, 2009 [104]	Unclear	Low	High	Unclear	High	Low	Low	Low
Brunelli et al, 2007 [167]	Unclear	Low	High	Low	Unclear	Low	Low	Low
Brunelli et al, 2007 [96]	Low	Unclear	Low	Low	High	Low	Low	Low
Ohno, 2007[168]	Low	Low	Low	Low	Low	Low	Low	Low
Beyer et al, 2006 [169]	High	Low	High	Unclear	Low	High	Low	Low
Mineo et al, 2006 [170]	Unclear	Low	High	Unclear	Low	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Win et al, 2006 [171]	Unclear	Low	High	Low	Low	Low	Low	Low
Varela et al, 2006 [172]	High	Unclear	High	Low	High	Low	Low	Low
Wang, 2006 [173]	Low	Low	Low	Low	Low	Low	Low	Low
Sudoh, 2006 [174]	Low	Low	Low	Low	High#	Low	Low	Low
Brunelli et al, 2005 [97]	Low	Low	High	Low	High	Low	Low	Low
Sverzellati et al, 2005 [175]	Unclear	Low	Low	Unclear	Low	Low	Low	Low
Sekine et al, 2005 [176]	Low	Low	High	Low	High	Low	Low	Low
Liu et al, 2005 [177]	Unclear	Low	High	Unclear	Low	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Win et al, 2004 [178]	Unclear	Low	High	Unclear	Low	High	Low	Low
Smulders et al, 2004 [124]	High	Low	Low	Low	High	Low	Low	Low
Yasukawa et al, 2004 [121]	High	Low	Low	High	High	High	Low	Low
Piai et al, 2004 [179]	Low	Low	High	Low	High	Low	Low	Low
Ohno et al, 2004 [180]	Unclear	Low	Low	Unclear	Low	Low	Low	Low
Koizumi et al, 2003 [181]	High	Low	Low	Low	High	High	Low	Low
Sekine et al, 2003 [114]	High	Low	High	High	Unclear	Low	Low	Low
Bolliger et al, 2002 [182]	Unclear	Low	Low	Unclear	Low	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Foroulis et al, 2002 [183]	Unclear	Low	Low	Unclear	High	Low	Low	Low
Wu et al, 2002 [108]	Low	Low	Low	Low	High#	Low	Low	Low
Edwards et al, 2001 [184]	Low	Low	Low	Unclear	Low	Low	Low	Low
Beccaria et al, 2001[185]	Low	Low	Low	Low	High#	Low	Low	Low
Young et al, 1999 [186]	High	Low	Low	Unclear	High	High	Low	Low
Furrer et al, 1997 [187]	High	Low	Low	Unclear	High	High	Low	Low
Giordano et al, 1997 [188]	Unclear	Low	High	Unclear	Low	Unclear	Low	Low
Leone et al, 1997 [189]	Unclear	Low	High	Low	High	Unclear	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Larsen et al, 1997[130]	Low	Low	Low	Low	Low	Low	Low	Low
Weiner et al, 1997 [190]	Unclear	Low	Low	Unclear	High	Low	Low	Low
Bolliger et al, 1996 [191]	Low	Low	Low	Low	High	High	Low	Low
Gaissert et al, 1996 [192]	High	Low	High	High	High	Unclear	Low	Low
Kikuchi et al, 1996 [117]	Unclear	Low	High	Unclear	High	Low	Low	Low
Imaeda et al, 1995 [125]	Unclear	Low	Low	Low	High	Low	Low	Low
Izquierdo et al, 1995 [193]	Unclear	High	High	Low	Low	Low	Low	Low
Zeiher et al, 1995 [115]	Low	Low	High	Unclear	High	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Hosokawa et al, 1995 [194]	Unclear	Low	Low	Unclear	High	Low	Low	Low
Giordano et al, 1995 [195]	Unclear	Low	High	Unclear	High	Low	Low	Low
Bolliger, 1995[196]	Low	Low	Low	Low	High#	Low	Low	Low
Romessis et al, 1995 [197]	Unclear	Low	Low	Low	High	Low	Low	Low
Khargi et al, 1994 [119]	High	Low	Low	Unclear	High	High	Low	Low
Wu et al, 1994 [109]	Low	Low	Low	Low	High#	Low	Low	Low
Cheon et al, 1994 [198]	Unclear	Low	High	Low	High	Low	Low	Low
Hirose et al, 1993 [199]	Unclear	Low	Low	Unclear	High	Unclear	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Omote et al, 1992 [200]	Unclear	Low	Low	Unclear	High	High	Low	Low
Sangalli et al, 1992 [120]	High	Low	Low	High	Low	High	Low	Low
Cangemi et al, 1992 [201]	High	Low	High	Unclear	High	Unclear	Unclear	Low
Cordiner et al, 1991 [202]	High	Low	Low	Unclear	High	High	Low	Low
Koizumi et al, 1991 [203]	High	Low	Unclear	High	High	Low	Low	Low
Ashino et al, 1991 [204]	Unclear	Low	High	Unclear	High	Unclear	Low	Low
Wang, 1991 [205]	High	Low	Low	High	High	Unclear	Low	Low
Mende et al, 1990 [206]	Unclear	Low	Low	Unclear	High	Unclear	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Markos et al, 1989 [207]	Low	Low	Low	Unclear	High	Low	Low	Low
Huang et al, 1989 [208]	Unclear	Low	Low	Low	High	High	Low	Low
Nonoyama et al, 1988 [209]	Low	Low	High	Low	High	High	Low	Low
Yoshikawa, 1988 [210]	Unclear	Low	High	Unclear	High	Low	Low	Low
Nonoyama et al, 1988 [211]	Unclear	Low	Low	Unclear	High	Low	Low	Low
Julius et al, 1987 [212]	Unclear	Low	Low	High	High	High	Low	Low
Veneskoski & Sovijärvi, 1986 [213]	High	Low	High	Unclear	High	Low	Low	Low
Egeblad et al, 1986 [214]	Low	Low	High	Low	High[#]	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Ladurie & Ranson-Bitker, 1986 [215]	High	Low	Low	Unclear	High	High	Low	Low
Veneskoski & Sovijärvi, 1985 [216]	Unclear	Low	Low	Unclear	High	High	Low	Low
Nakahara et al, 1985 [217]	Unclear	Low	Low	Unclear	High	High	Low	Low
Hara, 1985 [218]	Unclear	Low	High	Low	High	Low	Low	Low
Williams et al, 1984 [219]	High	Low	Low	High	High	High	Low	Low
Bins et al, 1984 [220]	High	Low	Low	Unclear	High	High	Low	Low
Bria et al, 1983 [116]	High	Low	High	High	High	High	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Ali et al, 1983 [221]	High	Low	High	High	High	High	High	Low
Nakahara et al, 1983 [222]	Unclear	Low	Low	Unclear	High	Low	Low	Low
Loddenkemper et al, 1983 [223]	Low	Low	Low	High	Low	Low	Low	Low
Nakahara et al, 1982 [224]	High	Low	Low	Low	High	Low	Low	Low
Konishi, 1982 [225]	Unclear	Low	High	High	High	Low	Low	Low
Ali et al, 1980 [226]	High	Low	High	Unclear	High	Unclear	Low	Low
Taube & Konietzko, 1980[227]	Low	Low	Low	Low	High[#]	Low	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Taube & Konietzko, 1980 [228]	Low	Low	Low	Unclear	High	Low	Low	Low
Walkup et al, 1980 [229]	Unclear	Low	High	Unclear	High	Unclear	Low	Low
Cooper et al, 1980 [230]	Low	High	High	Low	High	High	Low	Low
Wernly et al, 1980 [231]	Unclear	Low	High	Unclear	Low	Unclear	Low	Low
Nicoli et al, 1979 [232]	Unclear	Unclear	Low	High	High	High	Low	Low
Lipscomb & Pride, 1977 [127]	High	Low	Low	High	High	Unclear	Low	Low
Malm et al, 1977 [233]	Unclear	Low	Low	Unclear	High	Unclear	Low	Low

Author, year	Risk of bias					Applicability		
	Participant selection	Predictors	Outcome	Sample size and flow	Analysis	Participant selection	Predictors	Outcome
Juhl & Frost, 1975 [102]	Unclear	Low	High	High	High	Low	Low	Low
Wever et al, 1975 [234]	High	Low	High	Low	High	Low	Low	Low
Kristersson et al, 1973 [235]	High	Low	Low	High	High	Low	Low	Low
Kristersson et al, 1972 [236]	Unclear	Low	High	High	High	Low	Low	Low

Notes: # Denotes studies that reported data in sufficient detail to enable data extraction and appropriate analysis despite reported statistics not being low risk of bias.

Table 3 Study characteristics of the 17 studies with low risk of bias overall by year of publication

First author, year Country, language	Population	Procedures	Prediction technique	Time to postop lung function	Sample analysed (total)	Outcomes	Analysis
Fourdrain, 2017 [110] France, English	N= 23 83% male Mean age 61	Lobectomy & Pneumonectomy	Segment counting Subsegment counting Perfusion scintigraphy Ventilation scintigraphy CT partial density & volume	3 months	23 (37)	FEV1	Mean difference Correlation
Yabuuchi, 2016 [105] Japan, English	N=49 53% male Mean age 67	Lobectomy	Subsegment counting CT volumetry CT volume & density	6-7 months	49 (49)	FEV1 Change only	Mean difference Correlation
Ohno, 2015 [106] Japan, English	N=60 65% male Mean age 68	Segmentectomy, lobectomy & bilobectomy	Segment counting Perfusion scintigraphy CT volume & density MRI perfusion	6 months	60 (60)	FEV1 % only	Mean difference Correlation
Chae, 2013 [129] Korea, English	N=51 75% male Mean age 64	Lobectomy & pneumonectomy	Perfusion scintigraphy CT perfusion	6 months	51 (67)	FEV1	Mean difference Correlation
Yanagita, 2013 [147]	N=30 63% male	Lobectomy &	SPECT	6 months	30 (34)	FEV1	Mean difference

First author, year Country, language	Population	Procedures	Prediction technique	Time to postop lung function	Sample analysed (total)	Outcomes	Analysis
Japan, English	Mean age 70	pneumonectomy	CT ventilation				Correlation
Yamashita, 2010 [163] Canada, English	N=14 60% male Mean age 65	Lobectomy & pneumonectomy	Perfusion scintigraphy CT perfusion	3 months	14 (25)	FEV1	Mean difference Correlation
Yoshimoto, 2009 [107] Japan, English	N= 37 59% male Mean age 65	Lobectomy	Segment counting CT volume & density SPECT-CT	3 months	37 (37)	FEV1	Mean difference Correlation
Ohno, 2007 [168] Japan, English	N=60 50% male Mean age 70	Lobectomy & pneumonectomy	Perfusion scintigraphy Ventilation scintigraphy SPECT SPECT-CT	6 months	60 (60)	FEV1 % only	Mean difference Correlation
Sudoh, 2006 [174] Japan, English	N=22 86% male Mean age 71	Lobectomy & segmentectomy	Subsegment counting SPECT-CT	3-4 months	22 (22)	FEV1	Correlation
Wang, 2006 [173] Canada, English	N=28 61% male Mean age 65	Segmentectomy, lobectomy & pneumonectomy	Segment counting	12 months	28 (57)	TLCO % only	Mean difference

First author, year Country, language	Population	Procedures	Prediction technique	Time to postop lung function	Sample analysed (total)	Outcomes	Analysis
Wu, 2002 [108] Taiwan, English	N=34 80% male Mean age 67	Lobectomy & pneumonectomy	Perfusion scintigraphy CT volume & density	3 months	34(52)	FEV1	Mean difference Correlation
Beccaria, 2001 [185] Italy, English	N=62 82% male Mean age 62	Lobectomy & pneumonectomy	Segment counting	6 months	62 (93)	FEV1	Correlation
Larsen, 1997 [130] Denmark, English	N=23 65% male Mean age 67	Lobectomy & pneumonectomy	Perfusion scintigraphy	6 months	23 (41)	FEV1	Mean difference
Bolliger, 1995 [196] Switzerland, English	N= 22 68% male Mean age 63	Sublobar resection, lobectomy & pneumonectomy	Perfusion scintigraphy	6 months	22 (25)	FEV1 & TLCO	Correlation
Wu, 1994 [109] China, English	N= 38 87% male Mean age 68	Lobectomy & pneumonectomy	CT volume & density	3 months	38 (38)	FEV1	Mean difference Correlation
Egeblad, 1986 [214] Denmark, English	N=30 71% male	Lobectomy &	Segment counting	6 months	30 (30)	FEV1	Correlation

First author, year Country, language	Population	Procedures	Prediction technique	Time to postop lung function	Sample analysed (total)	Outcomes	Analysis
	Mean age 61	pneumonectomy					
Taube, 1980 [228] Germany, German	N=27 100% male Mean age 53	Pneumonectomy	Perfusion scintigraphy	6 months	27 (29)	FEV1	Correlation

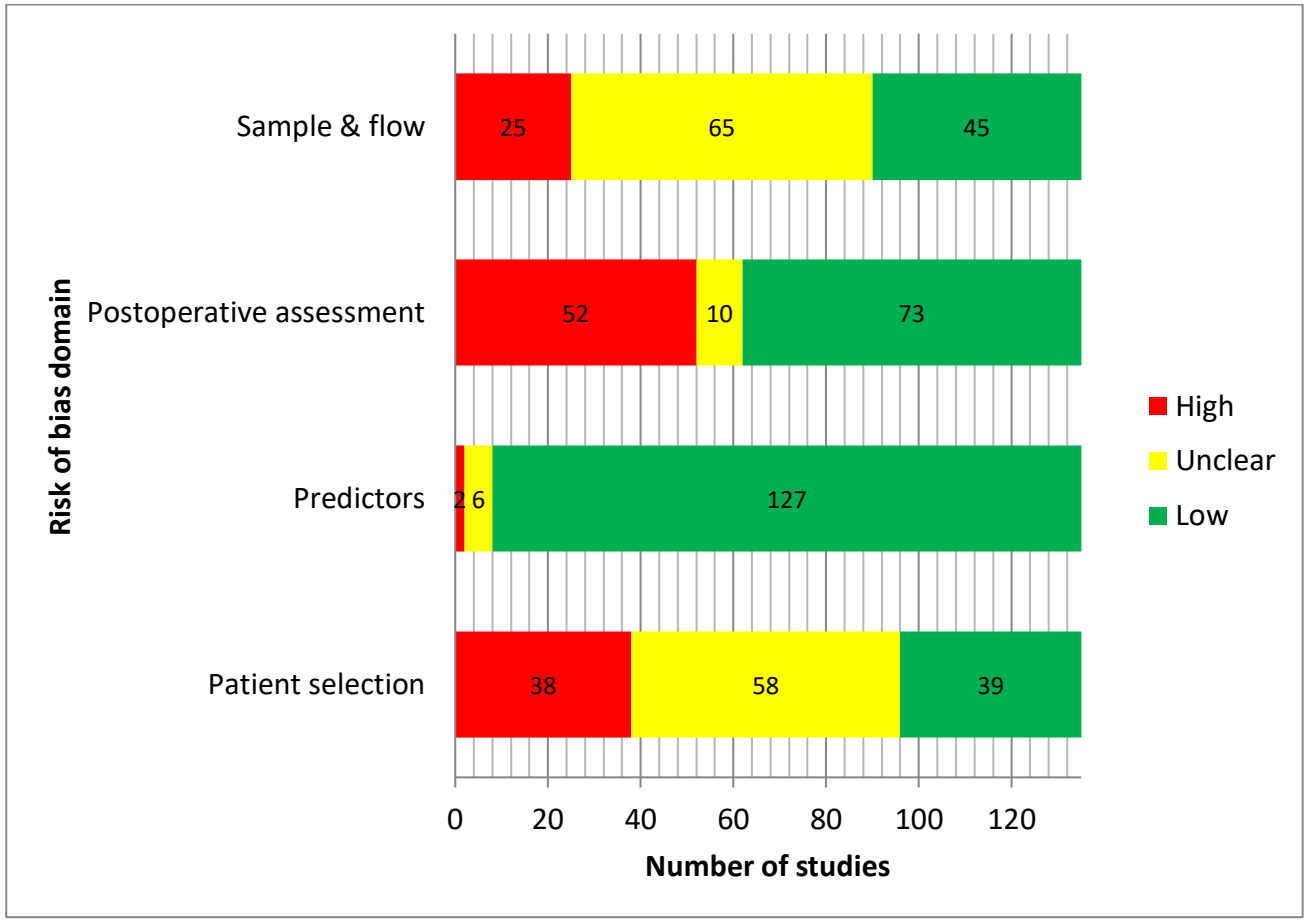


Figure 15 Risk of bias assessment for all eligible studies

2.3.3 Quantitative synthesis: Meta-analysis of mean difference

It was possible to perform meta-analysis for studies predicting FEV1; their results are presented in Table 4, corresponding Forest plots are displayed in Figure 16 to Figure 21. Prediction accuracy was measured by the difference between the measured and predicted postoperative FEV1, a negative difference indicated that predictions overestimated postoperative function and a positive difference indicated that predictions were underestimates. CT-VD was shown to be the most accurate technique with a mean difference of 71ml, 95%CI 38 - 103; all of the predictions underestimated postoperative FEV1. The minimum clinically important difference in FEV1 after surgery is not known but this has been established as 100ml in the context of airways disease; as such a difference in FEV1 in the measured versus the predicted should not be noticeable clinically if it is less than 100ml.[237] SPECT, CT ventilation, and CT volumetry may fulfill this criterion but there was only one study that reported each of these techniques. Heterogeneity was low for CT-VD and CT perfusion, moderate for SPECT-CT, segment counting and sub-segment counting, but high for perfusion scintigraphy using the descriptors as suggested by biostatisticians.[238]

2.3.4 Quantitative synthesis: Meta-analysis of standard deviation

Meta-analysis of precision of a result is a more recently developed technique and it can highlight important differences in the way an intervention of interest performs across a range of individuals as opposed to the overall result in a population. A clinically useful test needs to predict lung function at an individual level because treatment decisions are made for individual patients, thus precision may in fact be considered more important than accuracy because a correction factor can be applied to improve the performance of a test that is highly precise but consistently underestimates or overestimates

postoperative FEV1 by a known amount. Meta-analysis of precision was only possible for four prediction techniques because of missing data on variability of the mean difference in the full papers, results are displayed in Table 5. CT-VD was found to be the most precise FEV1 prediction method with an SD of 207ml, Cochran's Q did not provide evidence of heterogeneity in any of the techniques. To illustrate the clinical implications of this a near perfect test can be considered for comparison; the properties of the normal distribution associated with the differences between measured and predicted values would have a mean difference of 0ml, and 99.7% of the area under the curve (three SDs) could be used to ensure an accurate prediction for almost all patients. A predicted FEV1 within 100-150ml of the measured postoperative value, as is accepted in spirometry repeatability standards, or within 200ml, as is accepted for reversibility standards, would have a standard deviation of between 17-34ml, as such all methods of prediction showed much lower precision than would be desirable for clinical use.[60,239]

2.3.5 Qualitative synthesis

Three studies of FEV1 prediction could not be meta-analysed but did describe comparisons of the accuracy of different prediction techniques (Table 6). Yabuuchi et al reported change in FEV1 rather than absolute values, they found CT-VD to outperform sub-segment counting and CT volumetry.[105] Ohno et al 2015 reported FEV1 percent of expected values rather than absolute values; they reported CT-VD and perfusion MRI (with and without contrast) to be comparable to each other but superior to both segment counting and perfusion scintigraphy. [106] Ohno et al 2007 also reported FEV1 percent of expected values; they compared ventilation scintigraphy, perfusion scintigraphy, SPECT, and SPECT-CT. They found the latter two methods outperformed the former two methods.[168]

Only two studies with low risk of bias, and 23 of all eligible studies predicted TLCO. One of these papers reported segment counting and the other perfusion scintigraphy meaning quantitative synthesis was not possible.[173,196] The mean difference was 2 percentage points (standard error 1·5) for segment counting and mean difference 11 percentage points (standard error 1·7) for perfusion scintigraphy.

Table 4 Meta-analysis results for prediction of postoperative FEV1 - Mean difference

Prediction technique	**Studies**	**Mean difference** (measured – predicted FEV1)	**95% Confidence interval**	I^2
CT – volume & density	3 (n=109)	71ml	38 to 103	0%
Perfusion scintigraphy	7 (n=194)	101ml	-11 to 214	88%
SPECT-CT	2 (n=59)	107ml	-10 to 225	66%
CT – perfusion	2 (n=65)	143ml	59 to 228	0%
Segment counting	4 (n=145)	192ml	88 to 295	74%
Subsegment counting	3 (n=82)	233ml	135 to 332	65%
SPECT	*1 (n=30)*	*10ml*	*-114 to 134*	*Single study*
CT – ventilation	*1 (n=30)*	*70ml*	*-24 to 164*	*Single study*
CT – volumetry	*1 (n=30)*	*90ml*	*-21 to 201*	*Single study*
CT – volume & partial density	*1 (n=23)*	*266ml*	*172 to 360*	*Single study*
Ventilation scintigraphy	*1 (n=23)*	*312ml*	*188 to 435*	*Single study*

Table 5 Meta-analysis results of prediction of postoperative FEV1 - Standard deviation

Prediction technique	**Studies**	**Standard deviation**	**Cochran's Q test of heterogeneity (p value)**
CT – volume & density	2 (n=75)	207ml	1.569 (0.2103)
Subsegment counting	2 (n=60)	274ml	0.047 (0.8279)
Perfusion scintigraphy	5 (n=109)	285ml	3.690 (0.4495)
Segment counting	4 (n=145)	331ml	3.361 (0.3392)
CT – volume & partial density	*1 (n=23)*	*229ml*	*Single study*
SPECT-CT	*1 (n=37)*	*249ml*	*Single study*
Ventilation scintigraphy	*1 (n=23)*	*303ml*	*Single study*
CT – perfusion	*1 (n=14)*	*329ml*	*Single study*

Note: This meta-analysis produces a combined standard deviation of the mean difference based on the standard deviations quoted in included studies. It should be noted this is mathematically distinct from the standard error of the mean for the reported meta-analysis mean difference. Null hypothesis for Cochran's Q test is homogeneity.

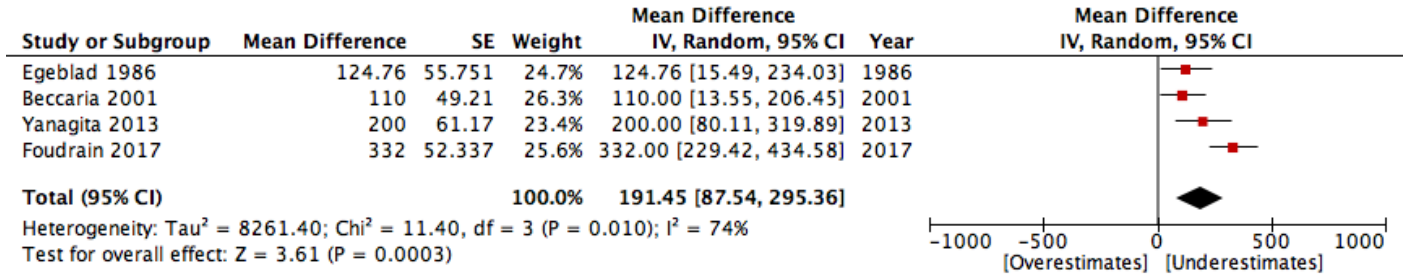


Figure 16 Forest plot for mean difference in predicted versus measured FEV1 for prediction using segment counting

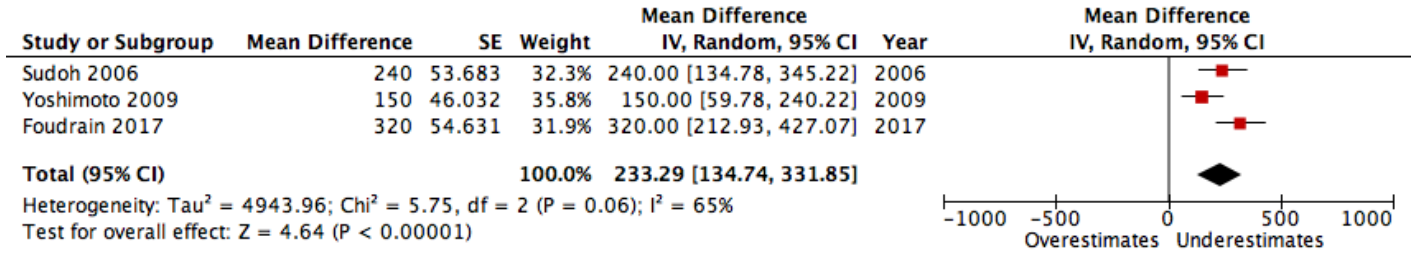


Figure 17 Forest plot for mean difference in predicted versus measured FEV1 for prediction using subsegment counting

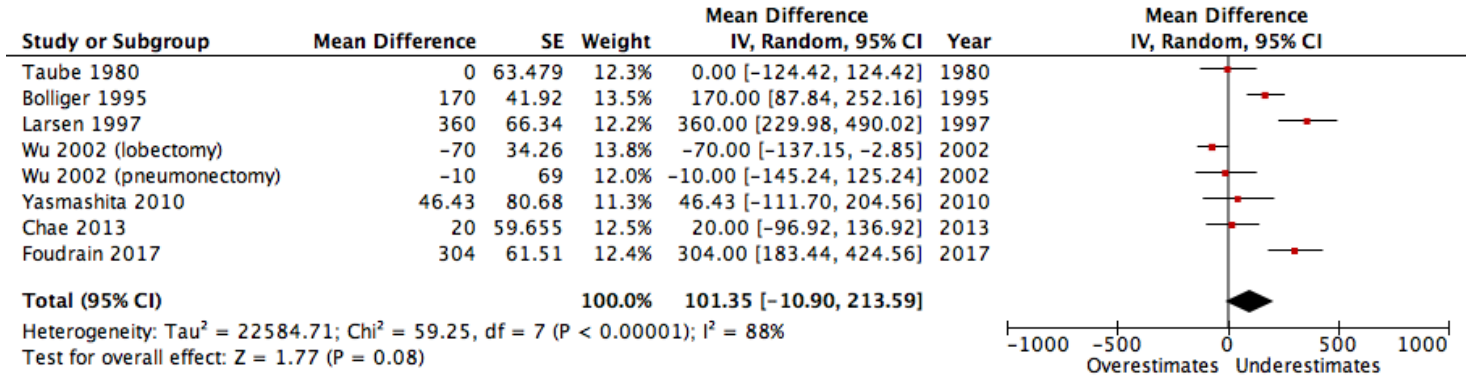


Figure 18 Forest plot for mean difference in predicted versus measured FEV1 for prediction using perfusion scintigraphy

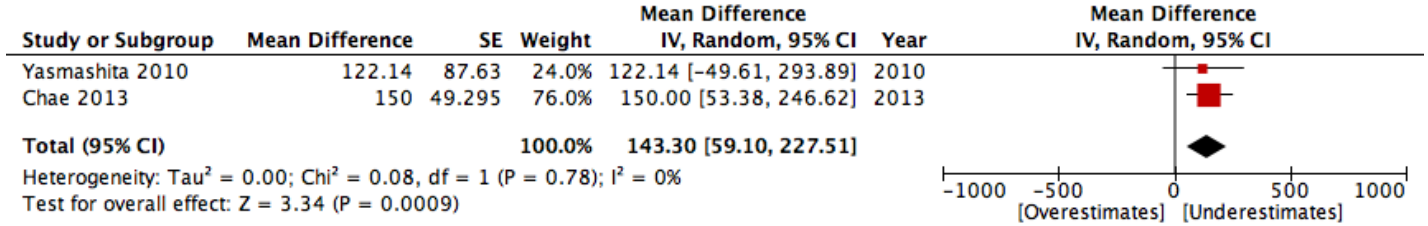


Figure 19 Forest plot for mean difference in predicted versus measured FEV1 for prediction using CT perfusion

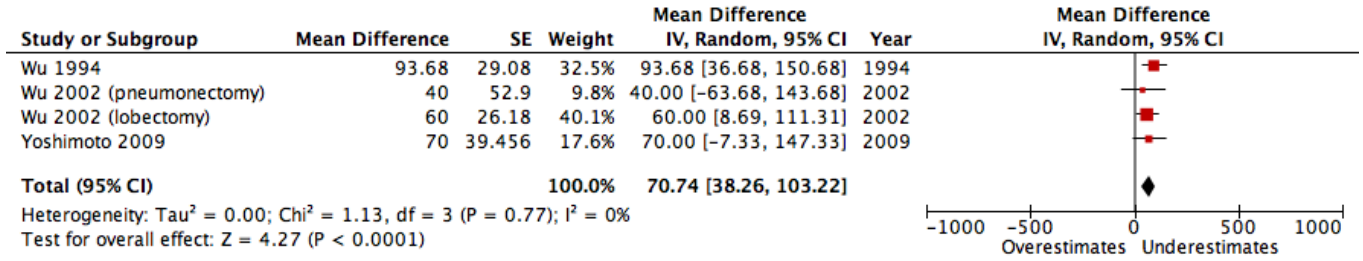


Figure 20 Forest plot for mean difference in predicted versus measured FEV1 for prediction using CT density and volume

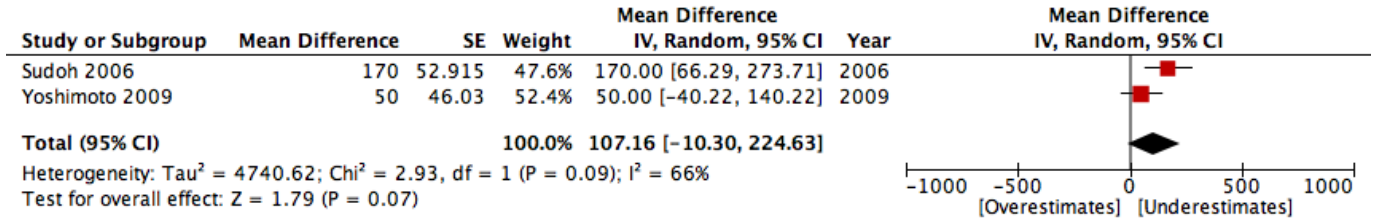


Figure 21 Forest plot for mean difference in predicted versus measured FEV1 for prediction using SPECT-CT

Table 6 Qualitative information for studies that could not be meta-analysed

Study	**Outcome**	**Techniques reported by smallest mean difference**	**Author conclusion**
Yabuuchi, 2016[105]	Change in FEV1	1. CT volumetry & densitometry 2. Subsegment counting 3. CT volumetry	CT volumetry & densitometry more strongly correlated with postopative FEV1 than subsegment counting or CT volumetry.
Ohno, 2015[106]	FEV1 % expected	1. Plain MRI 2. Dynamic contrast MRI 3. CT volumetry & densitometry 4. Segment counting 5. Perfusion scintigraphy	Plain MRI, dynamic contrast MRI and CT volumetry & densitometry equally useful. These are more accurate than segment counting and perfusion scintigraphy.
Ohno, 2007[168]	FEV1 % expected	1. SPECT-CT 2. SPECT 3. Ventilation scintigraphy 4. Perfusion scintigraphy	SPECT-CT and SPECT more accurate and reproducible than ventilation or perfusion scintigraphy

2.4 Discussion

The question of predicting postoperative lung function has persisted for over 40 years without resolution; a median number of three papers per year have been published on this topic from 1972 to 2017. This work is the first systematic review and meta-analysis to consider how best to predict postoperative lung function as part of perioperative risk assessment. Results have shown that prediction of FEV1 after lung resection is most accurate and precise when using CT-VD measures; however the precision of all existing methods to predict postoperative FEV1 is low. If CT-VD is to be used to predict FEV1 and the precision can be improved there are opportunities to integrate this technique into the normal clinical pathway of risk assessment prior to lung resection. Prediction of TLCO has a limited evidence base but seems to be more accurate using segment counting than perfusion scintigraphy.

2.4.1 Strengths and limitations

A key strength is that the results should be internationally applicable due to the wide range of countries that articles originated from, 34 were from Japan and 28 were from other countries outside Western Europe and North America. A significant number of articles that met eligibility criteria originated outside of Western Europe or the United States of America (62 articles of 135 eligible) and were written in languages other than English (31 of 135); Japan was noted to be particularly active in this area of research.

The exact CT settings used in analysis, such as slice thickness and reconstruction filter, varied and it would be useful to assess how these affect results to give a consensus about the optimal settings for CT analysis. CT density masks to define functional lung

tissue varied between -1024 and -910 for the lower limit -650 and -500 for the upper limit. [105–108,110] However, statistical advice (JH, February 2018) was still to combine the results. The range of clinical scenarios was also broad meaning variation in operative procedure; time to follow up lung function, and precise details of prediction technique could all contribute to heterogeneity. However, statistical heterogeneity was only high for perfusion scintigraphy in predicting FEV1. This could be because the clinical heterogeneity is consistent across studies and manifests as a reduction in test precision but there is an additional factor affecting heterogeneity of results for perfusion scintigraphy, such as a large inter-operator difference in analysis.

The work was often limited by insufficient information about study methodology being reported to enable risk of bias assessment resulting in bias being considered 'unclear' in many cases. These studies could in fact have been conducted thoroughly and if reporting had included more information the results could then have been used in meta-analysis; it should be concerning to the surgical research community that only 13% of studies that met eligibility criteria were judged as being at low risk of bias. It has been recognised that there is room for improvement in the quality of surgical research, which the research community is working to address.[240] Five studies could not be retrieved in full but this is a small proportion of the total studies considered for full paper assessment (2%).

2.4.2 Outcome reporting

Some papers did not report the primary outcome or sufficient data to enable independent calculation of this; as such additional patient data could not be included. Papers that did not report mean difference sometimes reported only correlation

statistics or reported comparisons between predicted and measured values such as Mann Whitney U tests; consequently the authors concluded that techniques with a high correlation with measured postoperative lung function were good predictors and that predictions that were not significantly different from the measured value were good predictors.[117,193,194] Reports also inferred that the magnitude of an r value could enable comparison of the precision of predictions, which is not the case.[136,166,235] All of these alternative statistics do not account for clinical significance and do not aid the clinician in appreciating how far away a prediction may be from the postoperative value.

Reviews are generally subject to limitations of reporting bias, it was not possible to assess this using funnel plots due to the low number of full papers included in meta-analysis.

2.4.3 Current risk assessment for surgery

Patients undergo CT scanning at least twice prior to resection in the form of the initial diagnostic CT and subsequent staging Positron Emission Tomography (PET) CT; utilising existing imaging without further appointments and concomitant delays makes CT an appealing technique for predicting postoperative lung function. Additionally, CT densitometry has been shown to be superior to spirometry in predicting postoperative pulmonary complications, including prolonged air leak, after pulmonary resection and identification of patients at increased risk of these complications could facilitate targeted interventions or adjustments to surgical technique as preventative measures.[241,242] CT density change also relates to many clinically relevant outcomes in emphysema, such as mortality, exacerbation risk, and quality of life.[243,244] Whilst the purpose of density measurement in emphysema may be different, such as assessing

response to therapy, supportive results for the technology in a related disease area add weight to this being considered viable in cancer too.[245] A combined CT based risk assessment of predicting postoperative pulmonary function and the risk of postoperative pulmonary complications would be an attractive and relevant tool for clinicians; lung CT analysis could potentially be combined with analysis of body composition outside the lungs, such as skeletal muscle or body mass index, for use as a global risk score.[246,247]

2.4.4 Future research recommendations

Future research in this field could focus on direct comparison of different prediction techniques to predict TLCO, as this parameter is a significant part of the operative decision making process but has little evidence base to demonstrate that predictions are accurate. Changes in TLCO after surgery are expected because removal of lung tissue reduces the lung surface area and the use of TLCO in decision-making is reasonable, as it has been shown to relate to perioperative mortality.[91] TLCO has also been shown to be associated with exercise capacity in patients with COPD and postoperative cancer specific quality of life is associated with exercise capacity so preservation of TLCO is likely to be important to patients' quality of life, however the associations are indirect and surrogate measures.[248,249] Further validation of the utility of postoperative FEV1 and TLCO prediction could include assessments of how these relate directly to patient reported outcome measures (PROMs) such as quality of life, dyspnoea, ability to live independently, and performance of preoperative activities unhindered. Postoperative quality of life has been shown to be equivalent in patients with impaired preoperative lung function compared to those without impairment, making the integration of PROMs

an important complementary part of risk assessment when counseling patients about treatment options.[250]

Finally the optimal CT protocol for obtaining reproducible predictions could be determined by direct comparison utilising different CT segmentation thresholds to define functional lung tissue within the same patient group. Different CT segmentation thresholds, slice thicknesses and filters (reconstruction kernels) have been used for densitometry and an international consensus is lacking.[244] The default slice thickness in commercial software and some academic centres has become 1mm, which enables 3D volume reconstruction.[251,252] Standard lung filters have been used as well as softer and harder filters, values obtained using different filters are not equivalent but it is not known whether one has advantages over the others clinically.[253]

In conclusion, using CT-VD is the most accurate and precise way to predict postoperative FEV1 but all prediction methods were imprecise. There is limited evidence about predicting postoperative TLCO but segment counting appears to outperform perfusion scintigraphy. The common practice of using segment counting to guide treatment decisions and patient counseling may warrant changing in light of this finding. Changes could include either implementing guidelines that the prediction technique to be used clinically should be the most accurate and precise method – CT-VD; alternatively risk prediction could move firmly away from assessing lung function as a key indicator and towards different global assessments of patient fitness. These findings are of particular relevance to the future guidelines regarding assessment of fitness for lung cancer resection; the most recent British guidelines having been archived in 2017.[17]

CHAPTER 3: ASSESSMENT OF SOFTWARE AND CLINICAL APPLICATION OF REGIONAL VENTILATION IN PREDICTING POSTOPERATIVE LUNG FUNCTION AFTER LUNG CANCER RESECTION

3.1 Introduction

3.1.1 Current prediction of postoperative lung function

Thoracic surgeons commonly use segment counting to estimate postoperative lung function for patients due to undergo resection of an early stage lung cancer. The technique of segment counting is simple; it is performed using the following formula for FEV1 or TLCO:

Predicted postoperative value = preoperative value x ((19 - obstructed segments – segments to be resected)/19-obstructed segments)

Using this formula assumes the function of lung tissue is equal across all segments of the lung; ventilation and perfusion are in fact distributed heterogeneously throughout the lung particularly in those affected by emphysema, which frequently coexists with lung cancer. [254–259]

The systematic review in Chapter 2 has shown CT volume and density measurement on inspiratory CT scans to be the most accurate and precise way to predict postoperative lung function and the structural information provided by CT can identify heterogeneous lung destruction. All methods that have been reported were not as accurate as would be

desirable, which has clinical implications both in the form of unexpectedly poor lung function after resection or patients being considered unfit for lung resection. Therefore refining the prediction technique may improve it to clinically acceptable levels. This study explores one such refinement of technique – using deltaSVg.

3.1.2 Specific gas volume

CT volume and density measurement on inspiratory scans takes account of lung structure at one point in the respiratory cycle but not of how the lung structure changes between inspiration and expiration. Recall from Section 1.3.2 that measurement of density and volume from CT scans can provide quantitative information about the changes in air volume with reference to lung tissue as deltaSVg. To reiterate, the SV of the whole lung can be estimated with the following formula:

$$SV_{tissue\ and\ gas} = 1000/(HU+1000) \quad [68]$$

The rescale intercept forms the numerical part of the above formula and is assigned by the CT data but it may be assigned to -1024 rather than -1000 depending on the CT scanner. This should be checked and the appropriate value for the scanner used in the formula. SVg can then be calculated using the formula to calculate the SV of the whole lung and the SV of lung tissue provided by histological study:

$$SVg = SV\ (tissue\ and\ gas) - SV_{tissue} \quad [68]$$

$$SVg = (1000/(HU+1000)) - (1/1.065) \quad [68]$$

These calculations are performed on a CT at a single point in the respiratory cycle; if two sets of CT images are obtained at different phases of the respiratory cycle, such as end

inspiration and end expiration, the deltaSVg can then be calculated and this is a measure of change in lung expansion between expiration and inspiration:

$$\text{DeltaSVg} = \text{inspiratory SVg} - \text{expiratory SVg} \quad [68]$$

DeltaSVg is thus a way of measuring the volume of air within regions of the lung per gram of tissue is in the same portion of lung.

3.1.3 Hypotheses

The aims of this study were to assess the feasibility and reproducibility of measuring deltaSVg, and assess the accuracy of using it to predict postoperative lung function in patients undergoing lung cancer resection. The specific hypotheses were:

- Calculating preoperative deltaSVg at a lobar level would be feasible in the local patient population
- Open access software could yield reproducible results
- Data from a small sample would be obtained and provide data to power a larger definitive study

3.2 Methods

3.2.1 Study design

A prospective observational study of consecutive patients was conducted at Heartlands Hospital, now part of University Hospitals Birmingham NHS Foundation Trust. Patients who were over 18 years of age, had mental capacity, and were expected to undergo anatomical resection for lung cancer were eligible to participate. The patient information sheet and consent form are included in Appendix 2 and Appendix 3.

Patients were invited to participate at outpatient clinics prior to surgery. Baseline data were collected after patients gave written informed consent; these data included demographics and pulmonary function. Patients then underwent a non-contrast CT scan at held inspiration and held expiration at a radiology appointment scheduled before surgery. Additional scans had to be performed because the routine clinical scans are performed using intravenous contrast, which alters the lung density of lung tissue. Operative data and any complications of surgical treatment were recorded at four to six weeks after surgery. Follow up assessments of pulmonary function were repeated at three to six months after surgery. Figure 22 shows an outline of the study procedure.

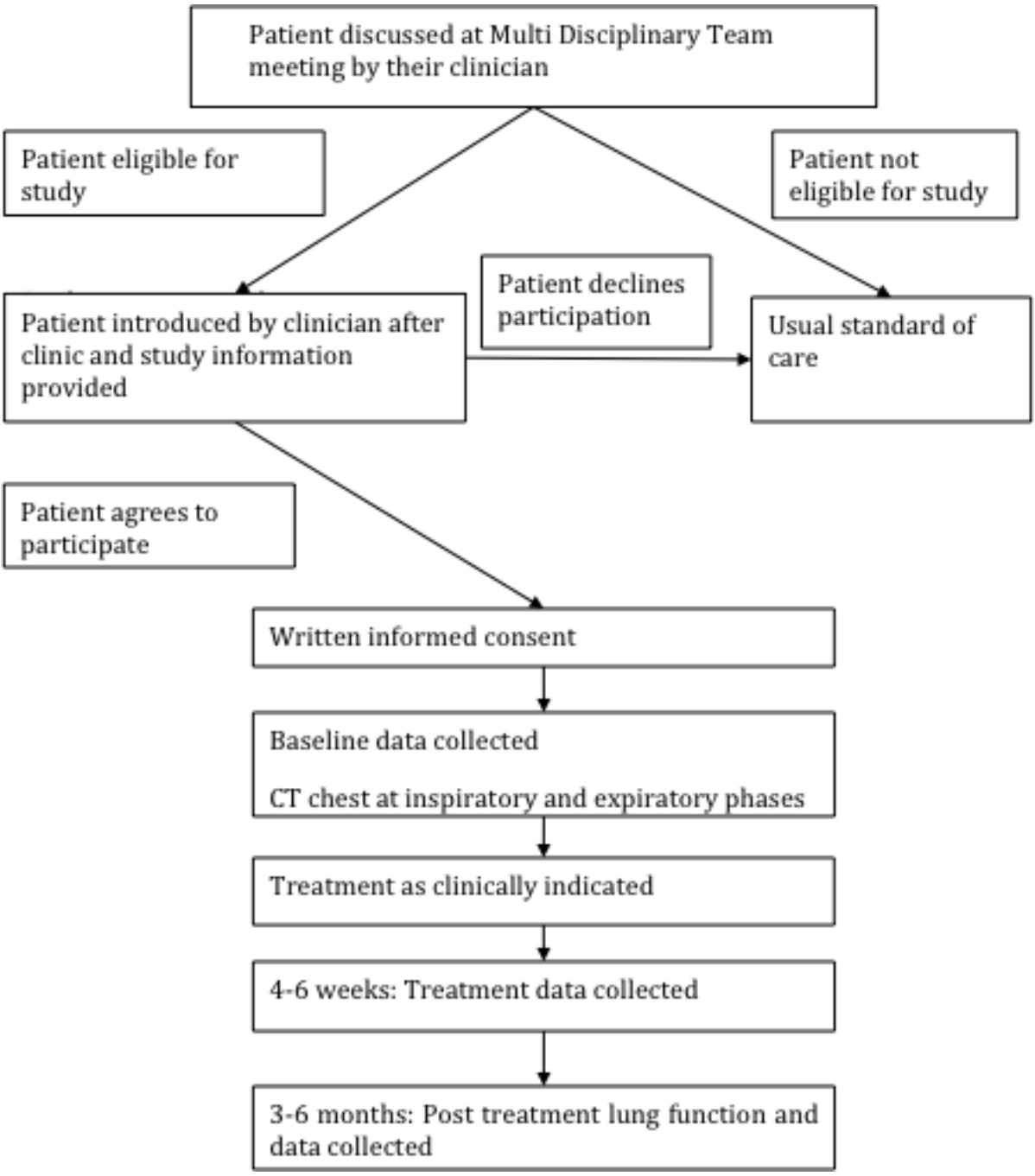


Figure 22 Study procedure flow diagram

3.2.2 Funding & regulatory approvals

The required documentation for ethical review via the Integrated Research Application System was completed under supervision and the Research Ethics Committee (REC) meeting for the study was attended. The study was adopted onto the National Institute for Health Research Portfolio of studies (REC reference 15/EM/0446) and registered at ClinicalTrials.gov (identifier NCT02879773). The study was awarded funding from the British Lung Foundation in the form of a Pump Priming Research Grant; the funding application was prepared under supervision.

3.2.3 CT acquisition

CT images were obtained using a single Aquilion ONE scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) for all patients. CT scanner settings were as follows: voltage 120kVp, current 110mA, rotation time 500ms, matrix 512x512, slice thickness 1mm. The slice thickness of 1mm was used to enable assessment of small lung structures and to aid comparison between this study and other studies of CT image processing, including nodule detection and tumour subtyping.[260,261] Images were reconstructed with an FC51 convolution kernel; the FC51 filter is a standard smooth lung algorithm that is recommended for volume measurement by the manufacturers of the scanner.[262] Scans were obtained without contrast at end inspiration and end expiration with patients in a supine position; automated voice instructions were played to the patients by the scanner to prompt them to perform the respiratory maneuvers. The Medical Physics Expert report determined a radiation dose of 10mSv per participant, equivalent to 5 years background radiation in the United Kingdom. The CT DICOM files were downloaded from the radiology department software (VitreaCore, Toshiba Medical Systems) onto a hospital computer.

3.2.4 Measures of feasibility

The National Institute for Health Research (NIHR) example outcomes for a feasibility study that are relevant to an observational study were planned for collection in this study. These include:[263]

- Number of eligible patients
- Recruitment rate
- Time needed to analyse data
- Follow up rate
- Standard deviation of the outcome measure

It was also important to test the practicalities of doing the CT analysis and the acceptability of the CT to patients.

3.2.5 Measures of reproducibility

Intra-observer and inter-observer variability were planned for assessment using the intra class correlation coefficient (ICC) as a measure of agreement whereby a coefficient of 0 indicates no agreement and 1 complete agreement. Two raters were used to analyse scans for all patients and this study included a sample of the surgical population, therefore a two-way random model was needed and this was used to analyse the absolute agreement for a single measurement (either the volume or density of different regions of the lung). The mean difference and Bland Altman plots with calculation of limits of agreement (LOA) were planned to quantify the size of any disagreement.

3.2.6 Statistical plan for sample data

A sample size of 40 has been reported to be sufficient for a pilot study to establish variance in the parameter of interest; the recruitment target was thus set at 44 patients to allow for a dropout rate of 10%.[264,265] The SVg of each lung lobe was defined using the average density of each lobe in the formulae stated in Section 3.1.2. Prediction of the postoperative FEV1 and TLCO was performed using the following formula:

Postoperative value = preoperative value x proportion of lung tissue remaining x (deltaSVg whole lung/deltaSVg tissue removed)

The proportion of lung tissue remaining was derived from lobar volumes on inspiratory scans. The agreement between the predicted and the measured postoperative lung function (FEV1 and TLCO) was examined using Bland Altman plots of the mean difference and LOA defined as follows:

LOA = mean observed difference ± 1.96 × SD of observed differences [266]

Statistical analysis was performed using SPSS version 26 (IBM Corp.) and RStudio version 1.1.463 (The R Foundation for Statistical Computing).

3.2.7 CT analysis software

Two types of software were used to analyse CT data; one was open access and a commercial company provided the other. Testing two sources was considered useful to establish if a freely available software could provide results to develop research hypotheses, which could then be transferred into clinical practice using approved algorithms provided by commercial software if the hypotheses could be clinically validated.

The Chest Imaging Platform (CIP) extension of 3D Slicer is an open source software which is freely available online.[267] This was developed as a tool for physicians and researchers to quantitatively analyse lung tissue, the developers anticipated the study of COPD in particular at the inception of the project. This unregulated availability means that, although international researchers could perform analyses to test novel applications of quantitative CT measures, these results could not be used for clinical purposes. Therefore it would be desirable to establish if any of the results obtained using the free software agree with the commercial results. It is not known how reproducible the lobar segmentation and lung parenchyma analysis would be using the CIP, or whether application of a smoothing filter would affect agreement with the commercial results.

Thirona is a commercial company and they can provide quantitative CT analysis of the lungs; some of their algorithms are validated and European Conformity (CE) certified for clinical use.[268] Their analyses of lung density and fissure integrity, under the label StratX, are currently in clinical use at Heartlands Hospital for patients with severe emphysema being considered for LVR procedures. The scans are uploaded anonymously to a secure server and result files are made visible to the clinician via a dashboard on the upload interface. The scans analysed as part of this study were anonymised and sent via secure file transfer, the results were returned as Excel files.

3.2.8 CT density analysis procedure with the Chest Imaging Platform

The step by step procedure for CT analysis as performed in this study is as follows:

Step 1. Open 3D Slicer

Step 2. Load inspiratory DICOM image series

Step 3. Select 'Interactive lobe segmentation' module from the 'Chest Imaging Platform' module

Step 4. Select '*Lung*' for the Input CT Volume and '*Create new LabelMapVolume*'

Step 5. Set filtering to '*Off*' and select '*Fast*' Label Map Creation

Your screen should look similar to Figure 23.

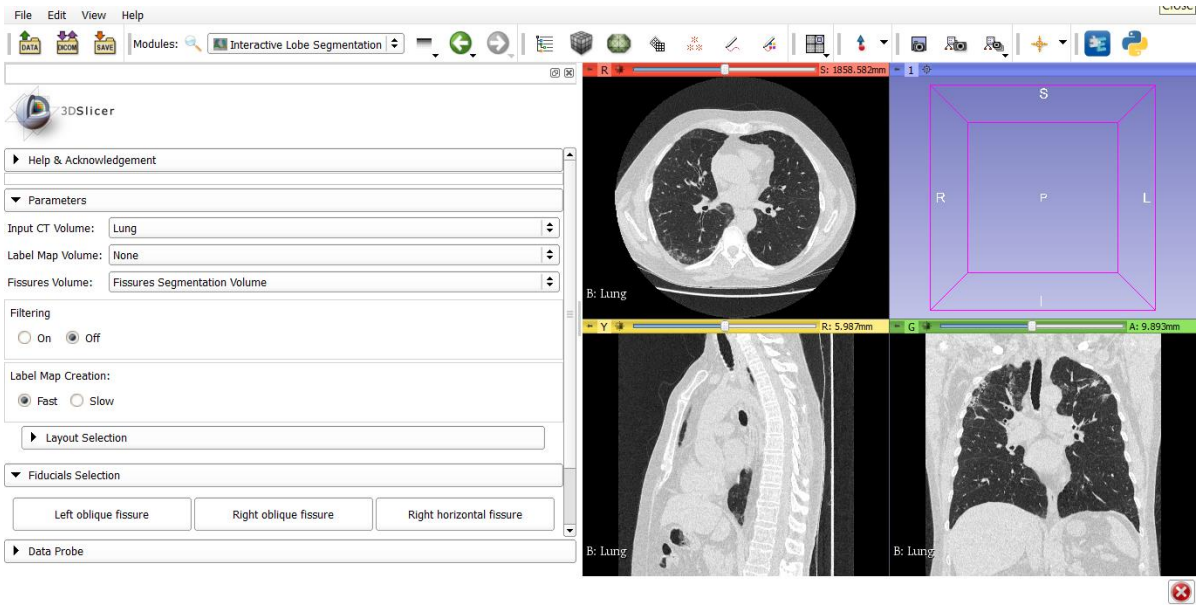


Figure 23 CIP view with scan series loaded

Step 6. View the sagittal (yellow) pane

Step 7. Select a fissure under '*Fiducials Sele*ction'

Step 8. Scroll through the scan and select around 15 – 20 points (fiducials) that lie on the relevant fissure in the sagittal view pane. Fewer points, around 5-15, are more likely to be possible for the right horizontal fissure

Your screen should look similar to Figure 24.

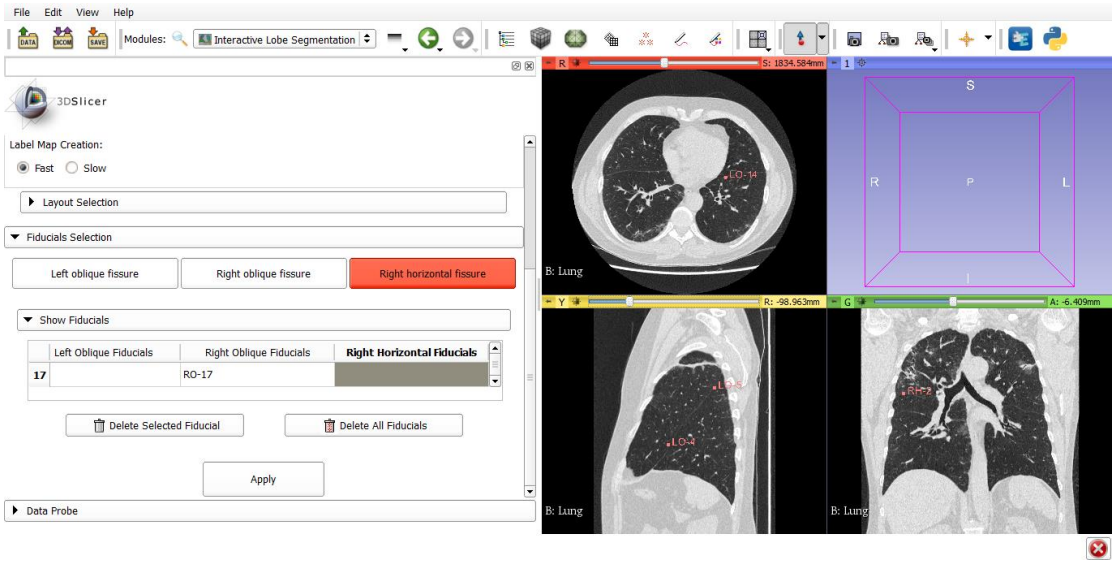


Figure 24 CIP view with fiducials placed on left oblique and right horizontal fissures

Step 9. Repeat Steps 7 and Step 8 so all three fissures have the appropriate number of fiducials selected

Step 10. Click '*Apply*'

Applying the map may take some time and will create a map of where the fissures are, thus dividing the lung into lobes. This is called lobar segmentation. Your CT images should look similar to Figure 25.

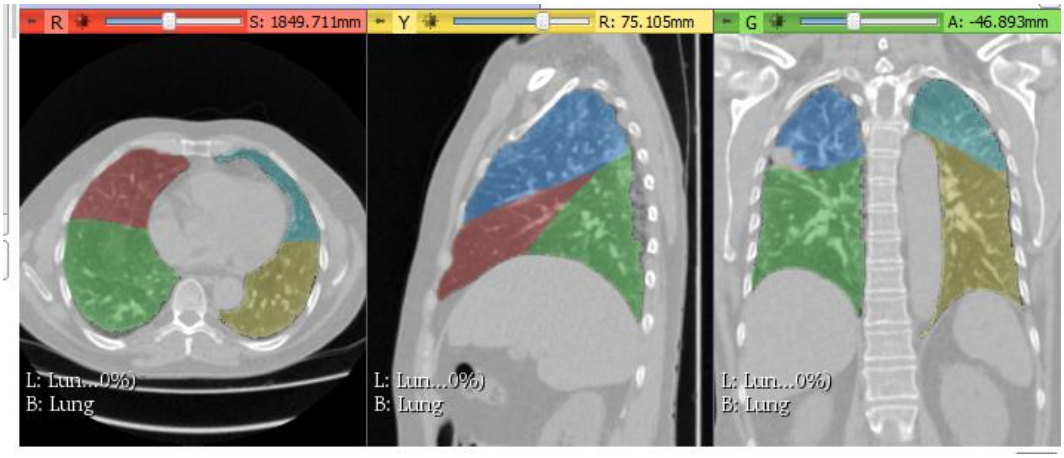


Figure 25 Segmented lobes after fiducial placement

Step 11. Scroll through the axial (red) and coronal (green) views to check the lobes have been accurately mapped. More fiducials may be needed if mapping is poor.

Step 12. Select the '*Parenchyma analysis*' module from the *'Chest Imaging Platform'* module

Step 13. Select '*Lung*' as the Input CT Volume

Step 14. Select '*Lung_InteractiveLobeSegmentation'* as the Label Map Volume

Step 15. Set Filtering to '*Off*'

Step 16. Click '*Apply'*

The parenchyma analysis may take some time and will analyse both the volume and density of the lung tissue as a whole and by anatomical divisions down to a lobar level.

Step 17. Click '*Clean cache'*

Step 18. Click '*Save*'

Step 19. Click '*Export*'

Step 20. Name and save the file with *'.csv'*

It is extremely important to name and save the file with '.csv' at the end, otherwise the saved data will be saved as one line and be essentially unusable.

Step 21. Click '*Close scene*'

This has now completed the analysis for one inspiratory scan series, Steps 1 to 21 will need to be repeated but with loading of the expiratory scan series to calculate deltaSVg for one patient.

Analysis using a smooth filter was also competed; to do this Step 15 was altered so that Filtering was set to '*On*' with '*Gaussian*' selected, Dimensions set to '*2D*', and Strength set to '*Smooth*'. Your screen should look similar to Figure 26 after parenchyma analysis using the filter.

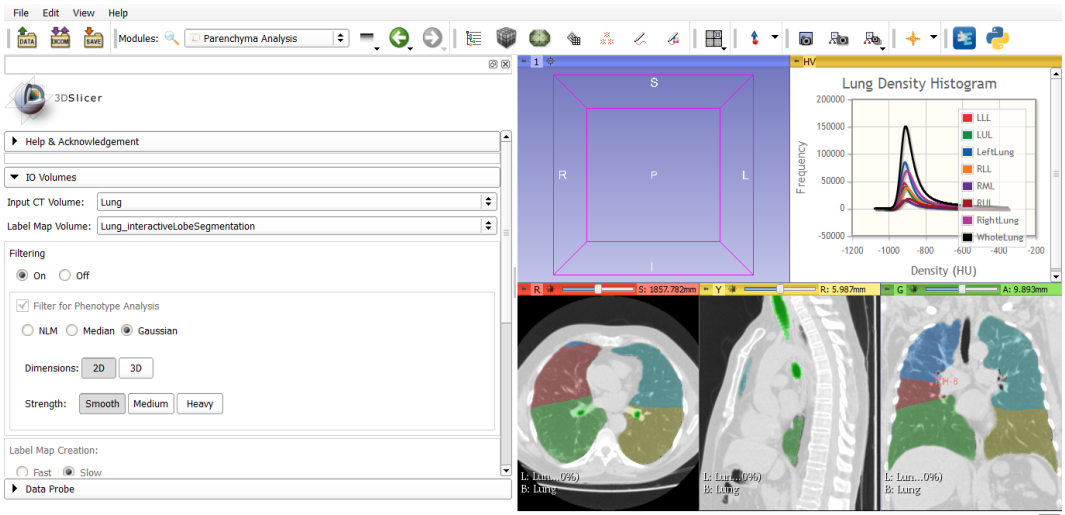


Figure 26 CIP view with parenchyma analysis performed using the lobar segmentation map

The software processes used by CIP to separate the lungs into lobes are described in detail by Ross et al. [269] In summary each CT slice is filtered to reduce noise, a grey level threshold is applied to extract the lung tissue from the surrounding structures, and the large airways are defined by region growing from an automatically placed seed point within the lumen of the trachea. The user defines points on the interlobar fissures as detailed in Steps 3 to 10 above and thin plate splines are used to define the fissures from the background lung parenchyma. Splines can be thought of as a smooth way of joining selected points and the thin plate type of spline prefers not to bend as it is drawn. This has the effect of creating a smooth definition of the fissure location that preferentially continues as an approximately flat surface. The fissures are then used to define the five lobes of the lungs. The filter applied in the segmentation process is a median filter with a 3 x 3 kernel.

The software processes within the parenchyma analysis module are not explicitly reported in the literature but appears to be the result of voxel counting within regions that have been defined as lung parenchyma, as opposed to airway or blood vessel, during the segmentation procedure.[270] An extra module to enable the user to calibrate density values according to air and blood densities was also requested. This has now been added to the CIP but there is not yet guidance on how to use the module and subsequently analyse a calibrated image series as per Steps 1 to 21, therefore it was not possible to calibrate the density values for this study.

3.2.9 CT analysis procedure with Thirona

The StratX software is proprietary, however the principles used by the developers of the software have been published. Segmentation of the lungs and their lobes is an essential

step before lobar values of volume or density can be obtained, but segmentation of the lungs using grey level thresholds alone often produces errors when the CT demonstrates pathological processes. Thirona have developed processes to overcome these errors.

Lung segmentation begins with region growing from an automatically placed seed point in the trachea to delineate the bronchial tree; the left and right lungs are then separated and the outline of each lung is smoothed. Errors are detected by assessing the volumes of the lungs, the ratio between the two lung volumes, and the convexity of the shape of the lungs. [271] Scans that contain errors are compared to a large set of training scans that were segmented manually and the outlines are adjusted to comply with the key features of the training scans. [271] Segmentation of the lobes can proceed after the lungs have been segmented.

Anatomical structures are used to create a map of the lobes without interaction; this is based on a combined map of airways, vasculature, and fissures. [272] The boundary between lobes should be far from large airways or vessels and lie exactly upon fissures, where these are present. Voxels in regions that satisfy these demands are assigned high values and regions that do not are assigned low values, the low values should be sited within the lobes. [272] The combination of anatomical structures improves the ability of the process to accurate locate the boundary between lobes over and above the accuracy of using one structure; it can also work in the absence of complete fissures and in the presence of lung pathology. Parts of the regions lying within a lobe are assigned a label based upon the lobar bronchus supplying the region and this defines which lobe lies on either side of a boundary between lobes; the boundaries are then smoothed with a filter. [272]

A final step involves interaction to correct the boundaries between lobes in cases where the lobar segmentation is unsatisfactory upon inspection. The user draws the correct boundary between lobes on a few scan slices where the boundary is incorrect, the user input is then automatically extended across the remaining slices. [273] This process is then repeated until the user considers the boundary to be satisfactory. The volumes of the lobes are obtained once the limits of the lobes are defined from the 3D scan data and the voxel counts within each lobe can be used to determine various measures of density for the lungs and their lobes.

3.3 Results

3.3.1 Feasibility outcomes

Recruitment was undertaken over 24 months and screening identified 260 eligible patients; the recruitment rate was 18% and the study completion rate was 53%. Reasons for declining to participate are detailed in Table 7 and patient flow through the study is shown in Figure 27.

Analysis of CT scans required files to be exported from the hospital medical imaging system and either analysed on a hospital computer with specific software installed or securely transferred to an analysis provider. This process is an additional step that adds time and inconvenience to the workflow that is not encountered in current clinical image reporting. Analysis of one scan phase, either inspiratory or expiratory, took a minimum of 15 minutes using the CIP. This equated to a minimum of 30 minutes per patient and would be longer in cases where the anatomy was more challenging due to

absent fissures. Further calculations were then required to calculate deltaSVg from the data points obtained in the CIP output.

CT scanning to assess lung function was generally acceptable in principle to patients with only 7 out of 260 (3%) citing radiation as a concern. Physically attending the CT appointment however was a significant concern and was the most common reason for declining to participate in the study. The requirement for an additional hospital visit in most cases for the study CT scan and repeat pulmonary function tests was a barrier to participation. The previously stated measures of feasibility were considered in the light of this study and judged as to whether a larger definitive study would be likely to be feasible as follows:

- Number of eligible patients – feasible
- Recruitment rate – feasible
- Time needed to analyse data – not feasible
- Follow up rate – not feasible
- Practicality – not feasible
- Acceptability – feasible

Overall the feasibility of analysing deltaSVg in patients due to undergo surgery for early stage lung cancer was not supported by this study. Further analysis of results that were obtained was undertaken to assess the reproducibility of results, and the accuracy of deltaSVg in predicting postoperative lung function, in order to ascertain whether further development of the practical aspects of CT analysis might still be desirable.

Table 7 Reasons for declining to participate

Reason	**Number**	**Percentage**
Unclear/no reason recorded	63	30%
Travel issues, distance to hospital, extra visit required	38	18%
Research staff availability	22	10%
Not possible to book CT before surgery	18	8%
Not listed for lobectomy	14	7%
Not appropriate to approach (emotional state, capacity, information overload)	14	7%
Did not attend or appointment cancelled	11	5%
Too much going on/didn't want to see a researcher	9	4%
Additional radiation	7	3%
Too busy, working, holiday booked	4	2%
Given information but didn't call back	4	2%
Missed	4	2%
No interpreter available	3	1%
Other	1	0.5%
	Total 212	

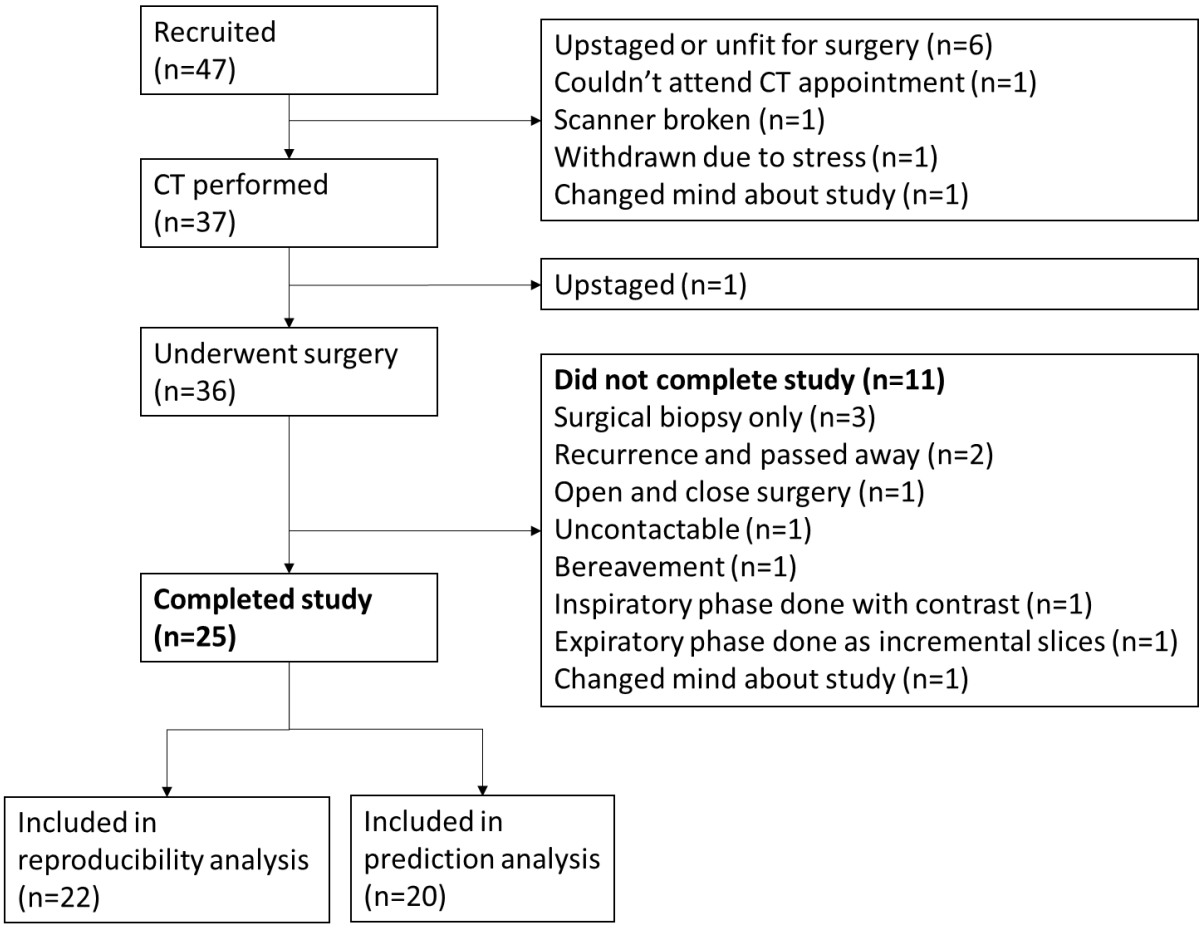


Figure 27 Patient flow through the study

Note: Upstaging was done by clinicians after preoperative assessment clinic and not as a result of the CT scan for the study. Analysis of 3 scans for reproducibility failed using CIP, prediction analysis using data from Thirona was limited to 20 free scans

3.3.2 Participants

The baseline data are shown in Table 8. Patients who had a CT and surgery but did not complete the study were not significantly different from patients who completed the study. This indicates that the reasons for not completing the study were not linked to these physical attributes. One participant clearly had a completely atelectatic right upper lobe and therefore the volume and density of that lobe was set to 0 for both CIP and Thirona analyses.

3.3.3 Chest Imaging Platform data output

The data provided by the CIP is a spreadsheet; the values are stated for the lungs as a whole, the right lung, the left lung, and each of the five lobes. The measures are:

- Percentage of voxels with attenuation below: -950HU, -925HU, -910HU, -856HU, -700HU, -600HU, -500HU, -250HU
- 10^{th} and 15^{th} percentile point
- Mean density and standard deviation
- Mass
- Volume
- Kurtosis
- Skewness
- Ventilation Heterogeneity

Ventilation on CT scans is not a term with a universally accepted definition and the CIP authors have not defined it; the open source forum was asked about this measure but an explanation has not yet been provided. There are some further uncertainties about the data processing. The density histograms provided show values limited to between -1100HU and -350HU. This is physiologically reasonable since values below -1100HU are extremely low and not representative of true anatomical structures and values above -350HU are more likely to be blood vessels, tumour tissue or calcification than functional

lung tissue. The lack of histogram data outside these values was taken to represent that values outside of the range were excluded from analysis, however this is not certain. An example of a density histogram provided by the CIP for an individual scan is in Figure 28. Inspection of histograms and skewness data confirmed that data was positively skewed and not normally distributed, however median values were not provided by the software and transformation of values was not possible due to the lack of individual data points for voxel densities.

Most scans passed through the CIP analysis steps smoothly, however the first three scans would not process. Images would load in the CIP viewer but were displayed upside down, the module then could not recognise the image as a lung structure. This was corrected by rotating the series of images, however the lobes would not segment as intended despite placement of additional fiducials. The failure of lobar segmentation is shown in Figure 29. Patient orientation is obtained from the DICOM data so corrections were made to the CT scanner storage settings at the time of scan acquisition and the problem was not present amongst the subsequent patients. [269]

3.3.4 Thirona data output

Voxel counts were provided in a spreadsheet for the lungs as a whole, the left lung, the right lung, and each of the five lobes. Voxel densities were used in the range -1100HU to -350HU to match the values provided by the CIP and also because values below -1100HU are extreme low densities and values above -350 are in the range of fat, blood, and calcification, which should be excluded. The densities provided were also positively skewed therefore median values were used to describe the central tendency of the data.

Table 8 Patient demographics

	Included in reproducibility analysis (n=22)	**Included in prediction analysis (n=20)**	**Did not complete study (n=11)**	**p-value**
Age in years Median IQR #	67 (63-72)	68 (65-71)	66 (59-67)	0.312
Gender Male:female ###	13:9	11:9	5:6	0.760
BMI Mean, SD ##	31.0 (7.6)	30.1 (6.6)	24.8 (6.0)	0.055
Baseline FEV1 % Mean, SD ##	87 (20)	85 (18)	78 (19)	0.426
Baseline FVC % Mean, SD ##	102 (21)	100 (21)	104 (15)	0.860
FEV1/FVC ratio Mean, SD ##	0.69 (0.10))	0.67 (0.10)	0.61 (0.16)	0.209
Baseline TLCO % Median IQR #	67 (63-75)	70 (65-80)	68 (50-85)	0.887
Operation: ###				
No lung resection	1	0	3	0.150
Cyst excision	1	1	0	
Wedge resection	1	1	2	
Lobectomy	18	17	5	
Pneumonectomy	1	1	1	

Normality of data was assessed using Shapiro-Wilk tests. Statistical tests were applied to compare the groups as follows: # Kruskal-Wallis test for continuous non-normally distributed data, ## one-way ANOVA for continuous normally distributed data, ### Freeman-Halton extension of Fisher's exact test for multiple categorical variables.

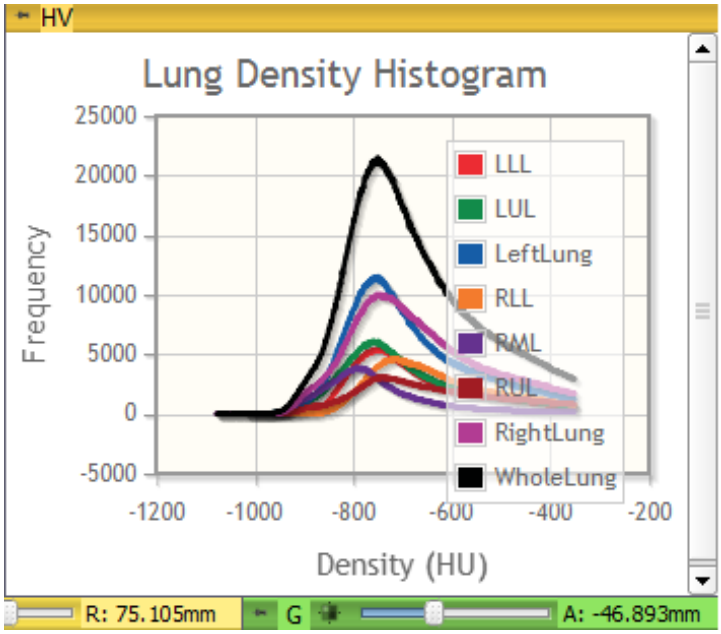


Figure 28 Density histogram of lung voxels from one scan using the CIP

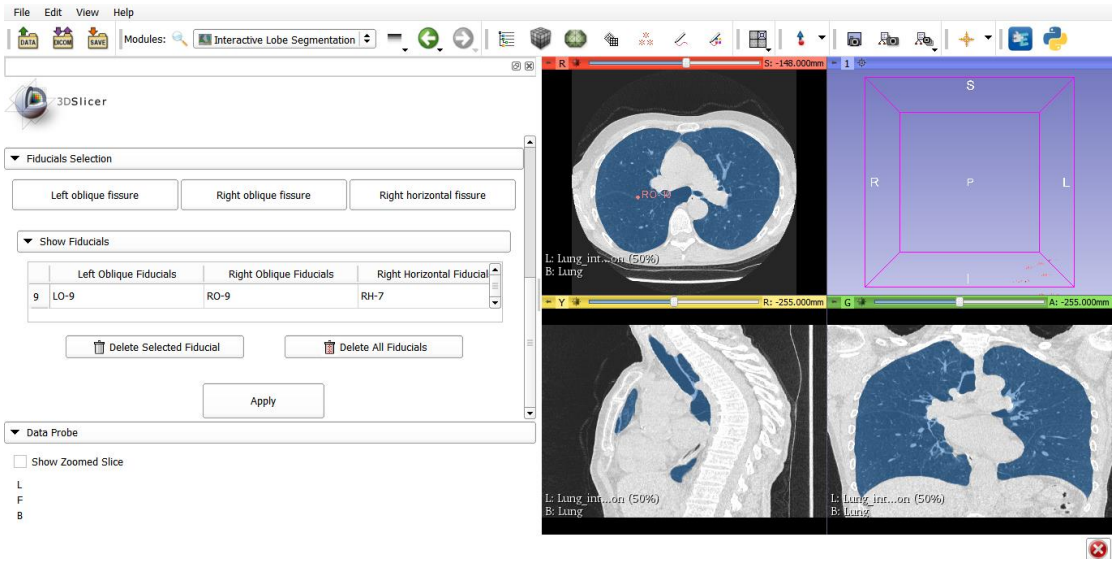


Figure 29 View of lobar segmentation failure in CIP

3.3.5 Chest Imaging Platform reproducibility testing

One observer was a medical student trained to use CIP but with no prior radiology experience and the other was the author of this thesis, with seven years of clinical training but also no formal radiology training. The intra-observer and inter-observer variability of volume and density data using mean values obtained from the CIP were assessed by performing the analysis with variable factors as follows:

- Step 1 to 21 performed twice by the same researcher with no filter
- Step 1 to 21 performed twice by the same researcher with a smooth filter
- Step 1 to 21 performed independently by two researchers with no filter
- Step 1 to 21 performed independently by two researchers with a smooth filter

Results showed that intra-rater reproducibility of volume was excellent with ICCs close to 1 and mean differences of 0ml, however the LOAs were greater than clinically acceptable limits of around 0.05L, and multiple points were outside of the statistical LOAs (Table 9 and Figure 30 to Figure 33). Expiratory scans showed slightly less variation, use of a smooth filter lead to more variation in inspiratory volumes but less variation in expiratory volumes. [274] Intra-rater reproducibility of density was excellent with ICCs close to 1 and mean differences for scans with smooth filters applied less than 1HU; scans with no filter had mean differences less than 3HU (Table 10). There is no agreed clinically acceptable limit for variation in HU, however it is reasonable to judge variation in excess of 5HU as problematic because normal lung tissue can have a density down to -900HU and studies have reported densities below -910HU as measures of emphysema.[244] The LOAs were clinically unacceptably wide using this judgment, and multiple points lay outside of the statistical LOAs (Figure 34 to Figure 37).

Table 9 Intra-rater reliability assessments of volume measurements using CIP – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
No filter Inspiratory	0.995 (0.988 to 0.998)	0.984 (0.960 to 0.994)	0.999 (0.998 to 1.000)	1.000 (0.999 to 1.000)	1.000 (0.999 to 1.000)
Smooth filter Inspiratory	0.997 (0.993 to 0.999)	0.980 (0.950 to 0.992)	0.997 (0.992 to 0.999)	0.999 (0.997 to 1.000)	0.999 (0.997 to 1.000)
No filter Expiratory	0.994 (0.983 to 0.998)	0.976 (0.922 to 0.991)	0.999 (0.998 to 1.000)	0.999 (0.998 to 1.000)	0.999 (0.998 to 1.000)
Smooth filter Expiratory	0.997 (0.993 to 0.999)	0.980 (0.950 to 0.992)	0.997 (0.992 to 0.999)	0.999 (0.997 to 1.000)	0.999 (0.997 to 1.000)

Table 10 Intra-rater reliability assessments of density measurements using CIP – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
No filter Inspiratory	0.982 (0.953 to 0.993)	0.988 (0.963 to 0.996)	0.999 (0.996 to 1.000)	0.995 (0.986 to 0.998)	0.990 (0.974 to 0.996)
Smooth filter Inspiratory	0.999 (0.998 to 1.000)	0.995 (0.986 to 0.998)	1.000 (0.999 to 1.000)	0.998 (0.996 to 0.999)	0.996 (0.990 to 0.998)
No filter Expiratory	0.996 (0.991 to 0.999)	0.987 (0.952 to 0.996)	0.997 (0.992 to 0.999)	0.997 (0.992 to 0.999)	0.992 (0.976 to 0.997)
Smooth filter Expiratory	0.999 (0.998 to 1.000)	0.989 (0.973 to 0.996)	0.999 (0.997 to 1.000)	0.999 (0.997 to 1.000)	0.995 (0.987 to 0.998)

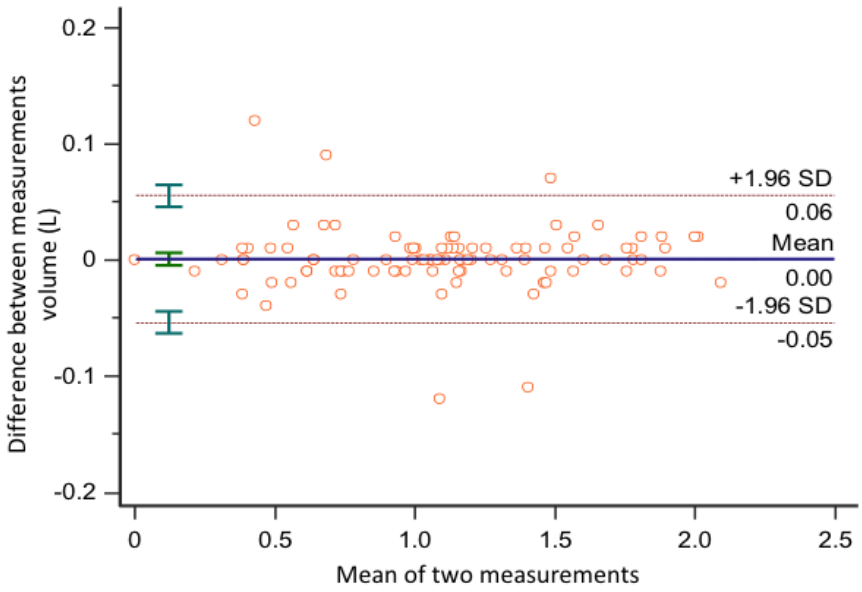


Figure 30 Intra-rater agreement of lobar volume (L) on inspiratory scans measured with no filter using CIP

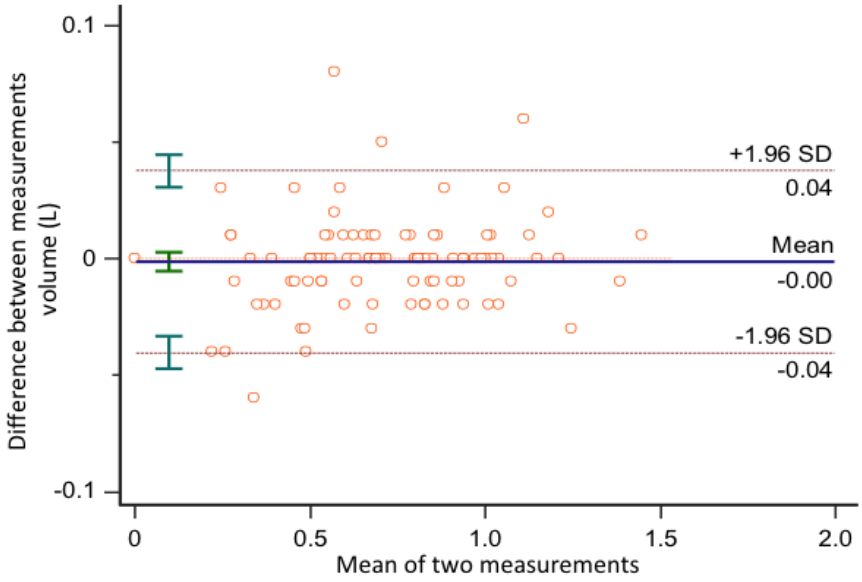


Figure 31 Intra-rater agreement of lobar volume (L) on expiratory scans measured with no filter using CIP

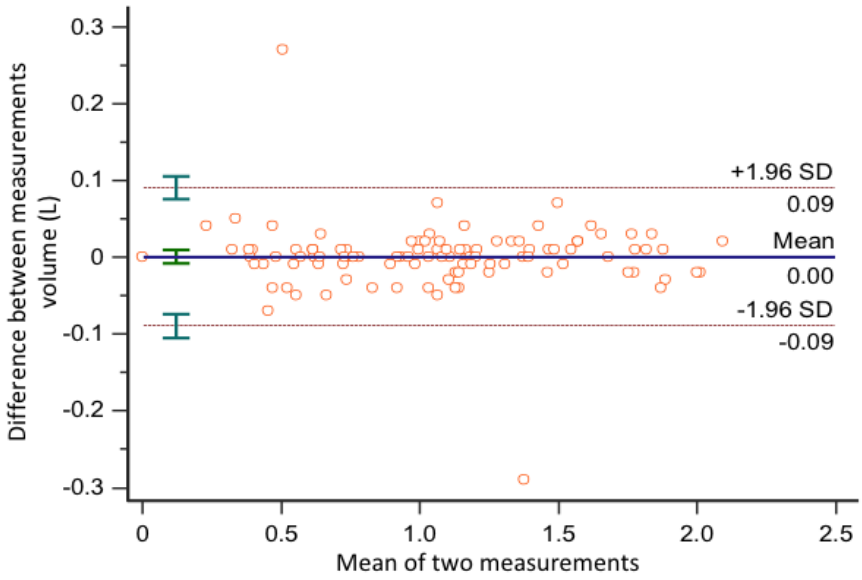


Figure 32 Intra-rater agreement of lobar volume (L) on inspiratory scans measured with a smooth filter using CIP

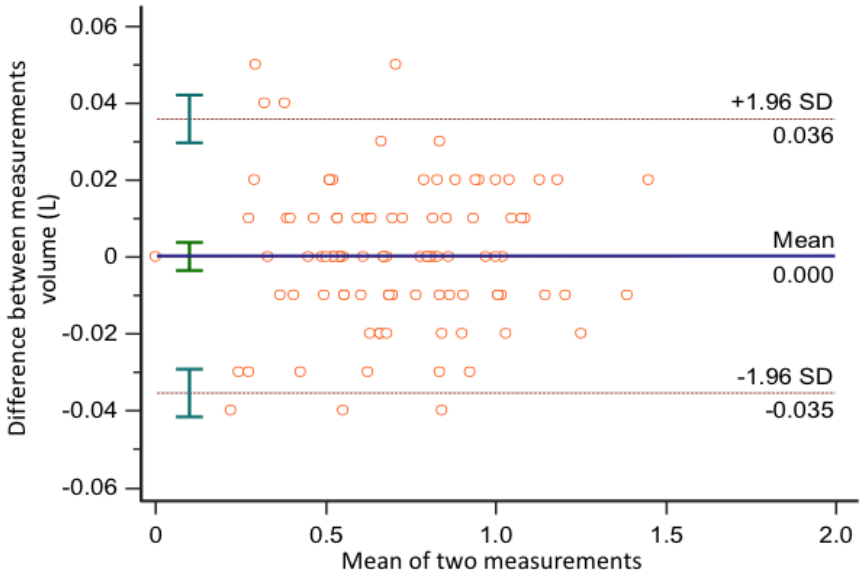


Figure 33 Intra-rater agreement of lobar volume (L) on expiratory scans measured with a smooth filter using CIP

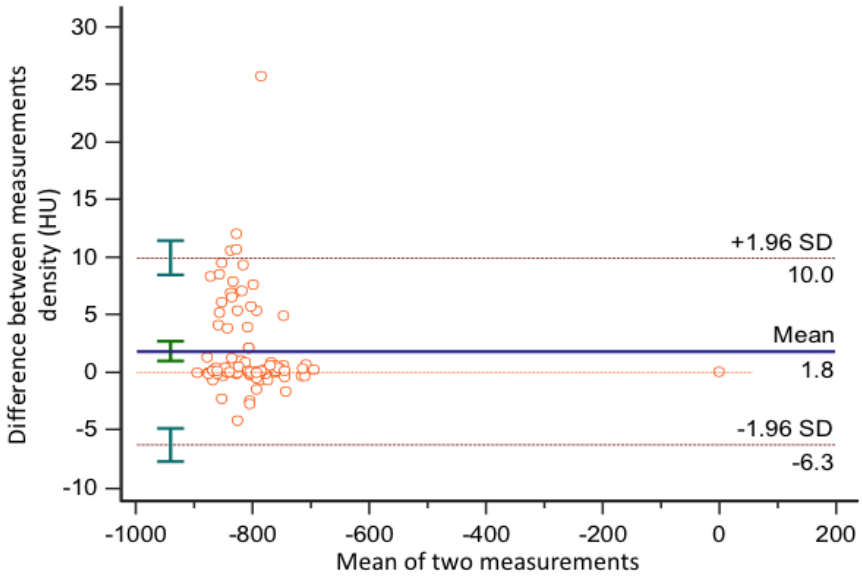


Figure 34 Intra-rater agreement of lobar density (HU) on inspiratory scans measured with no filter using CIP

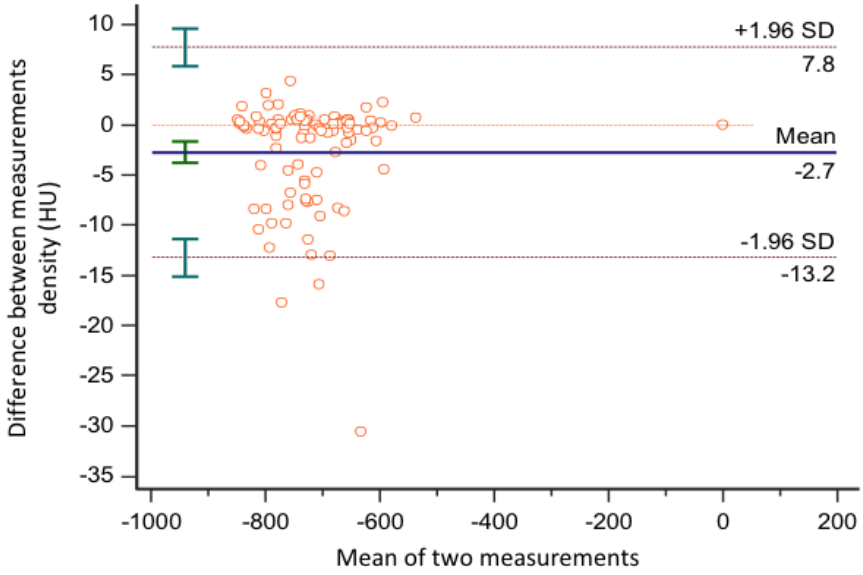


Figure 35 Intra-rater agreement of lobar density (HU) on expiratory scans measured with no filter using CIP

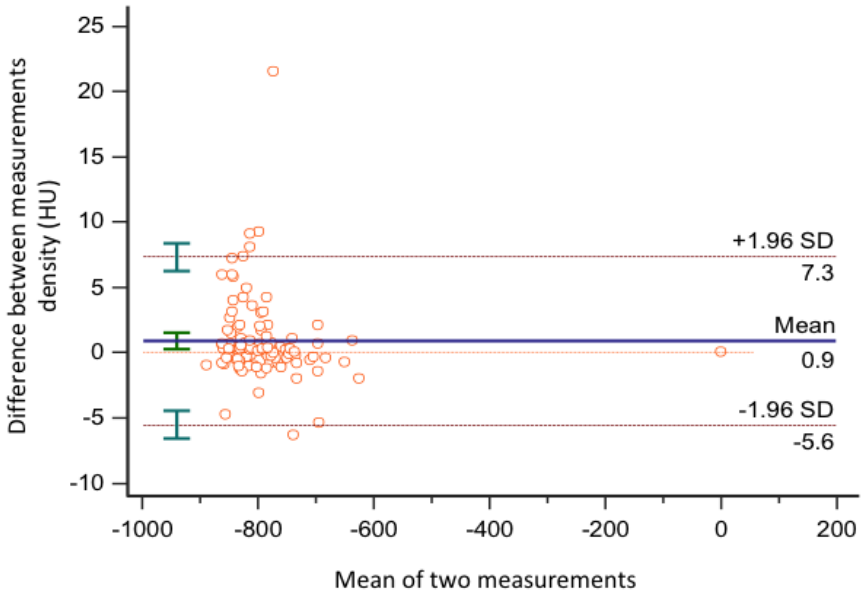


Figure 36 Intra-rater agreement of lobar density (HU) on inspiratory scans measured with a smooth filter using CIP

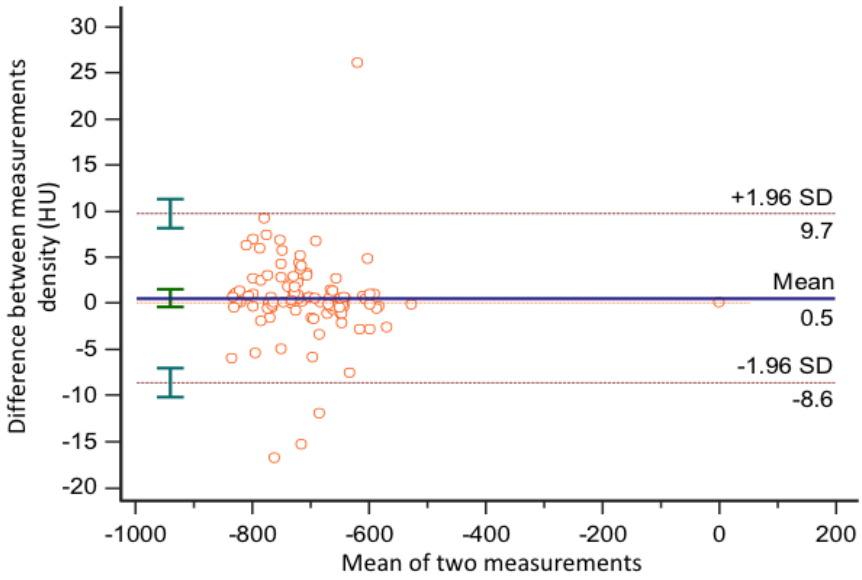


Figure 37 Intra-rater agreement of lobar density (HU) on expiratory scans measured with a smooth filter using CIP

Inter-rater variability of lobar volumes was between moderate and excellent with ICC 95% CIs between 0.603 and 0.999 (Table 11). The mean differences were less than 10ml but the LOAs extended considerably above the clinically acceptable limit and many points lay outside of the statistical LOAs (Figure 38 and Figure 39). The inter-rater variability of lobar densities was between good and excellent with ICC 95%CIs between 0.838 and 1.000 (Table 12). The mean differences were less than 3HU but again the LOAs were unacceptably large and multiple points lay outside of the statistical LOAs (Figure 40 and Figure 41).

Table 11 Inter-rater reliability of volume measurements using CIP – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
No filter Inspiratory	0.962 (0.908 to 0.985)	0.879 (0.725 to 0.950)	0.990 (0.966 to 0.996)	0.994 (0.986 to 0.998)	0.994 (0.986 to 0.998)
Smooth filter Inspiratory	0.965 (0.916 to 0.986)	0.882 (0.737 to 0.950)	0.990 (0.963 to 0.997)	0.995 (0.988 to 0.998)	0.995 (0.988 to 0.998)
No filter Expiratory	0.954 (0.879 to 0.983)	0.836 (0.603 0.937)	0.997 (0.993 to 0.999)	0.966 (0.910 to 0.987)	0.955 (0.882 to 0.983)
Smooth filter Expiratory	0.963 (0.906 to 0.986)	0.874 (0.697 to 0.951)	0.997 (0.991 to 0.999)	0.968 (0.917 to 0.988)	0.958 (0.893 to 0.984)

Table 12 Inter-rater reliability of density measurements using CIP – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
No filter Inspiratory	0.979 (0.948 to 0.992)	0.932 (0.838 to 0.972)	0.973 (0.935 to 0.989)	0.965 (0.916 to 0.986)	0.953 (0.887 to 0.981)
Smooth filter Inspiratory	0.961 (0.907 to 0.984)	0.963 (0.912 to 0.985)	0.984 (0.962 to 0.994)	0.979 (0.950 to 0.992)	0.965 (0.917 to 0.986)
No filter Expiratory	0.995 (0.987 to 0.998)	0.982 (0.949 to 0.993)	0.997 (0.992 to 0.999)	0.997 (0.990 to 0.999)	0.996 (0.987 to 0.998)
Smooth filter Expiratory	0.986 (0.963 to 0.995)	0.984 (0.959 to 0.994)	0.999 (0.998 to 1.000)	0.999 (0.996 to 1.000)	0.999 (0.997 to 1.000)

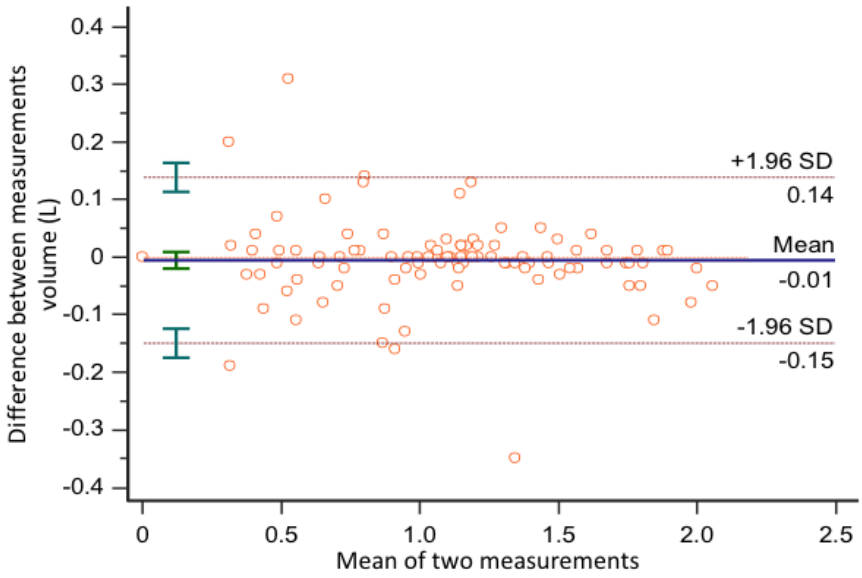


Figure 38 Inter-rater agreement of lobar volume (L) on inspiratory scans measured with no filter using CIP

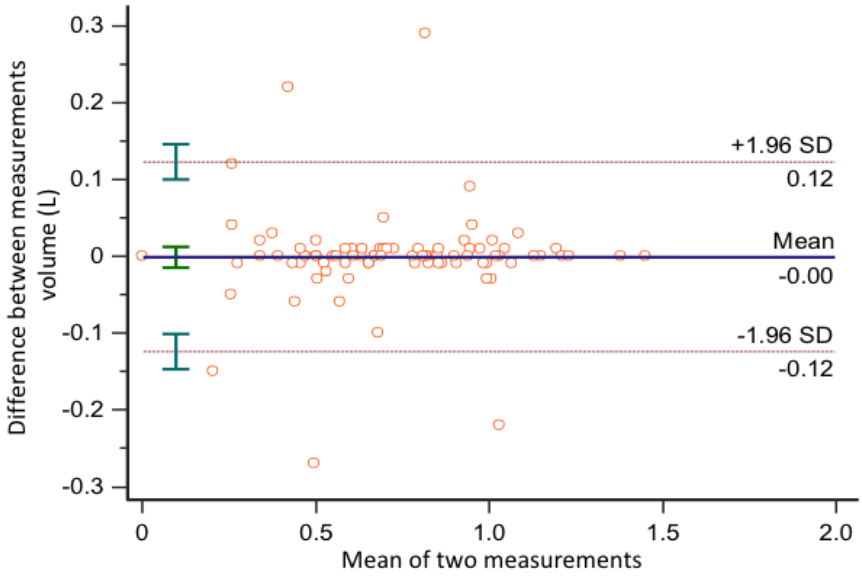


Figure 39 Inter-rater agreement of lobar volume (L) on expiratory scans measured with no filter using CIP

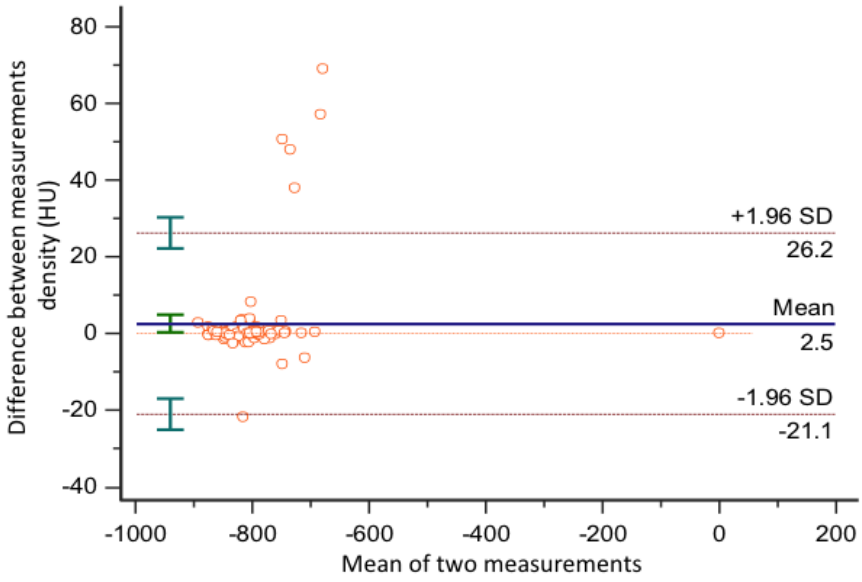


Figure 40 Inter-rater agreement of lobar density (HU) on inspiratory scans measured with no filter using CIP

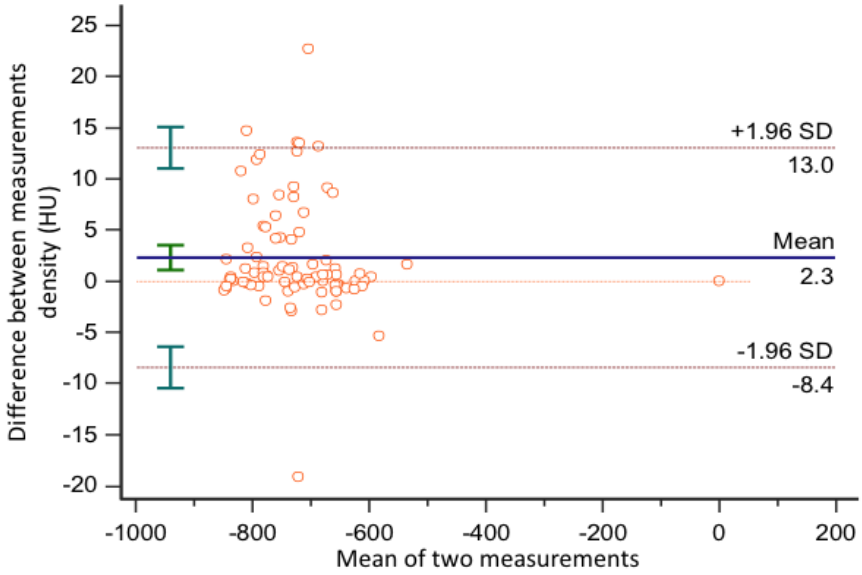


Figure 41 Inter-rater agreement of lobar density (HU) on expiratory scans measured with no filter using CIP

Agreement between volume measurement for unfiltered scans and those with a smooth filter applied was excellent with ICCs all being close to 1 (Table 13). The mean differences in volume were very small and LOAs were within clinically acceptable limits for inspiratory scans, however the expiratory scan data LOAs exceeded clinical limits and both types of scans had multiple points outside of the statistical LOAs (Figure 42 and Figure 43).

Measurements of density showed poor agreement between scans without a filter and scans with a smooth filter with ICCs being as low as 0.014 (Table 14). Both the mean differences and LOAs exceeded the clinically reasonable limit of 5HU and some points were located outside of the statistical LOAs (Figure 44 and Figure 45).

The same fiducial map and lung segmentation was used for the volume and density analysis of each scan. Therefore these results demonstrate that the results of the scan analysis process with CIP produces results that are not comparable when different filters are used, and this is not related to the training of the CIP user.

Table 13 Agreement of volume measurement with no filter and with a smooth filter using CIP – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
Rater 1 Inspiratory	1.000 (1.000 to 1.000)	0.999 (0.998 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)
Rater 2 Inspiratory	0.999 (0.998 to 1.000)	0.997 (0.993 to 0.999)	0.999 (0.997 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)
Rater 1 Expiratory	0.994 (0.981 to 0.998)	0.977 (0.911 to 0.992)	0.999 (0.998 to 1.000)	0.999 (0.998 to 1.000)	0.999 (0.998 to 1.000)
Rater 2 Expiratory	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)	1.000 (1.000 to 1.000)

Table 14 Agreement of density measurement with no filter and with a smooth filter using CIP – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
Rater 1 Inspiratory	0.939 (0.617 to 0.982)	0.955 (0.051 to 0.991)	0.977 (0.050 to 0.996)	0.973 (0.081 to 0.995)	0.975 (0.313 to 0.995)
Rater 2 Inspiratory	0.981 (0.070 to 0.997)	0.974 (0.045 to 0.995)	0.984 (0.069 to 0.997)	0.984 (0.070 to 0.997)	0.984 (0.069 to 0.997)
Rater 1 Expiratory	0.980 (0.337 to 0.996)	0.944 (0.014 to 0.989)	0.981 (0.113 to 0.997)	0.980 (0.092 to 0.996)	0.978 (0.159 to 0.996)
Rater 2 Expiratory	0.983 (0.071 to 0.997)	0.961 (0.020 to 0.993)	0.985 (0.078 to 0.997)	0.982 (0.062 to 0.997)	0.984 (0.093 to 0.997)

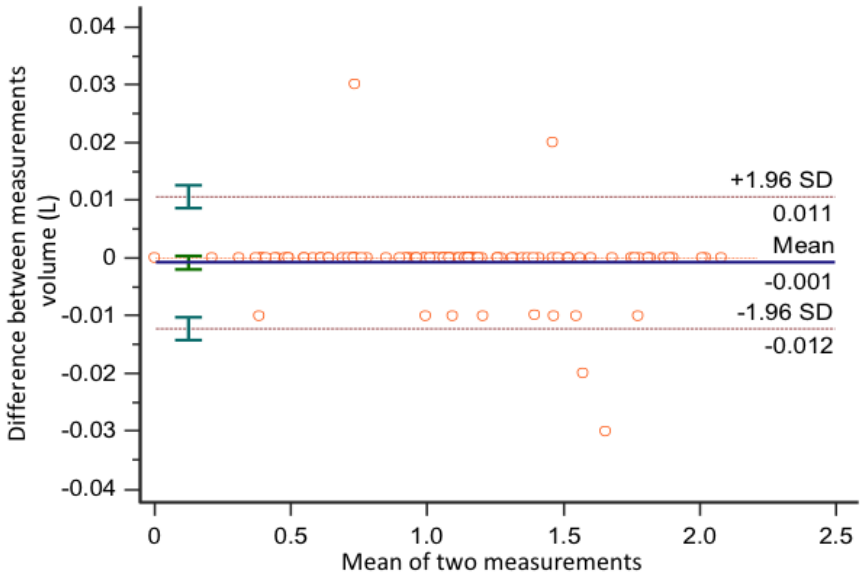


Figure 42 Agreement of lobar volume (L) measurement on inspiratory scans with no filter versus with a smooth filter using CIP

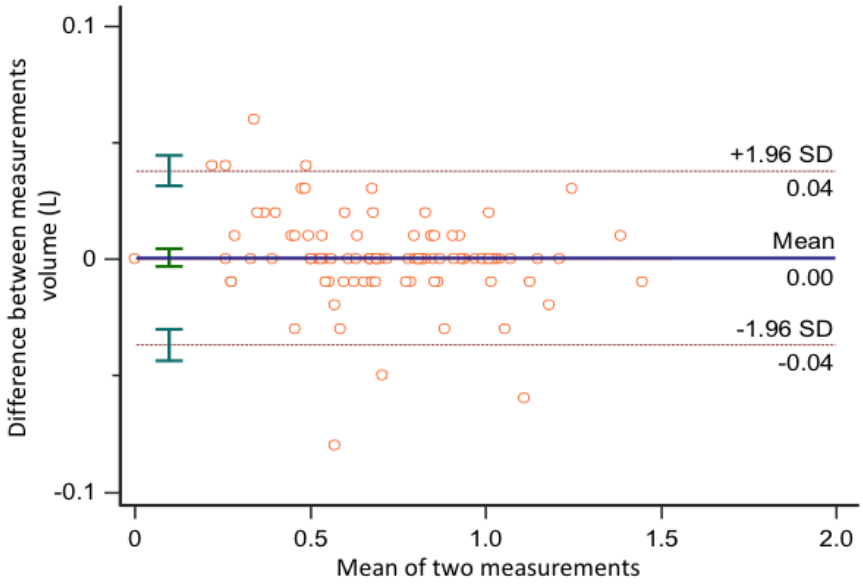


Figure 43 Agreement of lobar volume (L) measurement on expiratory scans with no filter versus with a smooth filter using CIP

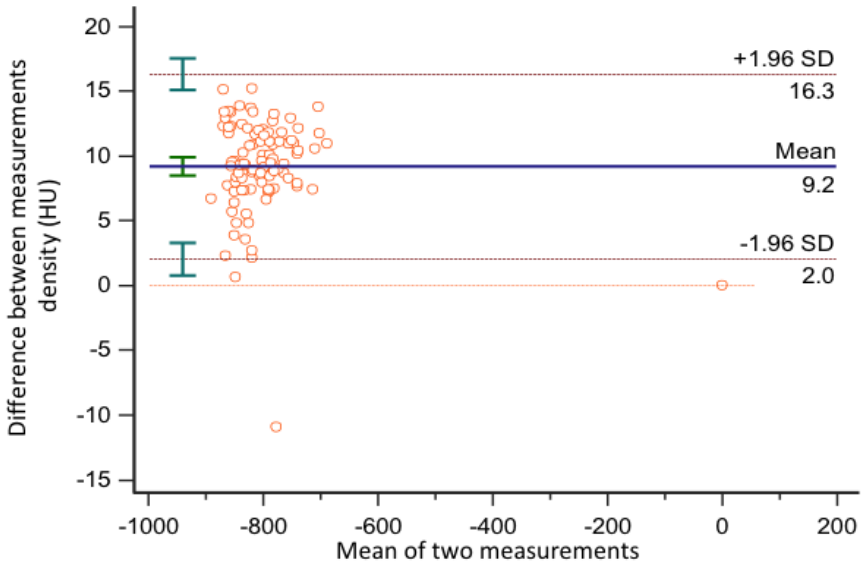


Figure 44 Agreement of lobar density (HU) measurement on inspiratory scans with no filter versus with a smooth filter using CIP

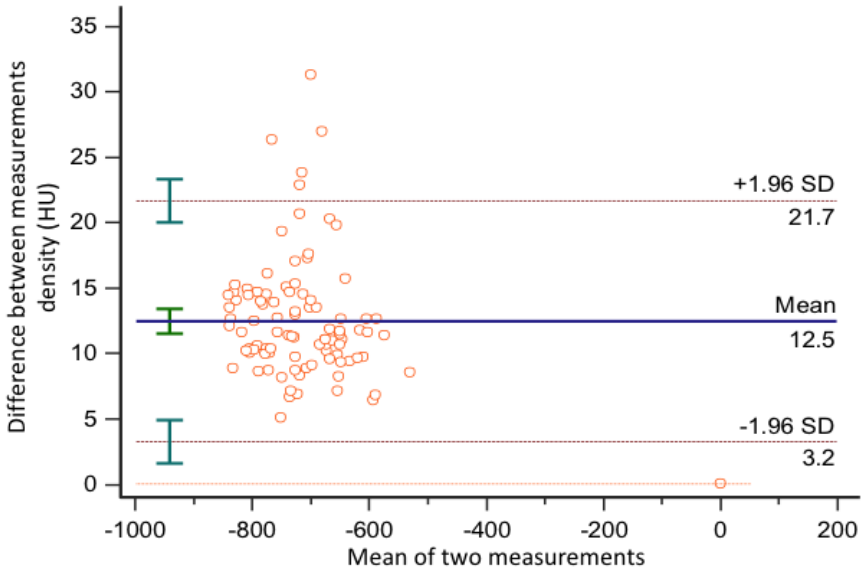


Figure 45 Agreement of lobar density (HU) measurement on expiratory scans with no filter versus with a smooth filter using CIP

Overall the results of intra-rater and inter-rater reproducibility analysis for CIP showed that the software did not provide results that were reproducible to within clinically acceptable limits when analysis was performed by persons without radiology training. It is not known whether the results would be acceptably reproducible if radiologists obtained them.

3.3.6 Comparison of Chest Imaging Platform and Thirona data outputs

The lobar volumes obtained using the two software programs showed moderate to excellent agreement with ICC 95%CIs between 0.633 and 1.000 (Table 15). The mean difference was less than 10ml but the LOAs far exceeded clinically acceptable limits; one of the points lay outside the statistical LOAs (Figure 46 and Figure 47).

The agreement between median densities obtained from Thirona and mean densities obtained from CIP was poor and ICC 95%CIs included negative values (Table 16). A negative ICC in this context indicates that the variability of the densities measured on individual patients exceeded the variability of the measures across the group of patients; this can also be visualised graphically as the spread of points having a greater spread in the vertical axis than the horizontal axis (Figure 48 and Figure 49). A mean difference of 57HU is definitely unacceptably high from a clinical perspective since a measurement error of this magnitude would change the assessment of a voxel from normal tissue at -900HU to beyond the limit for defining emphysema at -950HU.[275]

The differences in density measurement also affected the measurement of deltaSVg. Agreement between deltaSVg measured by the two software processes showed poor agreement, including low and negative ICC 95%CIs (Table 17). There is no established

clinical limit for acceptable variation in deltaSVg; the normal value of deltaSVg in health is 4.7ml/g (SD 1.0) and it is 1.3ml/g (SD 0.6) in patients with emphysema. The mean difference in deltaSVg between CIP and Thirona measures was -0.42ml/g and the lower LOA was 0.92; these values are close to SD values of deltaSVg in health and disease therefore they can be reasonably considered to be too large to be acceptable. The difference between deltaSVg measured by CIP and by Thirona appeared to be affected by the magnitude of deltaSVg, meaning that agreement between the two methods was worse as deltaSVg increased (Figure 50). These results indicate that measurements obtained using either CIP or Thirona processes cannot be considered equivalent.

Table 15 Agreement of volume values obtained using CIP versus Thirona – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
No filter Inspiratory	0.990 (0.973 to 0.997)	0.965 (0.898 to 0.988)	0.998 (0.993 to 0.999)	0.914 (0.783 to 0.968)	0.999 (0.998 to 1.000)
Smooth filter Inspiratory	0.990 (0.973 to 0.997)	0.965 (0.898 to 0.988)	0.998 (0.993 to 0.999)	0.914 (0.783 to 0.968)	0.999 (0.998 to 1.000)
No filter Expiratory	0.995 (0.986 to 0.998)	0.984 (0.956 to 0.995)	0.997 (0.991 to 0.999)	0.854 (0.641 to 0.946)	0.998 (0.994 to 0.999)
Smooth filter Expiratory	0.990 (0.945 to 0.997)	0.969 (0.869 to 0.990)	0.995 (0.986 to 0.998)	0.846 (0.633 to 0.941)	0.997 (0.992 to 0.999)

Table 16 Agreement of density values obtained using CIP versus Thirona – ICC (95% Confidence Interval)

	Right upper lobe	**Right middle lobe**	**Right lower lobe**	**Left upper lobe**	**Left lower lobe**
No filter Inspiratory	0.974 (0.149 to 0.995)	0.474 (-0.006 to 0.845)	0.553 (-0.013 to 0.881)	0.554 (-0.532 to 0.874)	0.585 (-0.023 to 0.893)
Smooth filter Inspiratory	0.964 (0.059 to 0.993)	0.379 (-0.005 to 0.787)	0.467 (-0.010 to 0.840)	0.457 (-0.038 to 0.829)	0.495 (-0.017 to 0.854)
No filter Expiratory	0.961 (0.074 to 0.993)	0.611 (-0.006 to 0.906)	0.626 (-0.020 to 0.909)	0.714 (-0.041 to 0.935)	0.664 (-0.017 to 0.922)
Smooth filter Expiratory	0.944 (0.014 to 0.989)	0.483 (-0.007 to 0.849)	0.546 (-0.011 to 0.878)	0.618 (-0.032 to 0.904)	0.585 (-0.011 to 0.894)

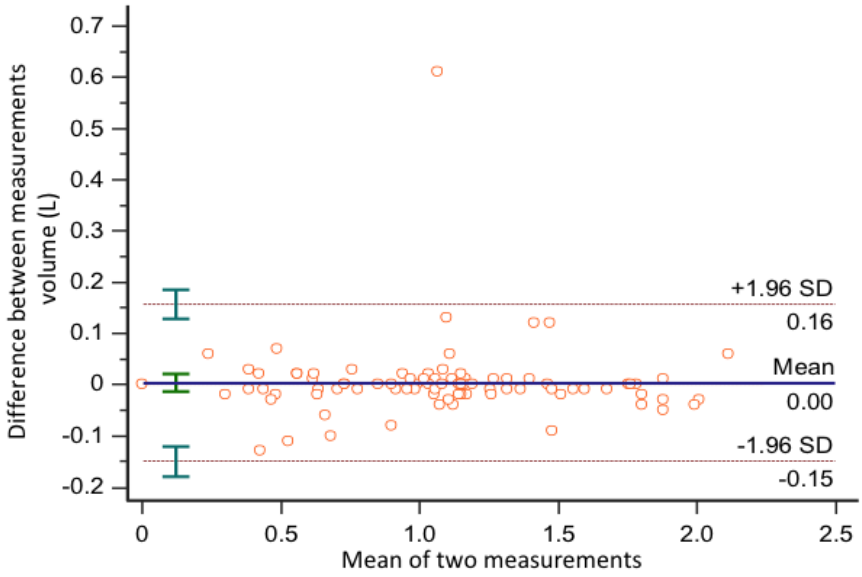


Figure 46 Agreement of lobar volume (L) measurement on inspiratory scans with no filter versus using CIP versus Thirona

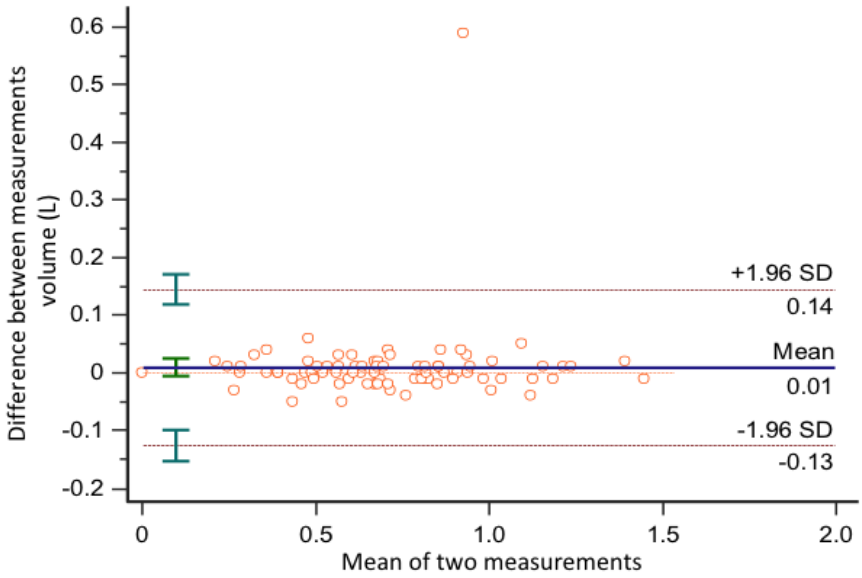


Figure 47 Agreement of lobar volume (L) measurement on expiratory scans with no filter versus using CIP versus Thirona

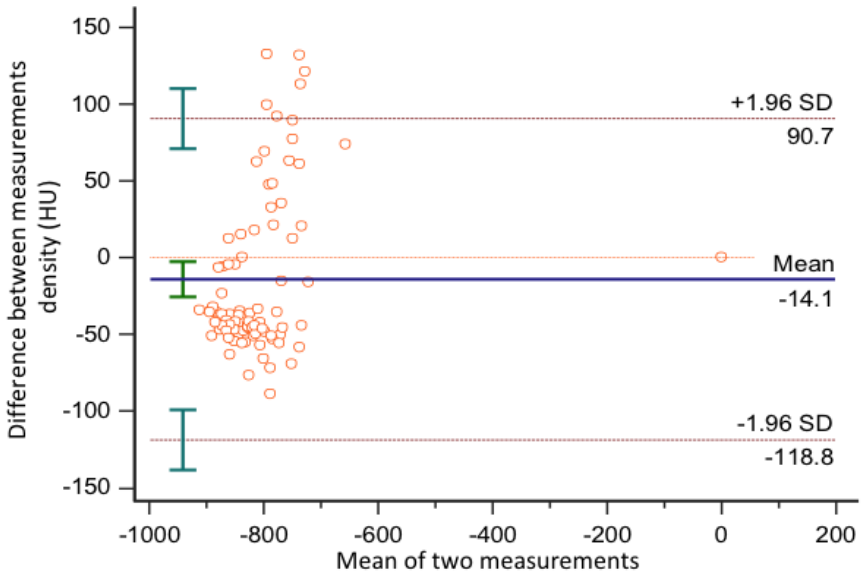


Figure 48 Agreement of lobar density (HU) measurement on inspiratory scans with no filter versus using CIP versus Thirona

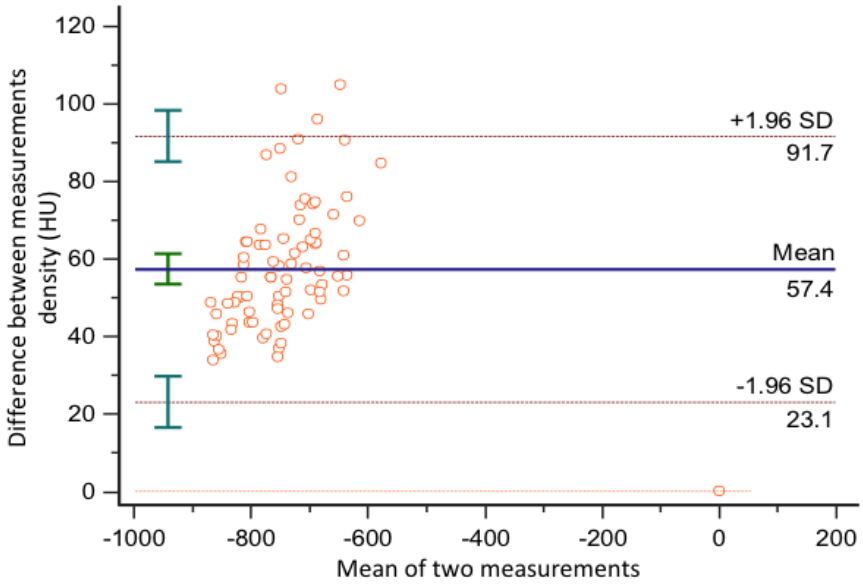


Figure 49 Agreement of lobar density (HU) measurement on expiratory scans with no filter versus using CIP versus Thirona

Table 17 Agreement of deltaSVg obtained from CIP with no filter versus Thirona – Intra class correlation coefficients

	ICC (95%CI)
Right upper lobe	0.933 (0.112 to 0.986)
Right middle lobe	0.871 (-0.008 to 0.971)
Right lower lobe	0.872 (0.025 to 0.971)
Left upper lobe	0.885 (-0.028 to 0.977)
Left lower lobe	0.905 (0.006 to 0.980)

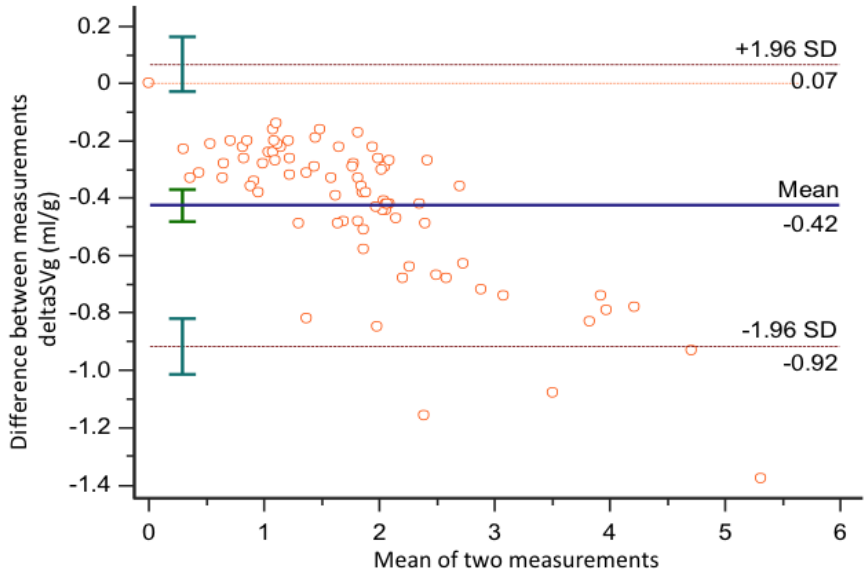


Figure 50 Agreement of deltaSVg measured using CIP with no filter and measured by Thirona

3.3.7 Comparing prediction of postoperative lung function by different methods

Prediction of postoperative lung function using deltaSVg was compared to prediction by segment counting, the current method used locally, and prediction by CT density and volume, the most accurate method identified by the systematic review. These preliminary data showed an improvement in accuracy of predicting postoperative FEV1 with deltaSVg over CT density and volume, which was itself more accurate than segment counting (Table 18). However, segment counting was the most precise method of prediction and deltaSVg was the least precise. Segment counting was the most accurate and precise predictor of postoperative TLCO, deltaSVg was the least accurate and precise (Table 19). There was also no significant correlation between deltaSVg predicted postoperative FEV1 or TLCO and measured postoperative FEV1 or TLCO. These results do not support pursuing further assessment of deltaSVg assessed by the methods reported herein for predicting postoperative lung function in patients undergoing lung cancer resection.

Table 18 Mean differences between actual and predicted postoperative FEV1 (L)

	Segment counting	**deltaSVg**	**CT density & volume***
Mean difference	0.241	-0.148	0.220
SD	0.188	0.386	0.245
Pearson **	0.956	0.083	0.929
p-value	<0.001	0.727	<0.001
N	20	20	20

*Functional lung volume was defined as inspiratory lung volume with density more than -910HU, the most frequently used parameter across studies included in the review of prediction techniques.[276] ** Pearson's correlation coefficient (2 tailed)

Table 19 Mean differences between actual and predicted postoperative TLCO (mmol/min/kPa)

	Segment counting	**deltaSVg**	**CT density & volume***
Mean difference	-0.063	-1.138	-0.133
SD	0.548	0.881	0.619
Pearson**	0.949	0.058	0.936
p-value	<0.001	0.815	<0.001
N	19	19	19

Notes: One patient did not have TLCO measured during lung function after surgery.
*Functional lung volume was defined as inspiratory lung volume with density more than -910HU, the most frequently used parameter across studies included in the review of prediction techniques.[276] ** Pearson's correlation coefficient (2 tailed)

3.4 Discussion

3.4.1 Comparison of results and hypotheses

The study hypotheses were:

- Calculating preoperative deltaSVg at a lobar level would be feasible in the local patient population
- Open access software could yield reproducible results
- Data from a small sample would be obtained and provide data to power a larger definitive study

This study has shown that deltaSVg measurement on additional non-contrast CT scans is currently not clinically feasible locally. The CIP open access software was found not to yield reproducible results for volume and density measurements within and between the two raters, both with and without the use of a smooth filter. Lobar volume and density measurements also did not agree when the same scans were analysed with no filter or using a smooth filter. The results obtained using CIP were not equivalent to those obtained from Thirona.

Preliminary results from this study found an dSVg improved the accuracy of predicting postoperative FEV1 but precision was worsened; accuracy and precision of predicting postoperative TLCO using deltaSVg was worse than either segment counting or CT density and volume on inspiratory scans, therefore powering for a larger definitive trial was not appropriate.

3.4.2 Results in context

CT analysis with reference to lung resection has been reported for at least 25 years, however to date it has not been incorporated into clinical care.[109] This study has

identified key reasons for the absence of uptake that have not been reported before and it is at least partly due to the practical difficulties of obtaining and analysing the scans.

The feasibility of measuring deltaSVg with CIP was partly impaired by the length of time needed to analyse scans, which was a minimum of 30 minutes per patient. This adds further information to a report on the time needed to perform semi-automated lobar segmentation; a previous study using two radiologists to test segmentation mapping found that lobar segmentation, without parenchymal density analysis, took between five and seven minutes.[269]

Overall the values obtained by non-radiologists using CIP cannot be considered reproducible to within clinically acceptable limits for measuring lobar volume and density; the density values obtained using either a smooth filter or no filter are also not equivalent. This indicates that, whilst CIP is a valuable tool for researchers because the ability to analyse scans at no cost can facilitate rapid hypothesis development and identification of trends, radiologists may need to analyse the scans or refinements in the lobar segmentation module may be needed. It is possible to request additional features for the software via the online community, which enables the software to be developed in clinically relevant ways so refinement may be possible. Comparison across different types of CT analysis software has previously reported high variability, these results confirm the same issue was encountered for the two types of software used in this study.[277] This means that it will be important to establish either which software process is the optimal one for clinical use or a way of adjusting results to allow meaningful comparison between software systems.

The superior performance of CT analysis over segment counting for predicting postoperative FEV1 and TLCO was not repeated in this study. The lack of reproducibility of accurate results using prediction based on CT density and volume is concerning and is evidence against the generalisability of published results outside of their study populations. Segment counting and both approaches to CT analysis performed poorly in predicting FEV1 being over 100ml different from the actual postoperative value on average. CT analysis using dSVg performed poorly in predicting postoperative TLCO but segment counting and CT density and volume were within 0.2mmol/min/kPa of the actual postoperative value on average. However, all three methods were imprecise.

The calculation of deltaSVg at lobar level in this study may be too simple to account for finer variation in regional ventilation at segmental levels within each lobe; as such refinements in the analysis process could still provide clinically significant improvements in prediction. Alternatively it may be that postoperative lung function is affected by so many different factors that improvements in accuracy of predictions may not be achieved through technological means. Surgical guidelines list 45 steps from before admission to discharge to aid the recovery of patients, all of these factors in addition to multiple unknown factors that occur after discharge may influence lung function.[278] Predictions are certainly of interest to thoracic surgeons and the number of publications on the topic attest to this, but attendance at thoracic surgical conferences reveals there are also vocal proponents of reducing the importance of lung function or exercise testing in preoperative assessment in light of the high mortality of lung cancer. However, the ability to assess segmental ventilation in three dimensions and understand how this affects lung function could have other diagnostic and monitoring uses and as

such it would be useful to establish whether clinical or technological issues underlie the findings of this study.

3.4.3 Challenges and weaknesses

3.4.3.1 Patient experience

Informal feedback from patients was received throughout the study. Extra hospital visits were viewed as a significant burden for patients since they already have to attend multiple appointments from the initial suspicion of lung cancer up to the day of operation. Hospital visits for research were coordinated with visits for clinical appointment as much as possible but this was not always achievable. Any further study of CT analysis in this setting would need to provide study interventions as close to the locality of patients as possible and further integrate research visits into the patient pathway. A potential solution would be to perform the study CT scans at the time of the PET CT scan required for routine care, however the operability of lung cancer is not confirmed until after the PET CT results are available. Integrating the scan timing is this way is technically possible but explanation of the study and obtaining informed consent at a time of such uncertainty would be exceptionally difficult and confusing for patients. Ideally any scans for analysis would need to be the same as the ones that are already used for routine care. These scans are currently always performed during inspiration and with the administration of contrast, therefore the possibility of an adjustment for the density of contrast media would need to be investigated.

3.4.3.2 CT analysis software sourcing

The study was commenced in good faith from all parties that using custom software developed by Prof Andrea Aliverti's team at Politecnico di Milano would be

straightforward. The author of this thesis travelled to Politecnico di Milano and trained with Francesca Pennati and Caterina Salito on using the code that had been developed there. The process involved analysing three CT slices for each inspiratory and expiratory image series, the slices were matched manually using an image viewer. The results did not provide analysis of lung parenchyma in three dimensions and results were provided as median values, which could not be combined to provide an assessment at a lobar level. Multiple meetings and writing communication with the team in Milan, a local Radiography Professor, and local Computer Sciences Professor finally confirmed that three dimensional analysis to give lobar information was not going to be possible using the custom software. The three dimensional analysis that had been published was performed as a single complex analysis to illustrate a biomechanical concept and was not suitable for analysis of multiple scans.[279] It was determined that the concept underlying the calculation of deltaSVg could still be used but this would require software that could provide both lobar volumes and lobar densities.

Alternative approaches to analyse the CT scans were sought and an Australian team had developed an open access program called VESPIR (VEntilation via Scripted Pulmonary Image Registration) to quantify regional lung ventilation; they had developed this for patients scheduled to undergo radiotherapy to treat lung cancer.[280,281] The team was contacted to obtain a copy of VESPIR and trial it. The software installed and loaded correctly but repeatedly displayed an error early in the processing of the DICOM images. The error was not one that the Australian team had come across in their work and it could not be resolved, they suggested CIP might provide the necessary analysis.

During this time CT analysis of interlobar fissures using the StratX platform had commenced at Heartlands Hospital for clinical care of patients being reviewed at the emphysema MDT for potential LVR surgery. The analysis process also provided densitometry measures, so the company providing StratX was approached to enquire about using their software to analyse the scans of patients undergoing lung cancer resection. The Netherlands based company, Thirona, was receptive to the idea and agreed to provide analysis of 20 scans free of charge. Unfortunately this was at the time the General Data Protection Regulation (GDPR) came into force and the hospital trust also underwent a major merger, which resulted in a significant delay of around nine months in signing the appropriate data sharing contracts for the anonymised scans.

A significant disadvantage of having to analyse the results with different software to that which was originally intended is that the measurement of deltaSVg was determined at a lobar level only; the custom software owned by Prof Aliverti may only provide analysis in two dimensions but the analysis included deltaSVg at a subsegmental level. The failure of this study to reproduce results reported in the literature or to provide an improvement over prediction with segment counting may be overcome if three dimensional subsegmental deltaSVg could be measured.

3.4.3.3 CT analysis

Analysis was undertaken on a small sample, however prospective studies in the literature do not report many more than 20 patients per study.[276] The small sample sizes may be indicative of similar feasibility issues identified in this study but they have not been explicitly reported.

A number of technical issues are relevant to the generalisability of pulmonary CT analysis. Firstly the optimal slice thickness has not been agreed, even the same authors have used and reported different slice thicknesses of between 1mm and 5mm. [106,155,168] Scanning at 1mm slice thickness is becoming the common standard of practice as this allows 3D reconstruction of scans, however this is based on pragmatism rather than evidence of optimal results of density analysis with the 1mm slice thickness. Secondly, calibration of the scan grey scale to air and blood densities has shown to be needed to account for variation in attenuation obtained from the same scanner over time and variation between scanners.[282] CIP calibration was requested and has been added to the software but it requires an instruction manual to be created and also the ability to integrate the calibration with the lobar segmentation and parenchymal analysis modules of CIP. Thirdly, a major limitation of the CIP analysis is that the average parenchymal density is provided as a mean value only rather than as voxel counts that can be transformed or as a median value, which is less flexible for use in analysis but more valid when describing skewed data. Finally the delineation of the upper density limit of -350HU for analyses of the data provided by Thirona may have biased results by excluding tumour volume from calculations. This limit was used for two reasons; the limits of the CIP data provided graphically had an upper limit of -350HU and values above this increasingly belong to non-pulmonary structures. This approach was pragmatic but evidence about the optimal cut off for CT density analysis when assessing deltaSVg is lacking.

3.4.4 Strengths of the study

This is the first study to report the clinical feasibility of a CT analysis instead of reporting only the technical feasibility; the significant issues identified may indicate that

further study should only proceed with careful mitigation of the difficulties described, such as patient transport, changeable surgical plans, emotional state of patients in the lung cancer pathway, and logistical issues of additional scans in busy radiology departments. These feasibility issues may indicate further investigation is not possible on a large scale or that lung function does not represent a priority area for patients.

The study has led to a new collaboration between the research teams at Thirona and Heartlands Hospital; a key difference in this collaboration is that Thirona have already developed lung analysis software that has been validated and CE marked for clinical use, thus any future findings that are potentially beneficial to patients can be translated into clinical care without undue delay.

The CIP CT analysis was performed by individuals who are not radiologists, as such the reliability data it applicable to research teams that do not have a radiologist; the reliability of the process may reach clinically acceptable levels if it were used by experienced radiologists.

3.4.5 Implications for practice and future research

This study does not advocate a change in clinical practice at the present time. The results indicate that further studies of deltaSVg using the existing patient pathways and analysis steps in this study are not feasible or advisable. The screening and study completion data indicate there may be complexity to the patient population that is potentially familiar to clinicians but not adequately captured in previous reports of CT analysis. This could underpin the failures to recruit and also failures to complete the study; the patients' perspective on their own priorities throughout care need to be

established. Lung cancer is conspicuous in its absence from the James Lind Alliance Priority Setting Partnership reports despite its high incidence and high mortality. Patient direction about the areas of research that matter to them is critical for future studies to succeed and address patient needs.

Further investigation of CT analysis in patients undergoing lung resection should include reporting of the impact of CT parameters, such as slice thickness, calibration, and density thresholds, on the reliability and validity of CT based lung analysis. To this end two-way communication between clinicians and software developers should facilitate the measurement of relevant parameters. The measure of deltaSVg could be obtained using different processes; refinements in software may yield more accurate predictions, particularly if 3D subsegmental measurement of deltaSVg can be achieved and combined to quantify lobar function. This will be assessed through the new collaboration with Thirona, results should be available more rapidly and at no cost to patients as the clinical data set can be reused in accordance with existing consent, which has already kindly been given for the data to be used in such a way.

CHAPTER 4: HETEROGENEITY OF REGIONAL VENTILATION AND PATTERNS OF INTERSTITIAL LUNG DISEASE

4.1 Introduction

4.1.1 The diagnostic process for ILD

There are over 300 types of interstitial lung disease (ILD) and the prognosis and treatment options vary considerably depending on the disease subtype. [48] Usual interstitial pneumonia (UIP) is a common histological subtype, which is known as idiopathic pulmonary fibrosis (IPF) when the aetiology of the disease is uncertain. IPF confers a poor prognosis with reported survival times of close to two years from diagnosis or close to four years from the onset of symptoms; the anti-fibrotic agents pirfenidone and nintedanib have been shown to slow the decline of functional vital capacity (FVC) in patients with IPF but survival and frequency of exacerbations are not improved with treatment.[283,284] Sarcoidosis, in contrast, has little effect on mortality compared to a matched general population and the disease generally responds both symptomatically and physiologically to treatment with corticosteroids.[285,286] It is clear from these brief illustrations that it is crucial clinicians are able to diagnose the subtype of ILD not only to guide therapy but also to enable appropriate counseling of patients; life choices may be drastically altered in the face of an adverse prognosis.

The current method for diagnosis of ILD subtype is by MDT consensus, which involves close clinical, radiological, and pathological correlation between the shared expertise of respiratory physicians, radiologists, and histopathologists respectively. Surgical lung biopsy was previously considered the gold standard for diagnosis but recommendations

to obtain lung tissue surgically are now regarded with more caution due to the risks involved with surgery in this patient population. Surgical biopsy entails a 19% risk of major complication and 9% risk of death at 30 days postoperatively, however the risk of postoperative mortality was up to 86% in patients with certain risk factors that included advanced age, preoperative intensive care admission, preoperative immunosuppression therapy, and open surgical approach.[287,288] It is thought that the surgical insult, including the effects of anaesthesia, is liable to initiate an acute exacerbation of ILD, which is the predominant cause of postoperative mortality.[287] In addition to the risk of death, patients are at risk of deterioration of quality of life due to pain; chronic pain occurs in between a quarter and a third of patients after thoracic surgery.[289] Chronic pain after thoracic surgery is of such importance that multicenter randomised controlled trials are in progress. [290,291] Novel non-invasive tests that may contribute to the MDT decision making process by providing additional information to current tests are desirable, particularly as they have the potential to further reduce the need for surgical lung biopsy.

4.1.2 Histological basis of altered regional ventilation in ILD

Determining the subtype of ILD from histology requires subspecialist training, however the basis for investigating evidence of histological alterations by quantitative CT analysis are conceptually accessible. In patients with chronic ILD, as opposed to acute presentations of ILD that lie out with the remit of this study, fibrosis is the most important pattern to be noted microscopically. [51] Characteristic honeycombing that is reported qualitatively by radiologists from CT scans is visible microscopically; these microscopic changes may be apparent prior to the macroscopic radiological changes. Temporal heterogeneity is a hallmark of UIP, this term refers to the combined presence

of established fibrosis, fibroblasts in the process of laying down fibrin, and healthy lung tissue that is yet to be involved in the disease process in the same tissue sample. Thus, variable 'timeframes' of the cellular disease process are present concurrently.

At physiological lung volumes elastic fibres are the main source of elastic recoil within the lung and help maintain the structure of the lung tissue; these fibres have a linear relationship between the load placed and the change in fibre length at normal volumes.[292] Collagen fibres are loosely curled at normal lung volumes and contribute little to the elastic recoil, unless the lung becomes over distended at which point the fibres are straightened and rigid, limiting further distension. In ILD, the alveolar structures are distorted and replaced by fibrosis, the predominant constituent of which is collagen. The parts of the lung that have become fibrotic with excessive deposition of collagen are less distensible than normal lung tissue, accordingly FVC is reduced and lung fibrosis is termed as restrictive. The focus of this study is whether the heterogeneous microscopic pattern of disease in UIP, which results in heterogeneous rigidity of collagen rich extracellular matrix, will produce differences in regional ventilation of the lung parenchyma that are detectable on radiological imaging in vivo.

4.1.3 Quantitative CT in classifying ILD

Previous studies have attempted to use quantitative density measures on CT to aid in the identification of UIP, with variable results. One group compared patients with UIP and the non-specific interstitial pneumonia (NSIP) subtypes of ILD; they found that kurtosis and skewness of the density histogram was significantly different between the patient groups.[293] IPF has also been shown to differ from non-fibrotic sarcoidosis of the lung in skewness and kurtosis of its density histograms.[294] However differences in

descriptors of density histograms did not seem to be reliably reproducible as another study did not find any difference in these measures between patients with UIP and patients with non-UIP ILD.[295]

Lung texture analysis on inspiratory scans in a small study has been able to discriminate between UIP and NSIP with a sensitivity of 79% and specificity of 85%.[296] The texture analysis had focused on identifying regions of particular abnormal patterns to aid in diagnosis and prognostication; this appears to have potential for clinical use but the changes in tissue throughout the respiratory cycle were not examined. [297,298] Detail may be lost in the categorization process since software was not trained to identify regions that a radiologist cannot identify as belonging to a certain pattern, in addition radiologists may disagree about patterns in some instances due to the subjective assessment. The added value of the paired expiratory scan in assessment of respiratory diseases has been recognised and integrated into quantitative assessment of CT density at a voxel level called parametric response mapping (PRM); this has so far been used to assess functional small airways diseases, which may not be identifiable on a lone inspiratory CT scan, but quantitative CT analysis of paired inspiratory and expiratory scans has not yet been reported in ILD.[299]

4.1.4 Hypotheses

The aims of this study were to assess whether the histological temporal heterogeneity that is present in UIP results in an increased heterogeneity of regional ventilation that is detectable on CT scanning. The specific hypotheses were:

- Calculation of regional ventilation on non-contrast paired inspiratory and expiratory CT scans is possible in patients with ILD
- Patients with UIP have higher heterogeneity of regional ventilation on analysis of paired inspiratory and expiratory CT scans compared to patients with non-UIP subtypes of ILD

4.2 Methods

4.2.1 Study design

A prospective observational study of consecutive patients was conducted at Heartlands Hospital, now part of University Hospitals Birmingham NHS Foundation Trust. Patients were approached in outpatient clinics at routine scheduled appointments with the ILD Specialist Nurse and at preoperative assessment clinics prior to diagnostic surgical biopsy. Adult patients with capacity to give informed consent and confirmed or suspected ILD were eligible to participate. Patients both with and without histological testing of their lung tissue were eligible. Patients underwent a non-contrast inspiratory and expiratory CT scan at a single radiology appointment after giving written informed consent to participate in the study, the consent form and patient information sheet are in Appendix 2 and Appendix 3. Demographic and clinical data were collected at baseline prior to CT scanning. ILD subtype was determined according to the ILD MDT consensus recorded in the patient notes.

4.2.2 Funding & regulatory approvals

The author of this thesis completed the required documentation for ethical review via the Integrated Research Application System under supervision and attended the REC meeting for the study. The study was adopted onto the National Institute for Health

Research Portfolio of studies (REC reference 15/EM/0446) and registered at ClinicalTrials.gov (identifier NCT02879773). The study was awarded funding from the British Lung Foundation in the form of a Pump Priming Research Grant; the funding application was prepared under supervision.

4.2.3 CT acquisition

CT images were obtained using a single Aquilion ONE scanner (Toshiba Medical Systems Corporation, Tokyo, Japan) for all patients. CT scanner settings were: voltage 120kVp, current 110mA, rotation time 500ms, matrix 512 x 512, slice thickness 1mm. Images were reconstructed with an FC51 convolution kernel; the FC51 filter is a standard smooth lung algorithm that is recommended for volume measurement by the manufacturers of the scanner.[262] Scans were obtained without contrast at end inspiration and end expiration with patients in a supine position; automated voice instructions were played to the patient by the scanner to perform the respiratory maneuvers. The Medical Physics Expert report determined a radiation dose of 10mSv per participant, equivalent to 5 years background radiation in the United Kingdom.

4.2.4 CT analysis

The inspiratory and expiratory CT slices were paired manually by recording the slice numbers at the level of the carina in the axial images using vascular and bronchial landmarks. The distribution of parenchymal changes in ILD is known to follow apicobasal gradients; therefore this consistent anatomical level was used for CT slice pairings. [300] The expiratory images were assessed first to identify the level of the carina, defined in this study as the first slice where the tissue of the carina was not visible, and

the inspiratory image that matched the expiratory image at the carina was identified as the second step.

Analysis of the paired images in DICOM format was performed using custom software in MATLAB version 9.1 R2016b (The MathWorksInc, Natick, MA, USA); the author of this thesis travelled to Politecnico di Milano and learnt the analysis process with Dr Francesca Pennati and Dr Catarina Salito who worked under Prof Andrea Aliverti in the Department of Bioengineering to developed the software.[301] The application of the analysis process was the result of this international collaboration between the two departments.

The sequence of steps for measurement of regional ventilation was as follows:[68]

1. Paired slice selection
2. Lung segmentation
3. Pre-processing
4. Mapping of movement during inspiration
5. Application of the map to the expiratory image
6. Subtraction of Hounsfield Units (HU) and Specific Volume of gas (SVg) values on a voxel by voxel basis*

* The data comes from voxels, however the software processes are performed in two dimensions and treats voxels as two-dimensional pixels entities. The term voxel has been used in this outline to avoid confusion.

The process was semi-automated after identifying paired images; manual steps included confirmation that the segmentation processes had completed correctly. Results were provided as median and quartile values for the anterior, middle, and posterior parts of

the left and right lungs, saved in an Excel spreadsheet at the conclusion of analysis. The median of these median values was used for analysis.

Lung segmentation was performed to separate the lung tissue in the image from mesenchymal structures and the proximal pulmonary blood vessels; this process was based upon grey level thresholding. [302] Pre-processing involved removing smaller blood vessels using a threshold of -400HU, removal of fissures using vertical and horizontal gradients within the image, and applying a Laplacian filter to minimise any intensity gradients across the image (known as field bias).

Vectors define the direction and magnitude of a movement. Mapping utilised the optical flow method to create a field of vectors that described the movement of features within the expiratory image when it was being deformed to match the inspiratory image. [303] The expiratory image could then be deformed to align voxels with the inspiratory image once the field of vectors had been determined; finally the SVg values of each expiratory voxel were subtracted from the inspiratory ones to give the deltaSVg as the measure of regional ventilation (see Section 3.1.2).

4.2.5 Statistical plan

This was an exploratory analysis to ascertain the effect sizes to power a future study and whether any trends were present to support proceeding to a larger study.[304] For a pilot study to establish variance in the parameter of interest a sample size of 40 should be sufficient; to allow for a dropout rate of 10% the study target for recruitment was 44 patients.[264,265] DeltaSVg is known to not follow a normal distribution, so the magnitude of the interquartile range (IQR) of deltaSVg was the measure of heterogeneity of

deltaSVg used for this study. The independent samples t test was planned to compare normally distributed variables, the Mann Whitney U test was planned to compare non-normally distributed variables and Fisher's exact test was planned for comparison of proportions between the two patient groups on univariable analysis. The distribution of data was assessed using Shapiro Wilk tests. Statistical analysis was performed using SPSS version 26 (IBM Corp.).

4.2.6 ILD severity

The severity of the ILD was considered to be a potential confounding factor that could affect deltaSVg. The wide range of clinical pictures encountered with ILD has made the development of a global classification of disease severity difficult; the closest measure reported across a variety of subtypes of ILD is a prognostic measure called the Interstitial Lung Disease Gender Age Physiology (ILD-GAP) model. This model was developed as a prognostication model for patients with IPF but it has now applied to other subtypes of ILD, including those that could not be classified.[305] Therefore the ILD-GAP score was planned for inclusion in a binary logistic regression model to enable the comparison of deltaSVg IQR whilst controlling for disease severity. The ILD-GAP model scoring system is included in Appendix 4. Receiver operator characteristics (ROC) and area under the curve (AUC) analysis was planned to give an overall assessment of the diagnostic performance of deltaSVg IQR in identifying UIP whilst controlling for the ILD-GAP score.

4.3 Results

4.3.1 Participants

A total of 36 patients were recruited over 24 months and 27 patients completed the study; patient flow through the study is shown in Figure 51. The ILD MDT concluded that one patient did not in fact have ILD prior to their intended CT appointment so the patient was withdrawn. The patient characteristics are displayed in Table 20. One patient did not have a TLCO recorded, the mean value (53% of expected) was imputed in this case, all other data fields were complete.

4.3.2 Univariable analysis

Processing of scans was problematic in some cases; the paired scans for five cases showed segmentation that was too poor to proceed with any further analysis, these are shown in Figure 52. Cases with good segmentation are shown in Figure 53; some cases showed good segmentation for part of the slice only and the results for the anterior part of the scan only were used in analysis, these are shown in Figure 54.

It was important to statistically compare the patients who did not complete the study to those that did due to the significant attrition. The tests used for comparison were adjusted to allow for comparison of three groups by employing a one-way analysis of variance (ANOVA) to compare age, FVC, and TLCO. The Kruskal-Wallis test was used to compare ILD-GAP score. The biggest reason for drop out from the study was that patients changed their mind about participation; it was noted that the CT appointments available for research use were either before 9am or after 5pm and transport to the hospital site at these times is particularly difficult due to rush hour traffic. Some of the

ILD clinics were held at a separate hospital site to the scanner, which meant further travel in addition to traffic compared to their usual clinical visits.

The patients with or without UIP had similar characteristics on univariable analysis apart from the ILD-GAP score, which was two points lower in patients without UIP (Table 20). The baseline characteristics of patients whose scans could not be analysed did not significantly differ from those that were included in analysis. The mean IQR of deltaSVg was slightly larger at 5.29 in the UIP group compared with 4.48 in the non-UIP group; with a p value of 0.388 this did not confirm a trend for more heterogeneous regional ventilation in UIP and the analysis would not be a clinically useful test in isolation. However, a trend could have been missed due to confounding from the difference in ILD-GAP score and analysis whilst controlling for the ILD-GAP score was undertaken. DeltaSVg in healthy lung tissue has an IQR of 2.2ml/g compared to the 4.4-4.9ml/g found for the study patients. [68]

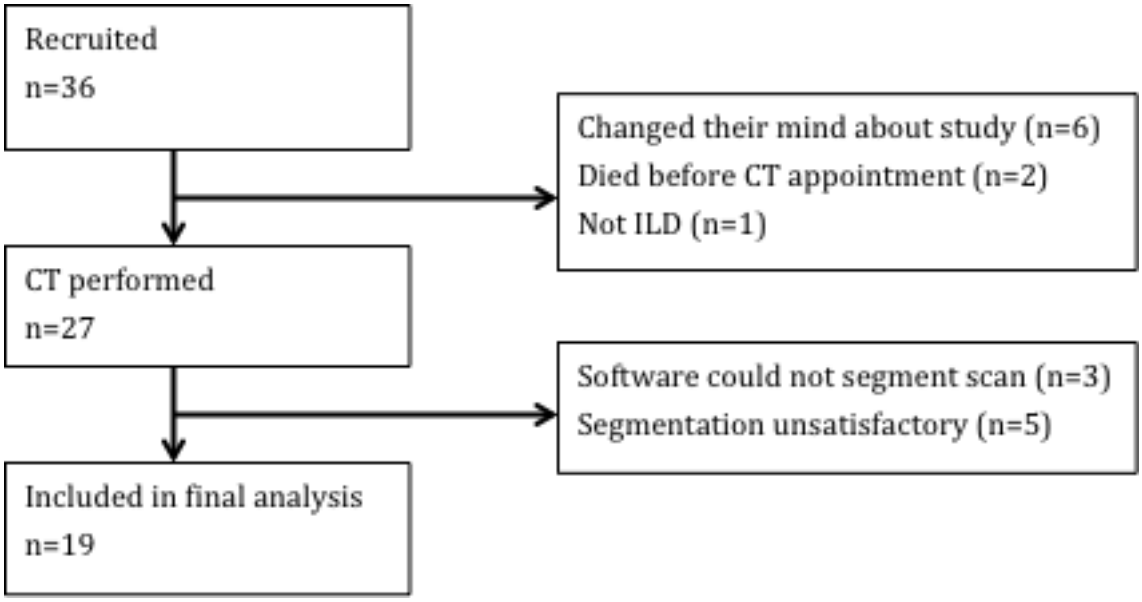


Figure 51 Patient flow through the study of heterogeneity of regional ventilation in ILD.

Table 20 Patient characteristics at baseline

	Shapiro Wilk p value	**UIP group (n=8)**	**Non-UIP group (n=11)**	**Failed analysis (n=8)**	**p-value**
Age #	0.464	67 (7)	63 (11)	66 (12)	0.642
Male sex ##	Not applicable	75%	45%	50%	0.496
Surgical biopsy ##	Not applicable	50%	36%	38%	0.889
FVC (%) #	0.787	93 (22)	84 (19)	87 (22)	0.635
TLCO (%) #	0.794	51 (22)	53 (16)	45 (12)	0.640
ILD-GAP score###	0.008	3 (2-4)	**1 (0-2)**	3 (1.5-4)	**0.039**
DeltaSVg IQR ####	0.204	5.29 (2.33)	4.48 (1.68)	Not applicable	0.388
ILD subtype	Not applicable	6 UIP only 2 UIP & emphysema	4 HP 6 NSIP 1 Sarcoidosis	6 UIP 1 UIP & emphysema 1 HP	Not applicable

Statistical tests: # One-way ANOVA, ## Fisher's exact test, ### Kruskal-Wallis test, ####Independent sample T test

Abbreviations for ILD subtypes: UIP - usual interstitial pneumonia, HP - hypersensitivity pneumonitis, NSIP - non-specific interstitial pneumonia

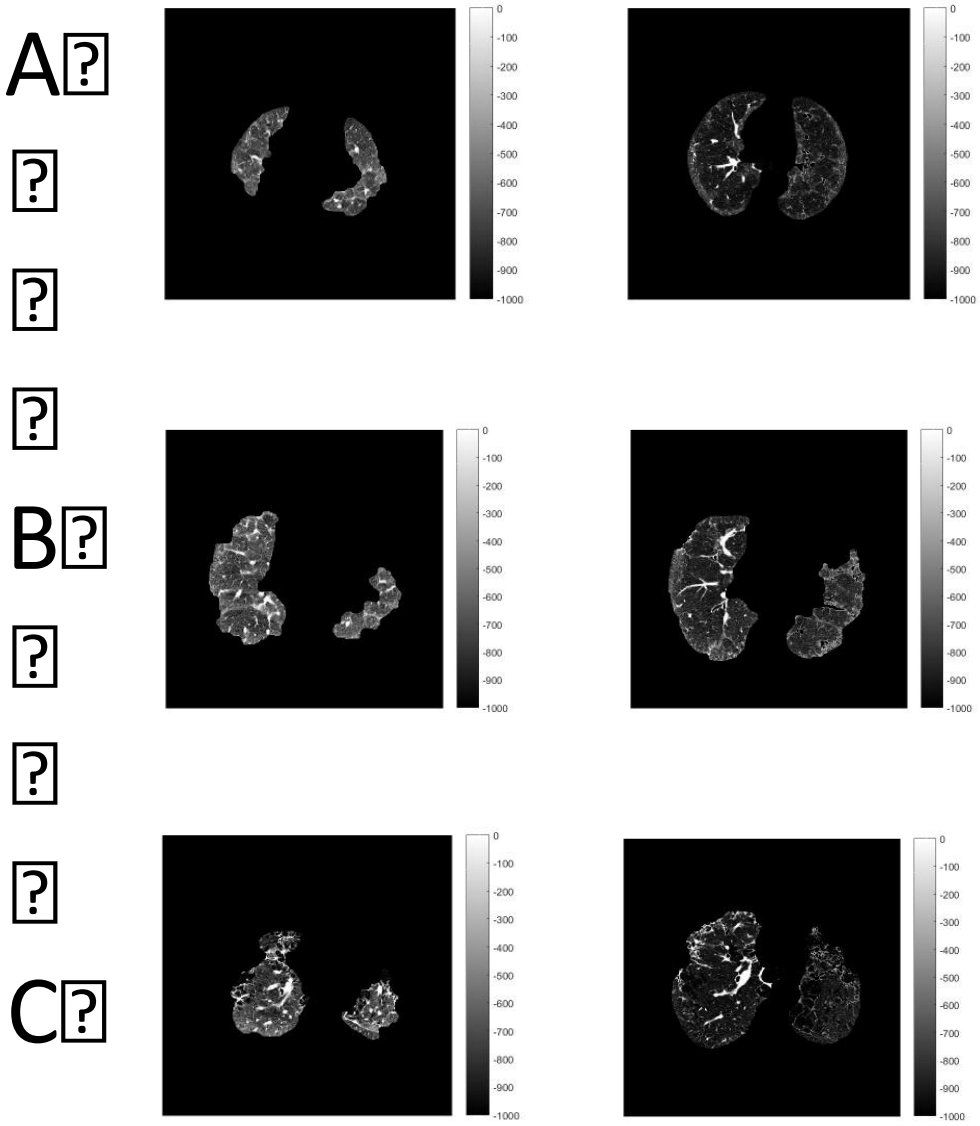


Figure 52 CT scans that could not be analysed due to poor segmentation of lung tissue (scan pairs A to E)

Note: Expiratory scans are displayed in the first column; inspiratory scans are displayed in the second column. The grey scale used is according to density in Hounsfield units, the left and right lungs are depicted on the opposite side, as is the convention in clinical images.

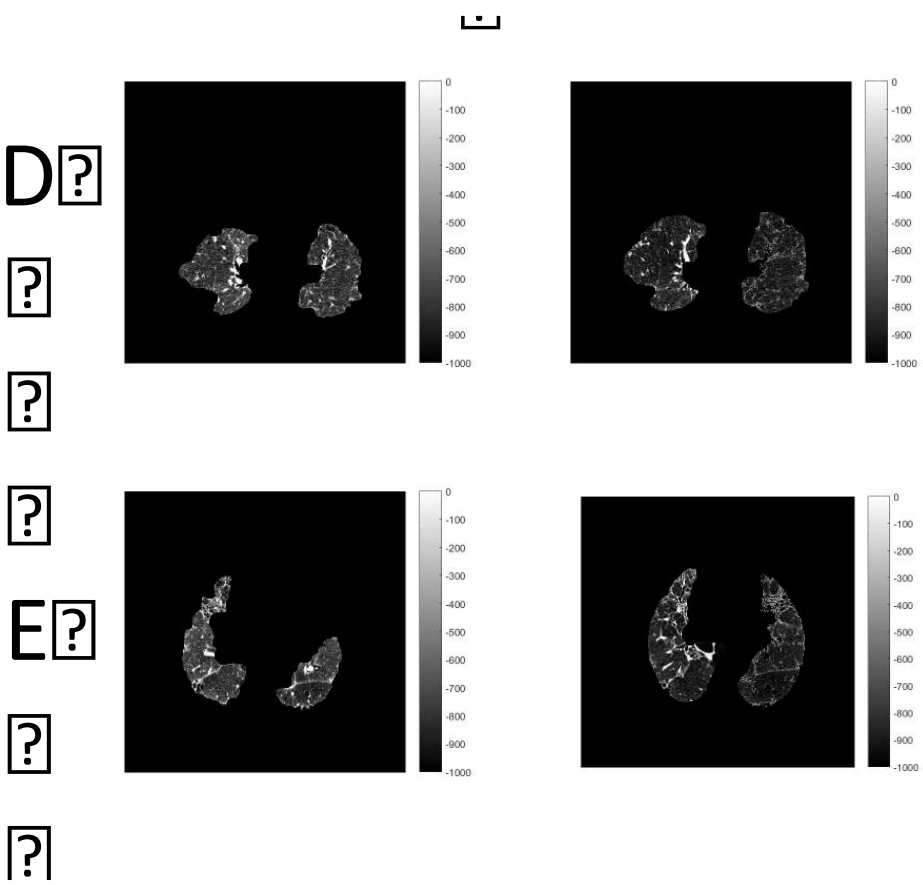


Figure 52 continued

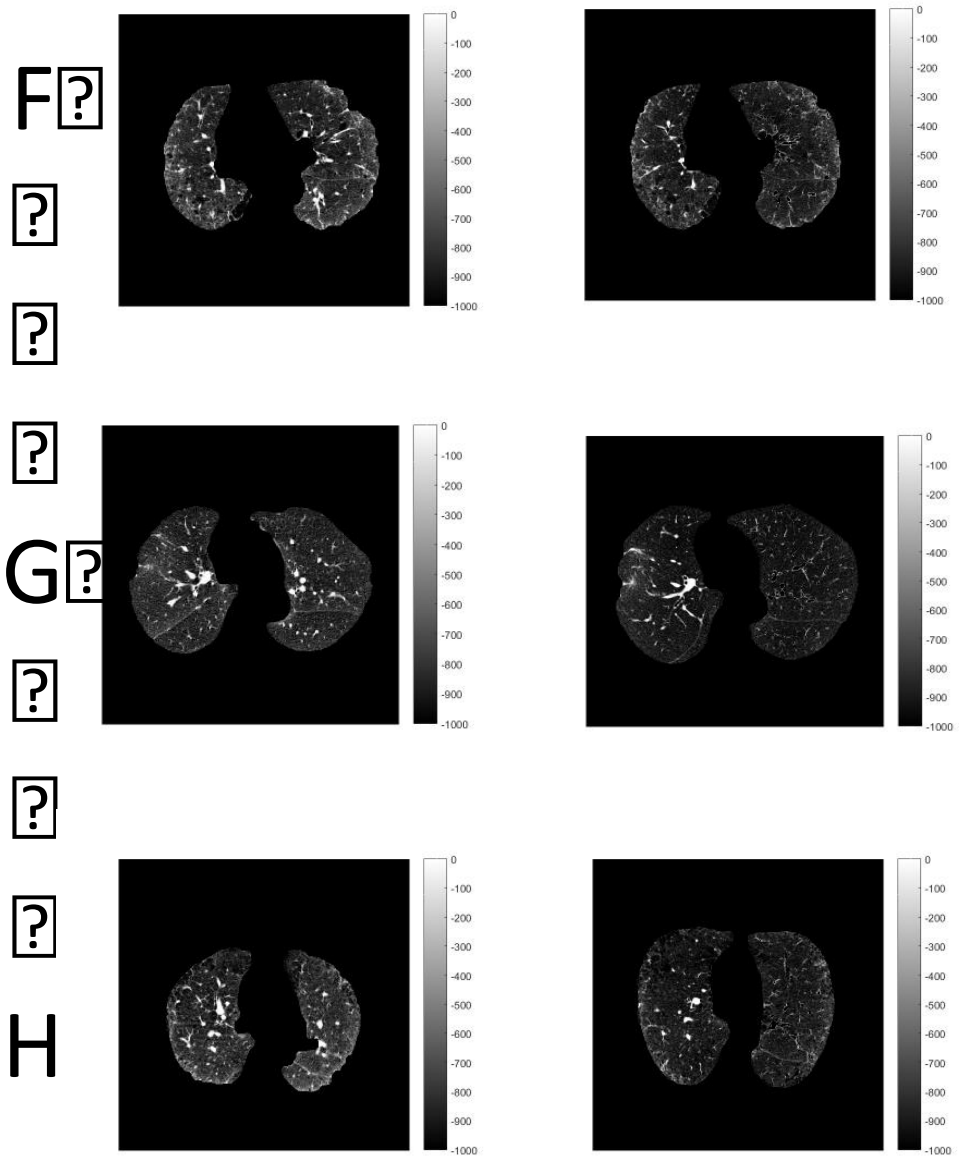


Figure 53 CT scans showing good segmentation (scan pairs F to Q)

Note: Expiratory scans are displayed in the first column, inspiratory scans are displayed in the second column. The grey scale used is according to density in Hounsfield units, the left and right lungs are depicted on the opposite side, as is the convention in clinical images.

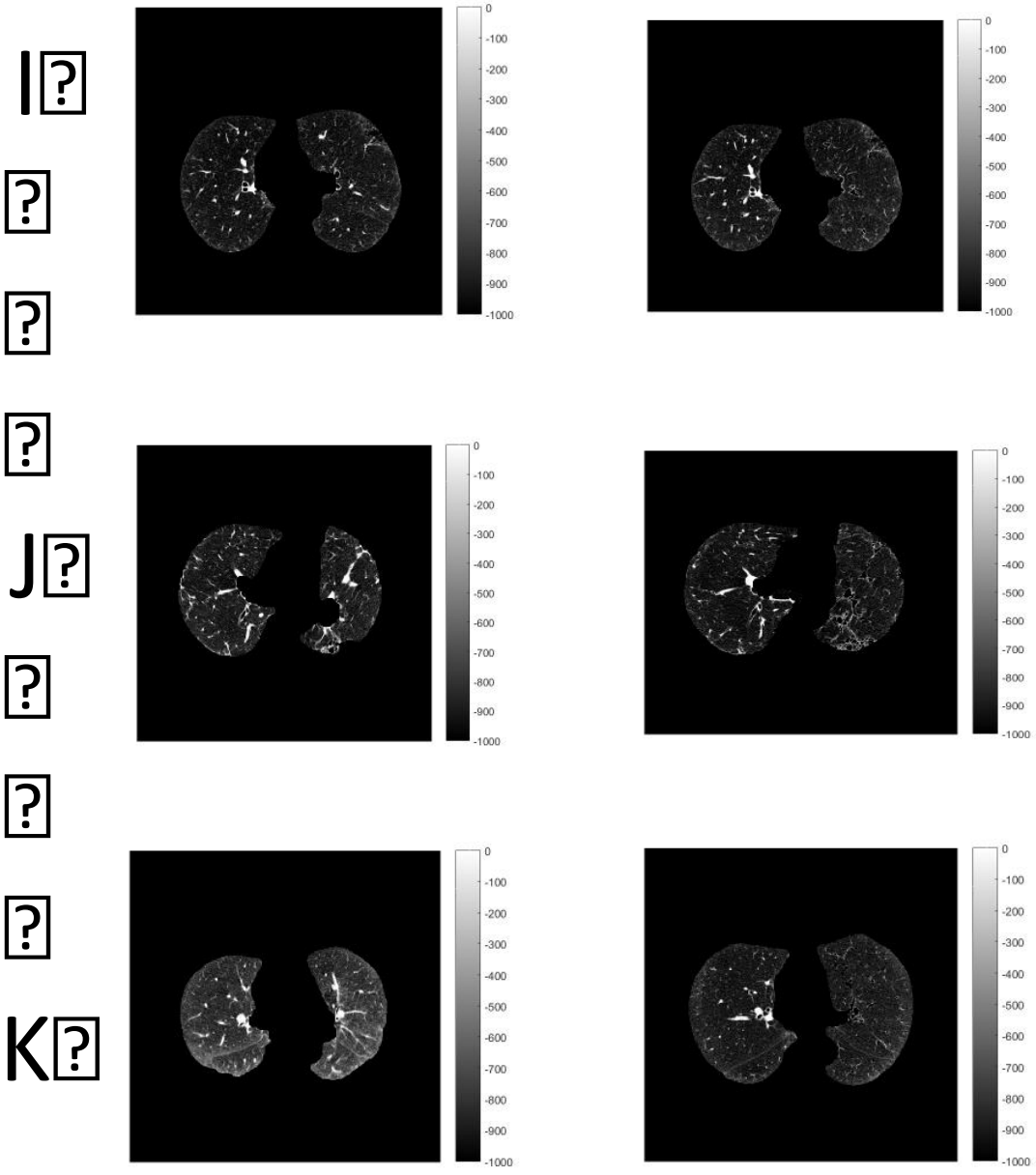


Figure 53 continued.

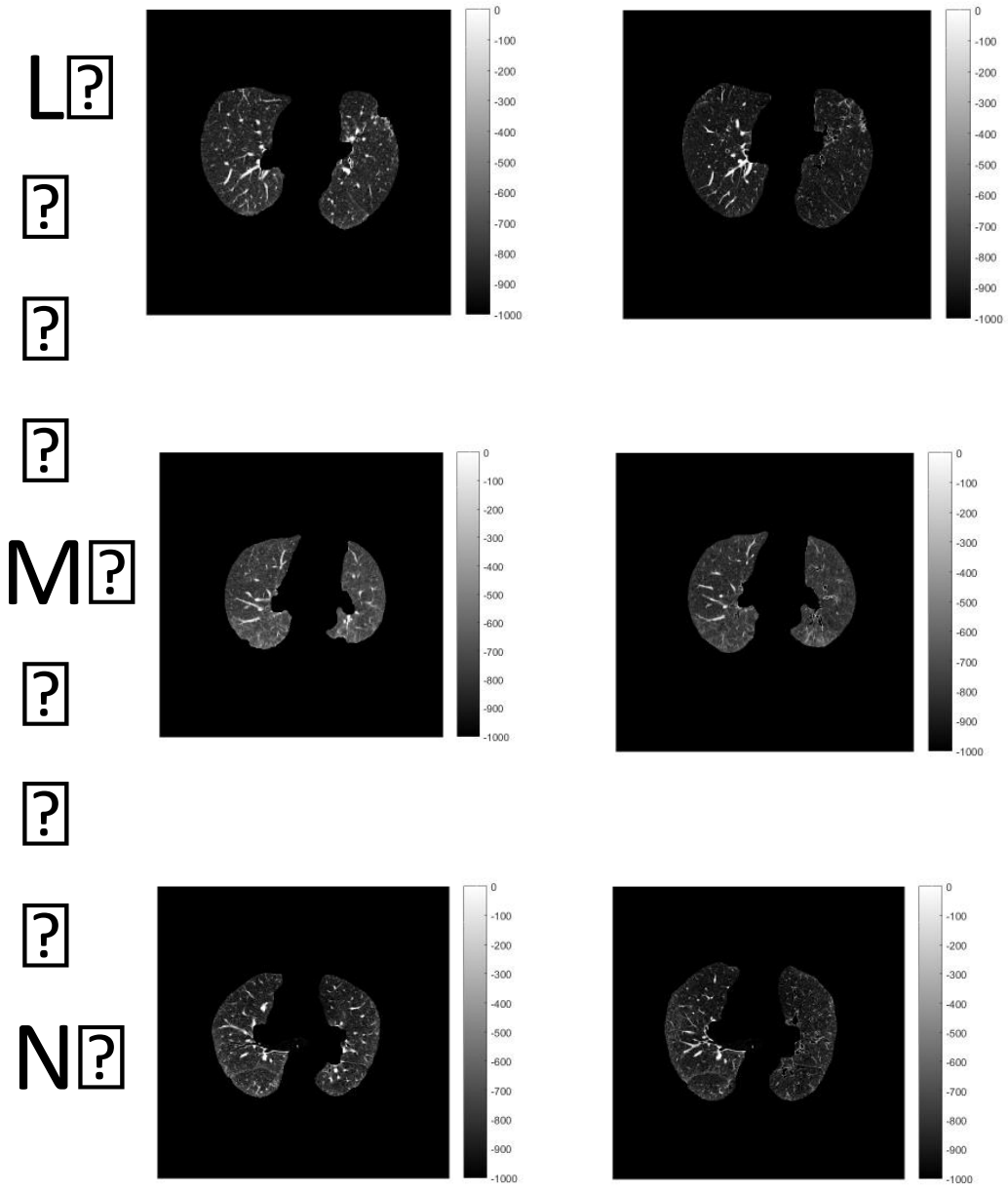


Figure 53 continued.

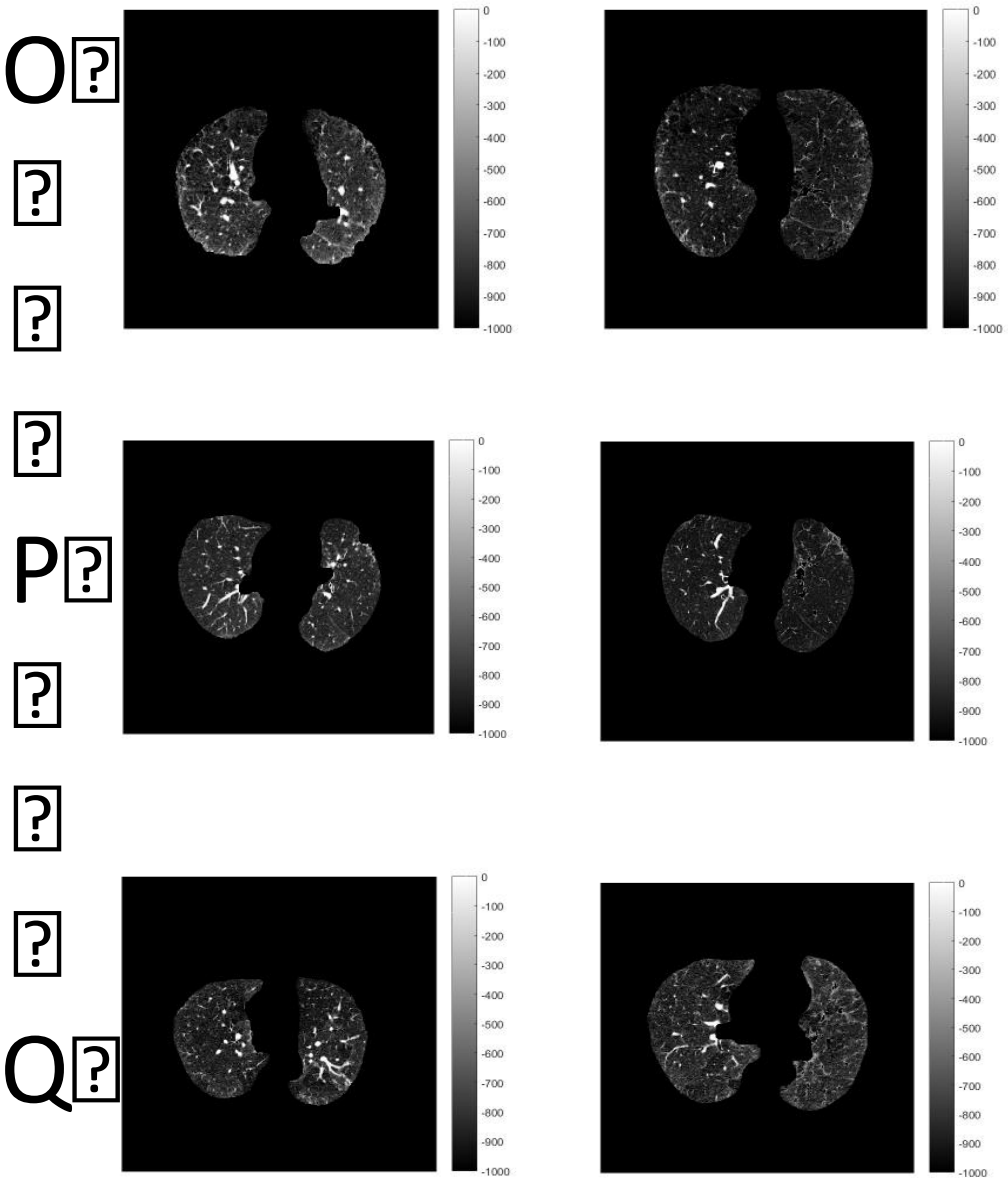


Figure 53 continued.

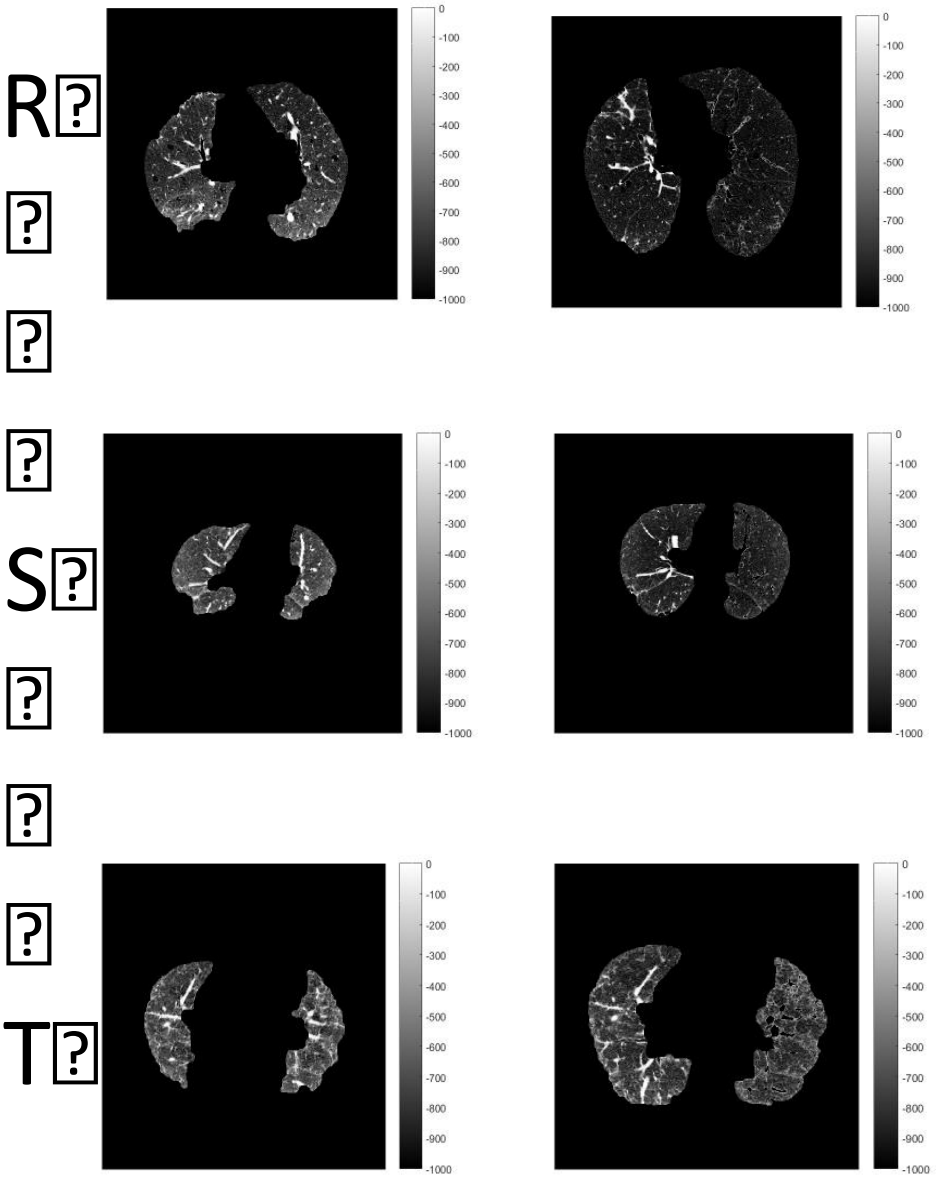


Figure 54 CT scans where only the anterior part of the scan showed sufficiently accurate segmentation to be used in analysis (scan pairs R to X)

Note: Expiratory scans are displayed in the first column, inspiratory scans are displayed in the second column. The grey scale used is according to density in Hounsfield units, the left and right lungs are depicted on the opposite side, as is the convention in clinical images.

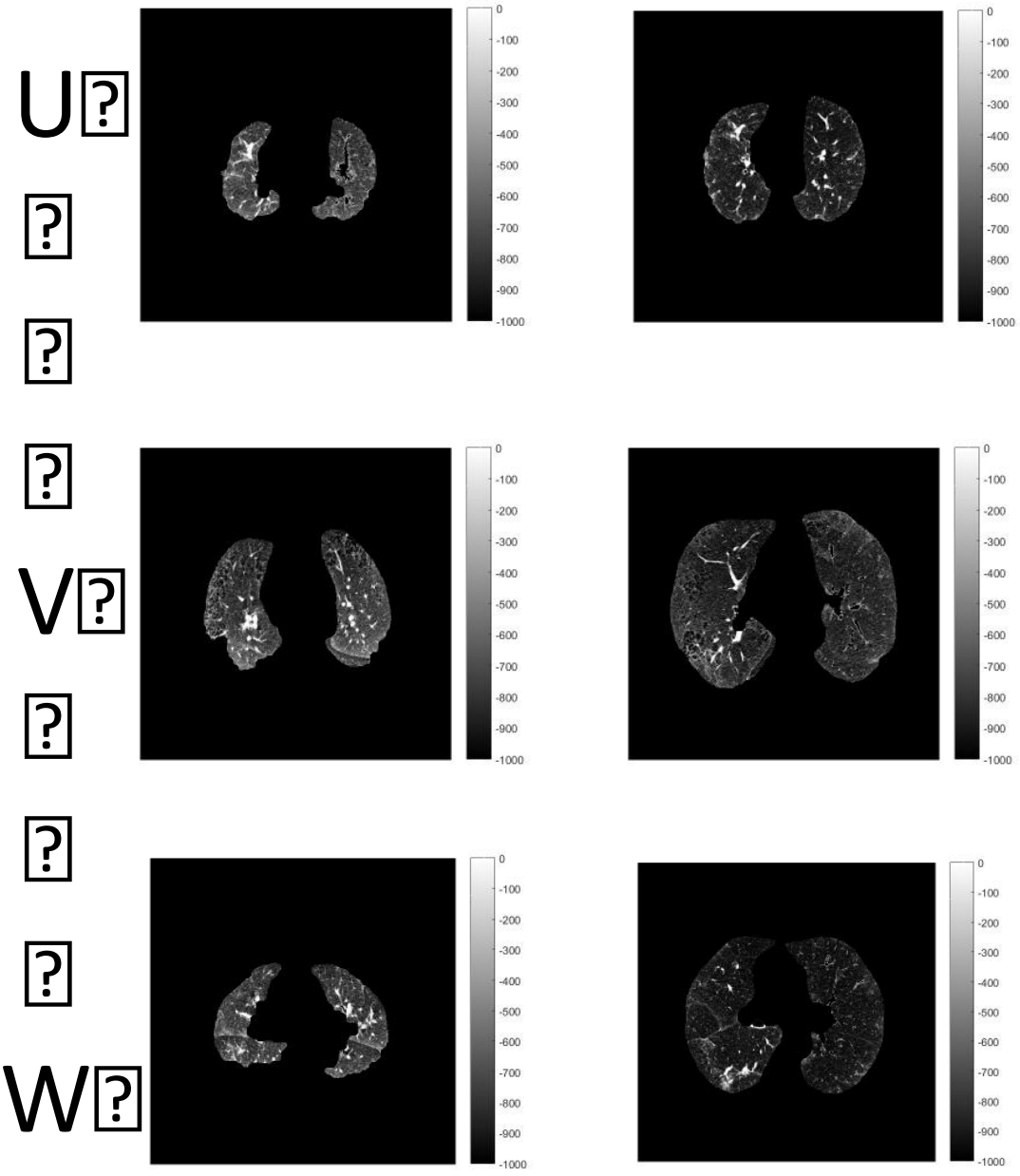


Figure 54 continued.

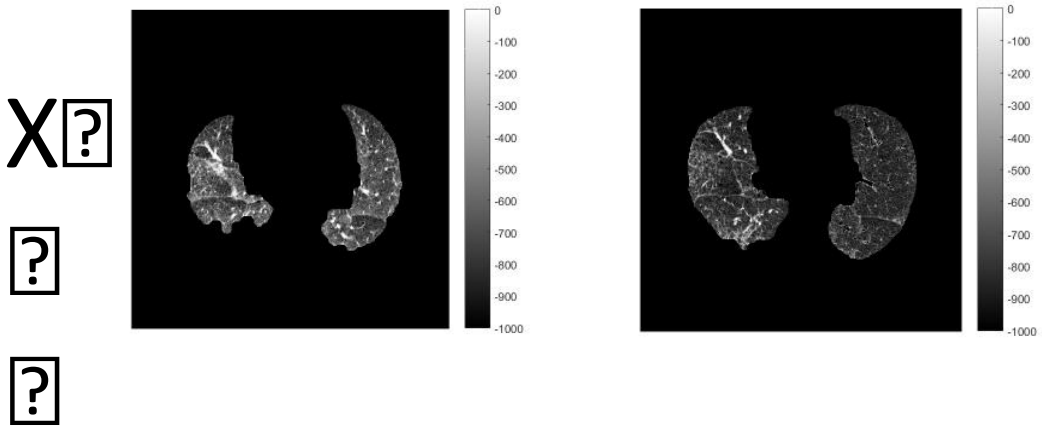


Figure 54 continued.

4.3.3 Testing adjusted for severity

4.3.3.1 Testing statistical assumptions

The assumptions of binary logistic regression are described in Section 5.3.3.1. The assumptions were met using the two variables planned for analysis. The delineation between UIP and non-UIP was dichotomous. Graphical analysis of the variables was performed and both were close to linear; the linear relationship was improved for deltaSVg IQR by performing a square transformation of the values (Figure 55 and Figure 56). Influential observations were tested using the standardised residual error, no values were found to be influential with a value above three (Figure 57). The variance inflation factor (VIF) showed minimal multi-collinearity (Table 21). A VIF of 1 is considered to show no correlation, 1 to 5 moderate correlation, and more than 5 high correlation.

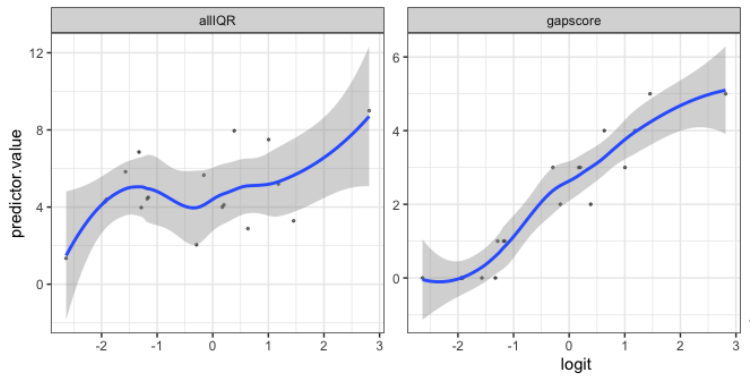


Figure 55 Linearity with the logit of the dependent variable for ILD-GAP score and deltaSVg IQR

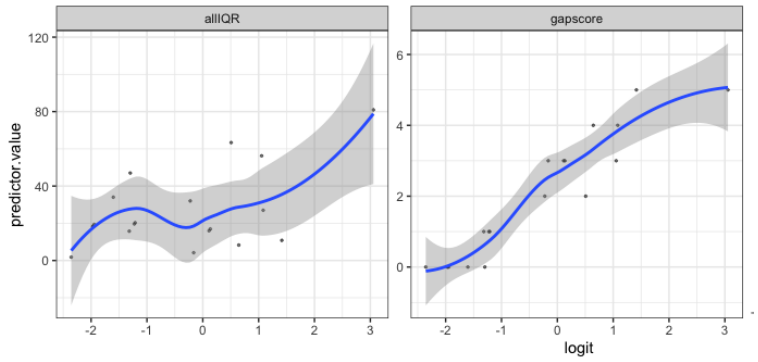


Figure 56 Linearity with the logit of the dependent variable for ILD-GAP score and with a square transformation of deltaSVg

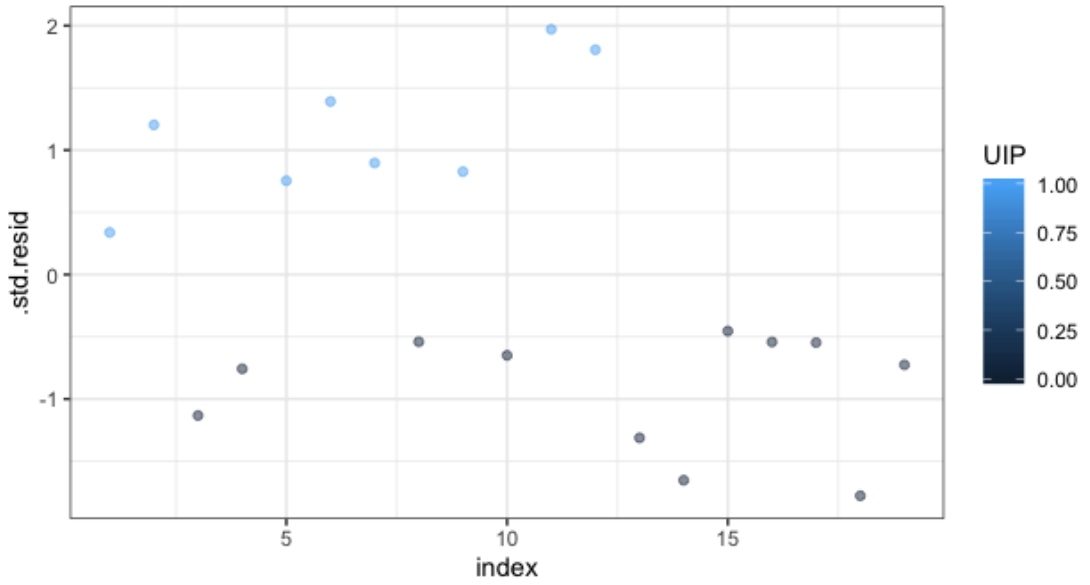


Figure 57 Testing for influential variables – standardised residual error plot.

Binary logistic regression yielded a model that was significantly better than a null model with no covariates, as demonstrated by the null deviance of 25.86 being greater than the residual deviance of 19.72, omnibus test of model coefficients (p=0.046). Coefficients and odds ratios for the model variables are shown in Table 22. The square root of the odd ratio values were obtained to account for the transformation used prior to binary logistic regression. The percentage correctly classified was 68%, without the model 58% were correct. Approximately 37% of the variation in presence of UIP was explained by the IQR of deltaSVg and the ILD-GAP score (Nagelkerke R square 0.372). The Hosmer and Lemeshow test significance value of 0.062 was above 0.05 giving no evidence of poor fit for the model. The performance of deltaSVg in identifying UIP whilst controlling for the ILD-GAP score gave an AUC of 0.818, but deltaSVg IQR was not a significant variable in the model.

Table 21 Variance inflation factors in testing for multi-collinearity

Variable	**VIF**	**Interpretation**
ILD-GAP score	1.009	Very low multi-collinearity
DeltaSVg IQR	1.009	Very low multi-collinearity

Table 22 Coefficients of variables in the binary logistic regression model

	Estimate	**Standard error**	**Odd ratio (95% CI)**	**p value**
ILD-GAP score	0.71	0.36	2.04 (1.003-4.14)	0.049
deltaSVg IQR	0.02	0.03	1.01 (0.98-1.04)	0.443
Intercept	-2.40	1.27	0.09	0.060

4.4 Discussion

4.4.1 Results in context

This study has not demonstrated additional diagnostic information from analysing heterogeneity of regional ventilation in two dimensions at a voxel level, either in isolation or with adjustment for the ILD-GAP score, when comparing patients with the UIP subtype of ILD to those who have other subtypes of ILD. A significant model was obtained using binary logistic regression, however the only significant factor in this model was the ILD-GAP score, not the IQR of deltaSVg. These results indicate that the technique we used to analyse scans did not reveal the spatial and temporal heterogeneity seen histologically in UIP to have a detectable functional impact in the form of more variable regional ventilation. A functional effect may be yet be detectable using different techniques, though these may require either analysis in three dimensions or analysis of scans that have a higher spatial resolution, such as micro-CT, so changes at alveolar level can be described.[306]

Relevant publications were released after the completion of this study. The degree of lung expansion in three dimensions has been reported; Park et al. reported that, in females, the degree of lung expansion was lower in patients with ILD compared to healthy subjects.[307] This is consistent with ILD being a restrictive lung disease with a reduced FVC. Lung expansion was also less heterogeneous, as demonstrated by a lower standard deviation and higher kurtosis of the histogram of distances moved for each voxel. Their findings are different to those found in this study and confirm the need for analysis of regional ventilation to be assessed in three dimensions. Further validation of regional ventilation at voxel level is also required. A recent review found good

correlation between CT ventilation imaging and other methods of defining ventilation, such as hyperpolarised helium MRI (^{3}He-MRI) or Xenon enhanced CT, but only at lobar or whole lung levels, not at segmental levels or beyond.[308] Whilst the technique used in this study used slightly different engineering principles it may suffer from the same limitations, as evidenced by data reported by the developers of the software and another group of researchers. R^2 was 0.54 (SD 0.09) for the technique compared to ^{3}He-MRI ventilation imaging for asthmatic patients, this was interpreted as reasonable correlation by the developers of this software.[309] R^2 was 0.6 (SD 0.2) for the technique compared to using proton MRI in infants, this was interpreted as good correlation by the developers of this software in support of using proton MRI to avoid radiation in paediatric assessment.[310] Murphy et al. have also developed a very similar method of analysing inspiratory and expiratory scans to this study and they found r values of between 0.71 and 0.82 when comparing their ventilation measures at whole lung and lobar levels to Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages of COPD.[311] A specific difficulty with validation of regional ventilation is that established methods, which may be considered as the gold standard tests by clinicians, only have a spatial resolution down to around 1cm whereas CT has spatial resolution of less than 1mm; if the two methods do not show good correlation or agreement it is not certain which technique is giving a value closer to the true physiological value.[312]

4.4.2 Comparison of results and hypotheses

The first pre-specified hypothesis was that calculation of deltaSVg on non-contrast paired inspiratory and expiratory CT scans would be possible in patients with ILD. Only one third of CT scans could be analysed across the full CT slice and one third of scans could not be segmented at all. Analysis of deltaSVg in fibrotic lung tissue is not

consistently possible and this hypothesis is disproven; poor contrast between musculoskeletal tissues and fibrotic lung tissue is an important limitation to the technique of calculating deltaSVg in its current format and it may be that different approaches to segmentation of the lung are necessary.[313]

The second hypothesis was that patients with UIP would have higher heterogeneity of deltaSVg compared to patients with non-UIP ILD. This small study did not identify any trend for the IQR of deltaSVg being different in patients with UIP because the odds ratio of 1.01 was very close to one and the 95% confidence interval was relatively centred on one (0.98-1.04).

4.4.3 Strengths of the study

The clinical application of regional ventilation to ILD in the manner used in this study was novel and addresses a key limitation in the patient pathway to obtaining treatment for ILD; even in the early stages of a medical career the author of this thesis has cared for two patients who died during their inpatient stay after diagnostic surgical biopsy for ILD so it appears clear that all potential avenues of phenotyping ILD should be explored. Not only would this potentially further reduce the need for surgical biopsy but objective and quantifiable measures of ILD may be useful to include in trials of therapy to aid assessment of patient eligibility and, potentially, response to treatment.

4.4.4 Weaknesses of the study

4.4.4.1 Sample size

The most significant limitation in this study is that it included a small sample of patients and unfortunately this problem was exacerbated by scans failing the processing

procedure. The small sample is problematic because it may lead to over fitting of the binary logistic regression model, meaning the statistical model is not generalisable outside of the study population or alternatively the 95% confidence intervals obtained in the model may be excessively wide leading to a significant effect being missed. The Lung Tissue Research Consortium (LTRC) based in the United States of America have a bank of clinical data, including paired inspiratory and expiratory CT scans, for patients with a range of subtypes of ILD was approached during the study to obtain further data.[314] They were receptive to the request, however an amendment to the study protocol to extend the duration of the study and include patients from the biobank would have been required, which meant it was not feasible to complete the analysis within the required timeframe. Proceeding with analysis of a small number of patients can be justified in the setting of examining data for potential trends that warrant further study on a larger scale; this small study could be completed relatively quickly, with lower costs than a large study.[304]

4.4.4.2 Reproducibility of paired CT slices

The automated instructions at the time of CT scanning rely on good co-operation from the patient; it may be desirable to add a gated pneumotachograph to the procedure to ensure sets of inspiratory and expiratory images are taken at similar points in the respiratory cycle across groups of patients. However, it remains to be established at what volumes the patient should pause in the respiratory cycle to obtain the most reproducible result and most interest in this approach has focused on PET-CT due to the prolonged period these scans take and the difficulties in aligning a free breathing PET image with a static CT image.[315] There was potential for bias in this study by the manual

step of pairing inspiratory and expiratory CT scans prior to calculation of deltaSVg; formal assessment of intra-observer and inter-observer variation in selection of paired CT slices is required. It was not possible to blind the research team to the ILD subtype, however MDT records were clear in their diagnosis and the CT analysis did not require a subjective assessment of outcomes.

4.4.4.3 Custom software

The technique described herein is far from ready for routine clinical use. Further development would be required in the technical aspects of analysis and appropriate integration with hospital imaging software would then need to be developed before clinical use could be attempted. Analysis of regional ventilation would need to be developed to work in 3D and employ advances in lung registration techniques that have occurred since the commencement of this study.[307]

CT analysis in expiration was problematic. A key difficulty with expiratory scans is that the reduction in alveolar air volume increased density of the lung tissue, which then approached the density of the soft tissues of the chest wall. The segmentation processes of the CT analysis software thus struggled to delineate between the two types of structure and errors in segmentation at the periphery of the lung were introduced. A different approach to lung segmentation would need to be employed in future to overcome this issue; one such technique is based upon region growing, smoothing, and error detection based on anatomical databases rather than relying solely on density.[271] This technique is available through a commercial company and collaboration with them has started. The possibility of performing deltaSVg in three dimensions was also explored during the duration of the study but there was not sufficient resource to

develop the custom software into three dimensions, to illustrate the complexity of this task it was estimated that a professional computer scientist would need one year of full time work to achieve the necessary developments.

4.4.4.4 Clinical scenarios

Patients in this study were at different stages of their disease, whereas analysis to aid the diagnostic process would hopefully be performed early during the disease process before the diagnosis of the subtype of ILD is known. A real difference in regional ventilation could have been missed if patients with UIP had more advanced fibrosis that had resulted in an end stage homogenous distribution of collagen throughout alveoli that resembles NSIP more than in the early stages of the disease. This potential problem is recognised and underlies the recommendation that surgical biopsy samples are taken from portions of lung adjacent to fibrosis rather than targeting areas of fibrosis themselves.[56] Further study of the use of regional ventilation in the diagnostic process would need to be employed prospectively in the same clinical setting in which it would be used; it is notable that this test would be used on patients that may not in fact end up with a diagnosis of ILD and as such the test would always need clinical correlation.

4.4.5 Implications for clinical practice and future research

Patients with ILD in this study had a larger deltaSVG IQR than the reported value for normal lung tissue, 4.4-4.9ml/g versus 2.2ml/g. [68] This indicates more heterogeneous regional ventilation in the presence of ILD versus no lung disease, thus further study of how regional ventilation is affected by different types of lung disease and how this varies with progression of lung diseases may be warranted. It would be relatively simple to undertake the same type of analysis on a larger sample of patients affected by

different types of lung disease by utilising the LTRC data.[314] It would be important to confirm the timing of the LTRC in the disease course and also to perform intra-observer and inter-observer variation analyses for the CT analysis process. There is an ongoing collaboration with the bioengineering team at Politecnico di Milano and development of analysis in three dimensions may be possible with further input from incoming academics at their institution.

Diagnosis of the subtype of ILD will continue to be a detailed process involving MDT discussion, however the addition of further information to aid this process, especially non-invasive procedures that place patients at negligible risk of harm, continue to be welcomed in this difficult area. Analysis of regional ventilation may be a useful tool but not using the method of analysis that was available for this study without further modification.

CHAPTER 5: CLINICAL APPLICATION OF CHEST WALL MOTION ANALYSIS IN THE ASSESSMENT OF MALIGNANT PLEURAL EFFUSION

This chapter has been published in abstract form: Oswald N, Kerr A, Mehdi R, Turner A, Naidu B, Assessment of Chest Wall Motion Using Structured Light Plethysmography (SLP) in Mesothelioma and Benign Pleural Disease, JTO, October 2018, 13(10):S753 DOI:10.1016/j.jtho.2018.08.1283

5.1 Introduction

5.1.1 The context of diagnosing mesothelioma

The import and new use of asbestos in the UK was banned in 1999 but exposure continues through previously installed material, particularly in high risk occupational groups such as carpenters, plumbers, and electricians.[316,317] A long interval between exposure and development of detectable disease is usual for cases of mesothelioma and it is thought the peak incidence of mesothelioma cases in currently in progress.[318] The prognosis of mesothelioma is dismal once the disease is diagnosed; a recent randomised controlled trial reported median survival times of between 16 and 19 months even with the most effective known chemotherapy regime.[319] Outcomes can be expected to be even worse in patients who are not as physiologically robust as these trial patients and quality of life is a priority for many patients until effective curative treatments become available.

The weeks and months leading up to a diagnosis of mesothelioma are likely to involve multiple tests to help differentiate between the extensive differential diagnoses for a pleural effusion and confirming mesothelioma relies upon tissue sampling; the gold standard diagnostic test being histological analysis of samples obtained by VATS biopsy, medical thoracoscopy or needle biopsy. [320–322] This diagnostic pathway can be a time of significant anxiety for patients and their families, many of whom are aware that they have been exposed to asbestos previously and the seriousness of mesothelioma. The James Lind Alliance, a collective of patients, carers and healthcare professionals that identify research priorities collaboratively, identified a need for improvements in the diagnostic tests for mesothelioma; this study explores the potential use of chest wall motion as part of the diagnostic pathway.[323]

5.1.2 Rationale for using chest wall motion to assess pleural disease

Relevant literature about chest wall motion in pleural disease is scarce; only two published articles were identified in literature searches. One study reported measurements of five patients with benign diffuse pleural thickening and found that the relative contributions of the ribcage and abdomen to tidal volumes were similar to normal subjects.[324] This was despite patients with pleural thickening demonstrating a restrictive pattern of lung disease on spirometry. The technique they used to measure chest wall motion was placement of magnetometers at the level of the nipples and 2cm above the umbilicus, providing information about displacement of the chest wall at two cross sectional levels. OEP (Section 1.3.3.1) has been performed on a small cohort of patients subsequently diagnosed with mesothelioma (n=4), empyema (n=6), or early stage lung cancer (considered pleural disease free controls, n=4) within the thoracic surgical department at Heartlands Hospital. This study found ribcage movements were

smaller in mesothelioma compared to benign pleural disease and controls, specifically on the side of the thorax affected by mesothelioma. [325] As such the available evidence prior to this study was that benign pleural thickening would have a minimal impact on chest wall motion and mesothelioma would produce a large reduction in motion of the affected hemithorax.

There are a number of potential mechanisms by which mesothelioma could alter chest wall motion. Firstly, neurological control of the respiratory cycle could be altered. Mesothelioma by definition invades the underlying tissues of the chest wall. [326] Invasion of the somatic intercostal nerves and spread of malignant cells along motor nerves could produce widespread alterations in respiratory muscle contraction and this could influence movement of the ribcage, however chest wall motion has not been found to be different between patients who had nerve blockade using local anaesthetics and those who had no nerve block.[327] Mesothelioma is known to invade sympathetic nerves and sympathectomy may cause a reduced FEV1 in otherwise healthy patients purportedly due to increased smooth muscle tone in bronchioles. [328–330] Involvement of the mediastinal pleura with tumour, a hallmark of mesothelioma, could result in invasion or encasement of the vagus and phrenic nerves with major subsequent changes in control of the ventilation; loss of diaphragm function, as would occur with phrenic nerve damage, has been confirmed to produce significant changes in chest wall motion assessed by OEP.[331–333] Animal studies of bilateral vagotomy have found the vagus nerve to be fundamentally important in control of depth and frequency of breaths and unilateral vagotomy in humans undergoing oesophageal surgery has been shown to alter the normal ventilatory responses to hypoxia and hypercapnia.[334–336]

A second potential mechanism is that the pleural thickening may physically restrict chest wall excursion as the tumour forms a tough rind around the lung.[337] Physical compression of the lung by this rind could alter chest wall motion in a detectably different way to the benign rind of fibrotic tissue that can result from resolved empyema or haemothorax. The arrangement of collagen and elastin fibres is known to influence the mechanical properties of parenchyma of the human lung. Collagen is arranged in coils in the absence of tension, these coils unfurl as the tissue is stretched and only provide resistance once the coils are straightened, limiting the extent to which the tissue can be distended.[338] A type 1 collagen variant, long spacing collagen, has been reported to be present in mesothelioma tissue and different types of collagen are produced by benign mesothelial cells (type I), mesothelioma cells (type I and IV) and carcinoma cells (type IV).[339,340] The impressive tensile strength of type I collagen is widely reported and this type of collagen is a key component of the musculoskeletal system, type IV collagen conversely has a specialised role as a flexible component of the basal laminae throughout the body.[341] The type of collagen present in a pathological rind as well as the arrangement of the fibres could influence chest wall motion by limiting expansion of the underlying lung.

Differences in the neurological control or mechanical determinants of breathing could potentially result in detectably different chest wall motion in patients and as such are a potential unexploited biomarker that could be used in stratifying patients within the diagnostic pathway. SLP, being straightforward and quick to perform, could be implemented widely if it were found to discriminate between benign and malignant pleural disease.

5.1.3 The technique of SLP

SLP is performed by projecting a grid of visible light onto the patient's trunk from a single source of light and recording the grid using two cameras next to the projector (Figure 58). The camera output is passed to software for processing and includes an automatic internal calibration, negating the need for separate calibration of the equipment prior to patient recordings. The point where four grid squares meet is identified by the software and tracked throughout the breathing cycle, this allows detection of deformation in the light grid and measurement of the change in distance between the patient's trunk and cameras. [79] The grid is only projected onto the anterior surface of the patient's trunk, consequently the position of the posterior surface of the trunk is set as an approximation of the plane of the surface that the patient is resting against. The changes in the volume of the trunk derived using this plane have a good correlation with pneumotachography volumes (r^2=0.091) and the measured respiratory rate has been validated against respiratory inductive plethysmography.[80,81] Although the left and right lungs usually differ in size the left and right contributions of chest wall motion using SLP should be 50%+/- 2% of vital capacity manoeuvres.[342]

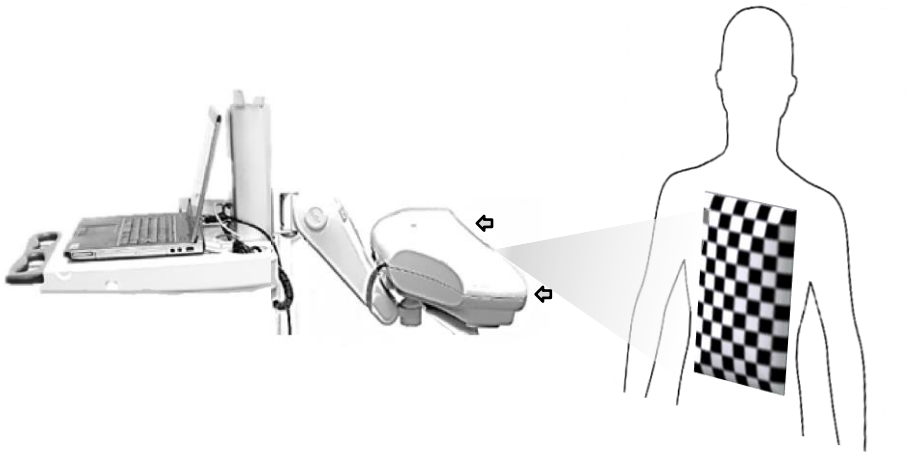


Figure 58 Illustration of SLP grid light projection and camera position (arrows) within the device head

The SLP recordings report thoraco-abdominal displacement; this is a distinct measure from flow and volumes indices that are used in spirometry and plethysmography tests but the measures are interpreted similarly. The total displacement is interpreted as a volume and the rate of displacement is interpreted as flow. The following relevant measures were provided for SLP:

- RR: respiratory rate (breaths per minute)
- Ti: inspiratory time (seconds)
- Te: expiratory time (seconds)
- Ttot: total breath time (seconds)
- Ti/Te
- Ti/Ttot
- IE50: ratio of tidal inspiratory displacement at 50% displacement to tidal expiratory displacement at 50% displacement
- $\text{Contribution}_{\text{left2thorax}}$: left thorax contribution to total trunk displacement (%)

- $Contribution_{rightt2horax}$: right thorax contribution to total trunk displacement (%)
- $Contribution_{ribcage}$: ribcage contribution to total trunk displacement (%)
- $Contribution_{left2ribcage}$: left thorax contribution to ribcage displacement (%)
- $Contribution_{right2ribcage}$: right thorax contribution to ribcage displacement (%)
- $Phase_{thorax}$: phase angle between hemithoraces (degrees)
- $Phase_{trunk}$: phase angle between thorax and abdomen (degrees)

SLP has not been tested in patients with pleural disease before, however respiratory conditions have been shown to cause differences in SLP measures (Table 23). [343,344] Conditions localised to one side of the chest have also shown detectable differences using SLP; chest wall movements are altered following lung resection, successful EBV insertion to treat emphysema, and in pneumonia.[345–347] It is important to note that the phase angles are not determined with one region as the reference and therefore the value obtained using SLP is always positive and does not indicate which region lags behind in movements.

5.1.4 Hypotheses

The hypotheses to be tested were based on the existing knowledge and expected effects of mesothelioma on chest wall motion, they are as follows:

1. The contribution of the affected hemithorax to total ribcage motion ($Contribution_{affected}$) would be reduced in patients with mesothelioma compared to patients with non-mesothelioma pleural thickening or effusion.
2. The phase angle of the ribcage and abdomen movement ($Phase_{trunk}$) would be increased (more asynchronous) in patients with mesothelioma compared to patients with non-mesothelioma pleural thickening or effusion.
3. A statistical model using $Phase_{trunk}$ and $Contribution_{affected}$, controlled for the presence of respiratory disease, would be able to differentiate patients with mesothelioma from patients with non-mesothelioma pleural thickening or effusion.
4. The extent of the reduction in contribution of the affected hemithorax to total ribcage motion ($Contribution_{affected}$), controlled for known prognostic variables, would be linked to length of survival in mesothelioma.

The $Contribution_{affected}$ measure was ascertained by matching the hemithorax affected by pleural thickening to either $Contribution_{left2ribcage}$ or $Contribution_{right2ribcage}$.

Table 23 Summary of SLP measures found to be different in respiratory conditions or to be altered by treatment

Article	Patient groups	Findings
Hmeidi et al 2017[343]	Healthy children Children with asthma	Ti/Te lower in asthma (0.82 versus 0.69) Ti/Ttot lower in asthma (0.45 versus 0.41) IE50 higher in asthma (1.22 versus 1.53) IE50IQR higher in asthma (0.47 versus 0.63) IE50 fell with bronchodilator use in asthma (1.53 versus 1.45) IE50IQR fell with bronchodilator use in asthma (0.63 versus 0.60)
Motamedi et al 2016[344]	Healthy adults Adults with COPD	Ti lower in COPD (1.70 versus 1.33) Ti IQR lower in COPD (0.42 versus 0.20) Ti/Te lower in COPD (0.70 versus 0.58) Ti/Te IQR lower in COPD (0.17 versus 0.06) Ti/Ttot lower in COPD (0.41 versus 0.37) $Phase_{trunk}$ higher in COPD (4.25 versus 6.33)
Elshafie & Naidu 2015[345]	Adult with emphysema before and after endobronchial valve therapy	Reduction in contribution of treated side to trunk displacement from 55% to 48%
Elshafie et al 2016[346]	Adults before and after lung resection	Reduction in contribution of operated side after lobectomy $Phase_{ribcage}$ increased after lobectomy $Phase_{trunk}$ increased after lobectomy or wedge resection
Stockley et al 2018[348]	Healthy adults Patients with respiratory muscle weakness	$Phase_{trunk}$ increased in patients with weakness 'Abnormal contribution' of thorax to total trunk displacement in patients with weakness
Ghezzi et al 2017[347]	Child with pneumonia	IE50 was increased then reduced as pneumonia resolved (1.87 to 1.10) $Contribution_{affected}$ was reduced then increased as pneumonia resolved (44% to 52%) $Phase_{thorax}$ was increased then reduced as pneumonia resolved (15.5 to 2.1)

5.2 Methods

5.2.1 Study design

The study designed as a prospective single blinded observational study among adult patients with pleural effusion and/or thickening. All patients attending the preoperative assessment clinic prior to diagnostic pleural biopsy were eligible and invited to participate. Patients who were under 18 years of age, lacked capacity, had a chest drain in situ, or did not have any pleural disease were excluded. Written informed consent was given prior to any study intervention. Patient demographics were recorded at baseline and all SLP recordings (index test) were done prior to surgery. The recordings were done using the Thora-3Di device (PneumaCare, Cambridge, UK) with the 14x10 square large grid. The SLP trace was processed by a blinded technician (Shayan Motamedi) at PneumaCare, the company supplying the Thora-3Di for the duration of the study. The SLP output variables for each study participant were median and IQR values; the technician did not receive any identifiable data about the participants at any time. The patients proceeded with usual preoperative and postoperative clinical care and the final histological diagnosis was retrieved as the gold standard test for comparison and to group patients by diagnosis. Histopathologists assessing the tissue samples for diagnosis were blinded to SLP results as they had no access to the research department computer storage drives. In cases where the biopsy did not give a definitive diagnosis the final clinical diagnosis using further tests, including repeat surgical biopsy or MDT consensus, was awaited. Researchers recording the diagnosis were blind to the results of the SLP recording until the time of data analysis.

5.2.2 Funding & regulatory approvals

The study was granted ethical approval (Research Ethics Committee reference 10/H1202/58) after a substantial amendment of the most recent protocol and was awarded joint funding in the form of a Mesothelioma UK and Pat Stone Research Grant to the value of £20,000. The study was registered at ClinicalTrials.gov (Identifier: NCT02958683).

5.2.3 SLP recording procedure

Patients were in an upright seated position on a firm backed chair with arms relaxed next to the patients' side and no specific respiratory manoeuvres were performed during timed five minute recordings. In most cases patients were bare-chested for the recordings, however if the tracking of respiratory movements was not smooth on the real time computer feedback a clean plain white t-shirt was provided and secured with tape where necessary to obtain a smooth trace. All female participants wore a t-shirt for recording due to the potential for interference in the grid tracking from breast tissue. Study participants were reassured of the study room privacy and efforts were made to make them feel at ease so they could relax during the recordings, which were performed in a dark, quiet room. Companions were permitted to join the patient in the recording room if the patient desired this but all persons in the room were asked not to speak or interact with non-verbal signals during the recording; chairs for companions were positioned to the side of the patient to reduce opportunity for eye contact and help patients feel they were not the focus of observation. The equipment set up is shown in Figure 59.

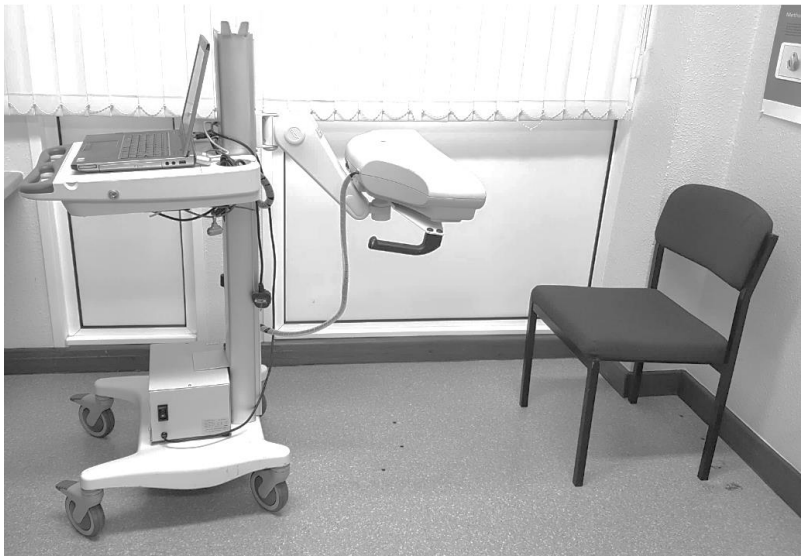


Figure 59 Equipment set up for performing SLP recordings

5.2.4 Statistical plan

5.2.4.1 Univariable analysis

Cases of mesothelioma were compared to cases of non-mesothelioma with univariable analyses before proceeding to multivariable modelling. Categorical demographic data were assessed as proportions and compared using Fisher's exact tests. Continuous demographic data and variables reported from the SLP recordings were assessed for normality of their distributions using visual inspection of density distribution curves and Shapiro Wilk tests. Continuous variables were compared using t tests for normally distributed data and Mann Whitney U tests for non-normal data. A p value of less than 0.05 was considered statistically significant.

5.2.4.2 Multivariable analysis

Binary logistic regression was performed for multivariable analysis of SLP in differentiating mesothelioma from non-mesothelioma prior to diagnostic surgery. The

covariates expected to differ were $Contribution_{affected}$, $Phase_{trunk}$, and IE50 IQR based on prior publications. The presence of respiratory disease as a binary factor was included in the model to control for known and unknown effects on SLP. ROC with AUC analysis were used to assess the performance of the statistical model for excluding or diagnosing mesothelioma. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were also calculated.

5.2.4.3 Survival analysis

Cox proportional hazard ratio analysis was planned to assess the utility of SLP in prognostication for patients with confirmed mesothelioma, the $Contribution_{affected}$ and IE50 IQR were planned for assessment in survival analysis. Comparison with an existing prognostic tool was planned to ensure that any information provided by SLP was additive to current information. Decision tree analysis as reported by Brims et al (Appendix 5) was chosen for comparison as it is a current test that is simple to calculate; a complex tool may not yield interpretable results for the study sample, which was expected to be comparatively small.[349] Multiple prognostic tools are available but guidelines state the Brims decision tree was most likely to be useful clinically, in part due to its simplicity.

5.2.4.4 Sample size and power calculation

Before commencing the study it was hypothesised that mesothelioma would cause a reduction in $Contribution_{affected}$, increase in $Phase_{trunk}$, and an increase in IE50 IQR. These three measures were planned for inclusion in the statistical model. The presence of respiratory disease would also need to be accounted for in any model, this was included

as a binary factor (respiratory disease present or absent). It was anticipated that one third of patients undergoing pleural biopsy would be diagnosed with mesothelioma.

The minimum number of cases to include was determined by the rule of thumb by Green et al.: [350]

$$N>50+8C$$

Where N is the minimum sample size and C is the number of covariates. Four covariates would be assessed for inclusion in the regression model and thus a sample of 82 patients was required. The sample size was crosschecked for ROC AUC analysis using MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium). The sample size required using this method was 75 patients (25 mesothelioma, 50 non-mesothelioma). This should achieve 90% power to detect an area under the curve of 0.725 with a significance level of 0.05, assuming there are twice as many non-mesothelioma diagnoses as there are mesothelioma diagnoses. In order to satisfy the calculations for statistical power and also the minimum sample size 82 patients were required. Statistical tests other than sample size calculation were performed using RStudio, version 3.6.0. The R markdown script used in performing diagnostic accuracy analysis and survival analysis are included in Appendix 6 and Appendix 7.

5.3 Results

5.3.1 Patient flow through the study

A total of 90 patients were recruited giving a recruitment rate of 63% and no patients were lost to follow up; baseline demographics of patient are displayed in Table 24 and flow of patients through the study is displayed in Figure 60.

Eight patients who were recruited could not be included in the final analysis. Two SLP recordings failed to give an interpretable result; review of these cases and previous recordings found that contours on the surface of the trunk due to obesity, breasts and scar tissue that cause folds or significant body hair can be difficult for the Thora-3Di to process. This difficulty can be overcome by optimising patient positioning and use of a tight white top to smooth the surface of the trunk; since introduction of this to our protocol (after 18 patients) no further recordings needed to be discarded. Four patients had been listed for pleural biopsy however upon review of the operative notes they were operated on to obtain tissue samples to guide chemotherapy to treat a known metastatic malignancy, as opposed to the operation being performed for diagnostic purposes. These patients fall outside the clinical question for this study and it would introduce bias to include their SLP results in analysis. One patient had SLP results that included an implausible number that was an extreme outlier (Figure 61); the $Contribution_{affected}$ was between 30% and 60% for all other patients but the outlier data point was less than 10%, research records noted that the recording produced a good trace and the report from the technician was that the data quality was good, however, the report for the patient only included six analysed breaths whereas the median number of breaths analysed was between 79 and 82 for the rest of the cohort. The exact

reason underlying the outlier could not be identified but it was considered to be a technical problem and not representative of the disease process, as such the dataset for that patient was also excluded from analysis. Finally, one patient is yet to undergo surgery for non-clinical reasons.

Informal feedback from patients and their families was that they found the test very acceptable and welcomed the aims of the study. There were no adverse events associated with performing SLP.

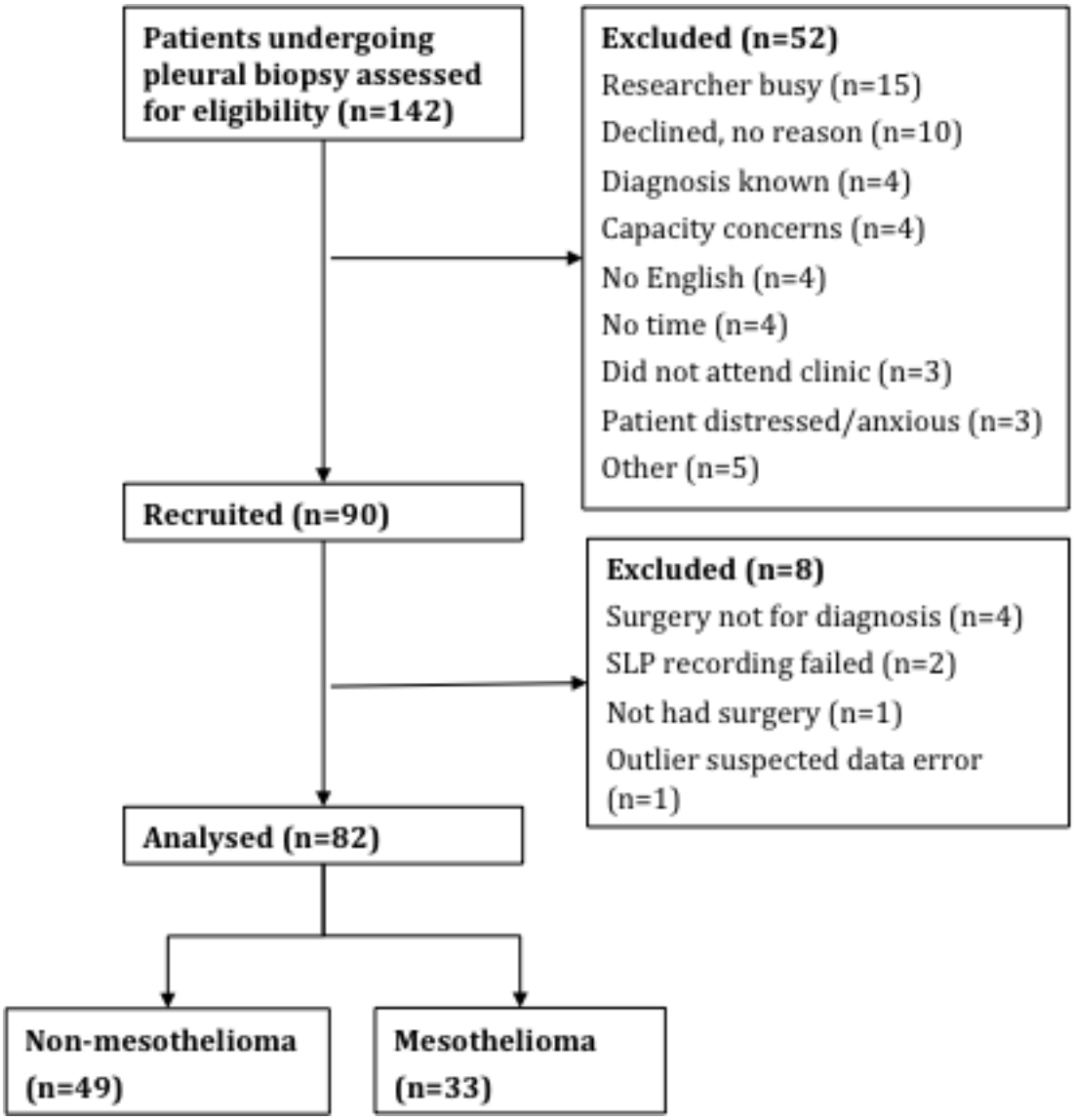


Figure 60 Flow of patients through the study of SLP in assessment of pleural disease

Table 24 Patient demographics

	Non-mesothelioma (n=49)	**Mesothelioma (n=33)**	**p-value**
Age Median (IQR)	67 (62-77)	75 (71-81)	0.003*
Male gender % (n)	92% (45)	88% (29)	0.708
Left side affected % (n)	55.1% (27)	48.5% (16)	0.654
Histology % (n)	35% (17) Benign, NOS* 22% (11) Inflammation 8% (4) Pleural plaque 8% (4) Post infection 6% (3) Mycobacterium 6% (3) Metastatic malignancy 6% (3) Benign mesothelial proliferation 6% (3) Post cardiac surgery/haemothorax 2% (1) Atypical cells & evidence of cardiac failure	52% (17) Epithelioid 24% (8) Sarcomatoid 12% (4) Biphasic 6% (2) Desmoplastic 6% (2) NOS*	Not applicable
Respiratory disease % (n)	20% (10)	9% (3)	0.224

Note: NOS not otherwise specified, *statistically significant p value. Categorical variables were compared using Fisher's exact tests. Continuous variables were compared using t tests for normally distributed data and Mann Whitney U tests for non-normal data.

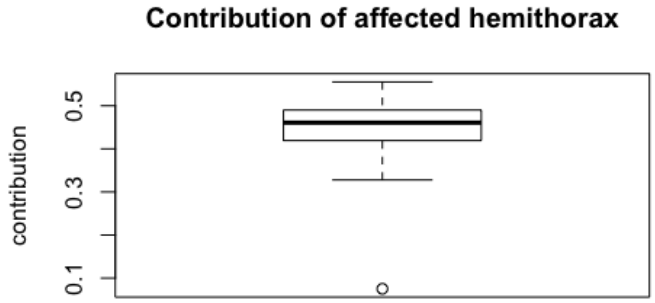


Figure 61 Box and whisker plot of the proportional contribution of the affected hemithorax to overall ribcage motion demonstrating a clear outlying data point

5.3.2 Univariable analysis

Patient with mesothelioma were statistically significantly older, at 8 years this difference may also be clinically significant. The proportion of mesothelioma diagnoses was slightly higher than anticipated (40% versus 33% anticipated), but this was still in keeping with the prediction that the majority of cases would not be mesothelioma. IE50 IQR was the only other statistically significantly different variable on univariable analysis; the value for patients with mesothelioma was lower than non-mesothelioma, which is the opposite trend to the hypothesis. Contrary to the hypotheses, there was no statistical difference in $Phase_{trunk}$ or $Contribution_{affected}$. Results of univariable analyses and normality tests are in Table 25.

Table 25 Univariable testing according to histology group and assessment of distribution

	Non-mesothelioma	**Mesothelioma**	**Assessment of distribution**	**p value**
Breaths analysed	79 (61-88)	82 (73-92)	<0.001 Positive skew	0.408
Respiratory rate Breaths/minute	18 (16-21)	19 (16-22)	0.003 Positive skew	0.729
Respiratory rate IQR	3 (2-3)	3 (2-4)	<0.001	0.777
Ti (seconds)	1.38 (1.16-1.55)	1.33 (1.10-1.43)	<0.001 Positive skew	0.600
Ti IQR	0.167 (0.133-0.400)	0.175 (0.167-0.242)	<0.001	0.938
Te (seconds)	1.95 (1.60-2.30)	1.87 (1.60-2.33)	<0.001 Positive skew	0.889
Te IQR	0.321 (0.200-0.523)	0.400 (0.233-0.475)	<0.001	0.564
Ttot (seconds)	3.33 (2.79-3.77)	3.13 (2.73-3.70)	<0.001 Positive skew	0.729
Ttot IQR	0.417 (0.317-0.702)	0.533 (0.333-0.683)	<0.001	0.600
Ti/Te	0.708 (0.0939)	0.705 (0.110)	0.780 Normal	0.905
Ti/Te IQR	0.127 (0.113-0.170)	0.130 (0.109-0.160)	<0.001	0.727
Ti/Ttot	0.413 (0.0327)	0.411 (0.0381)	0.523 Normal	0.845
Ti/Ttot IQR	0.0463 (0.0380-0.0531)	0.0461 (0.0380-0.0512)	<0.001	0.671
Contribution$_{ribcage}$	47.1 (13.2)	52.1 (14.0)	0.343 Normal	0.114
Contribution$_{ribcage}$ IQR	5.32 (3.56-8.13)	4.49 (3.12-5.99)	<0.001	0.073
Phase$_{thorax}$	2.21 (1.50-3.43)	2.12 (1.80-2.88)	<0.001 Positive skew	0.756
Phase$_{thorax}$ IQR	2.43 (1.76-4.46)	2.40 (1.84-3.07)	<0.001	0.356
Phase$_{trunk}$	7.80 (4.78-10.7)	6.86 (4.08-10.9)	<0.001 Positive skew	0.531

	Non-mesothelioma	Mesothelioma	Assessment of distribution	p value
$Phase_{trunk}$ IQR	5.96 (4.89-9.30)	5.33 (4.81-7.24)	<0.001	0.222
IE50	1.35 (1.13-1.56)	1.27 (1.19-1.45)	0.008 Positive skew	0.441
IE50 IQR	0.464 (0.334-0.590)	0.374 (0.280-0.443)	<0.001 Positive skew	0.006*
$Contribution_{affected}$	45.3 (4.86)	45.8 (6.00)	0.143 Normal	0.718

Note: Phase angles have no reference region and are always positive. Categorical were compared using Fisher's exact tests. Continuous variables were compared using t tests for normally distributed data and Mann Whitney U tests for non-normal data. * Denotes statistically significant p value.

5.3.3 Multivariable analysis

5.3.3.1 Testing statistical assumptions

The assumptions of binary logistic regression were testing prior to proceeding with analysis to ensure the technique was appropriate for the data. These assumptions for are:

1. The dependent variable must be dichotomous and cannot take more than one value per participant
2. There should be a linear relationship between continuous independent variables and the logit of the dependent variable
3. There should be no influential points
4. There should be no multi-collinearity between independent variables

The dichotomous disease category to be used was the presence versus absence of mesothelioma; a small number of patients had metastatic malignancy as opposed to mesothelioma however the clinical question was whether or not SLP could identify mesothelioma specifically, not simply malignancy, and metastatic malignancy is more often diagnosable with cytology of pleural fluid. A patient could not be assigned to two group categories in the setting of pleural disease.

A binary variable, in this case the presence of respiratory disease, follows a linear relationship with the logit by definition. Graphical analysis of Model A (the pre-planned model) was performed and showed non-linearity for the $Phase_{trunk}$ and $Contribution_{affected}$ (Figure 62). The distribution of $Phase_{trunk}$ was processed with a square root transformation, whilst this improved the linearity of the distribution it was

still non-linear. The violation of assumptions rendered the Model A inappropriate for binary logistic regression. Therefore, $Phase_{trunk}$ and $Contribution_{affected}$ were converted to binary variables. Binary variables, by definition, meet the linearity assumption and so were included in a model (Model B) for analysis.

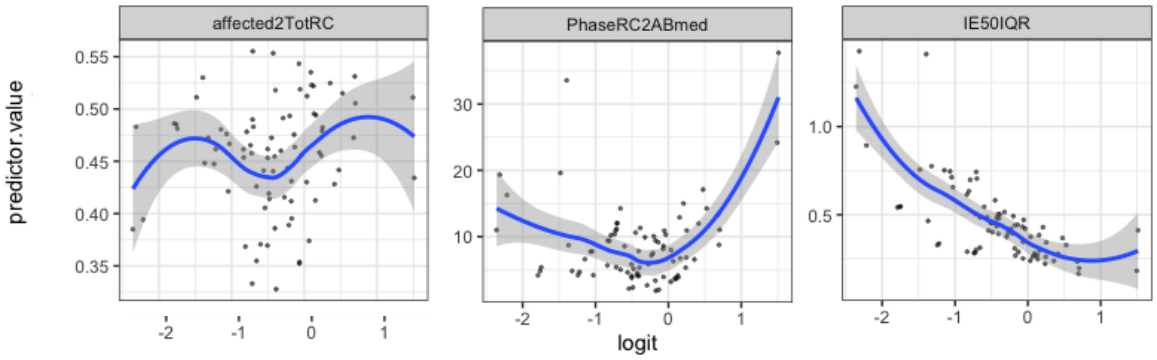


Figure 62 Linearity with the logit of the dependent variable testing for Model A – pre-planned variables

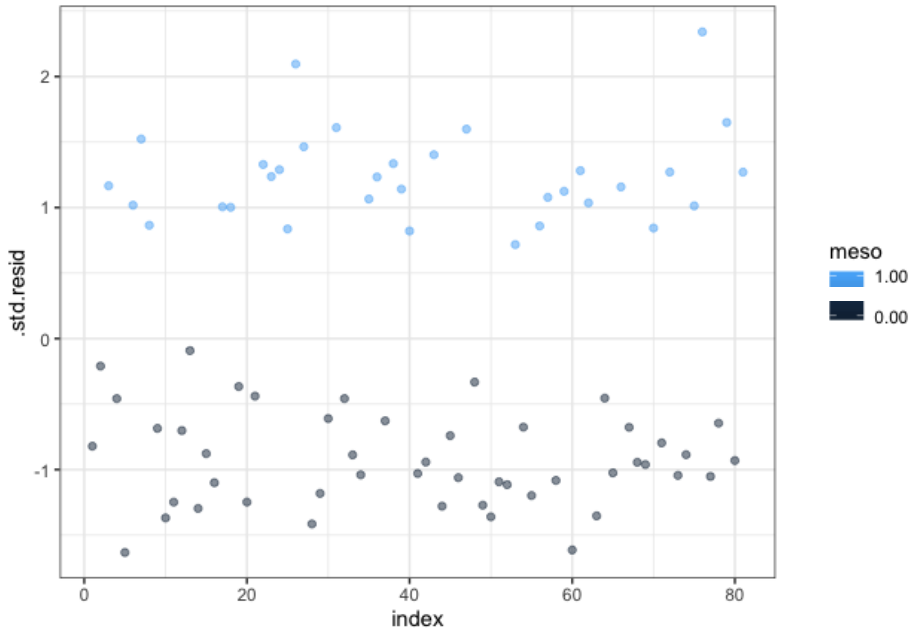


Figure 63 Testing for influential variables - standardised residual error plot.

Table 26 Variance inflation factors in testing for multi-collinearity

Variable	**VIF**	**Interpretation**
Binary Contribution$_{affected}$	1.01	Very low multicollinearity
Binary Phase$_{trunk}$	1.04	Very low multicollinearity
IE50 IQR	1.04	Very low multicollinearity
Disease	1.01	Very low multicollinearity

Influential observations were tested using the standardised residual error whereby a value above three is taken to represent an important outlier, no values were found to be above three (Figure 63). The VIF showed minimal multi-collinearity; a VIF of 1 is considered to show no correlation, 1 to 5 moderate correlation, and more than 5 high correlation. The VIF for each variable is shown in Table 26. All assumptions for binary logistic regression had hence been satisfied so Model B proceeded to binary logistic regression analysis.

5.3.3.2 Binary logistic regression

Binary logistic regression using Model B yielded a model that is not significantly better than a null model with no covariates, as demonstrated by the null deviance of 109.5 being very close to the residual deviance of 102.2, and this was confirmed with chi squared of 7.31, 4 degrees of freedom, p=0.121. Coefficients and odds ratios for the model for each variable are shown in Table 27. Only IE50 IQR was independently statistically significant, for every increase in IE50 IQR by 1, the patient is 0.09 times more likely to have mesothelioma, which would in fact be a reduction in risk of mesothelioma. Having a $Contribution_{affected}$ of greater than the group median or having a respiratory disease was associated with a lower risk of mesothelioma, and having a $Phase_{trunk}$ lower than the group median was associated with a higher risk of mesothelioma, however these associations were not statistically significant with an odds ratio that crossed the value of one, therefore the associations are not significant.

AUC analysis found an area of 0.690 (Figure 64), indicating that a randomly chosen patient with mesothelioma has a 69% chance of having a higher model score than a randomly chosen patient without mesothelioma. The optimal cut off score for the curve

was 0.429; with this cut off sensitivity of the model was found to be 39% and specificity 83%. PPV and NPV, as calculated from the sensitivity, specificity and prevalence of mesothelioma, were 61%, and 67% respectively.

Table 27 Coefficients of variables in the binary logistic regression Model B

	Estimate	**Standard error**	**Odds ratio (95% CI)**
Binary Contribution$_{affected}$	-0.41	0.48	0.67 (0.26-1.68)
Binary Phase$_{trunk}$	0.09	0.48	1.09 (0.42-2.82)
IE50 IQR	-2.46	1.32	**0.09 (0.01-0.88)**
Respiratory disease	-1.03	0.72	0.33 (0.07-1.34)
Intercept	1.02	0.77	2.77 (0.65-13.66)

Note: Odds ratios determined using likelihood ratios tests, bold type denotes statistical significance

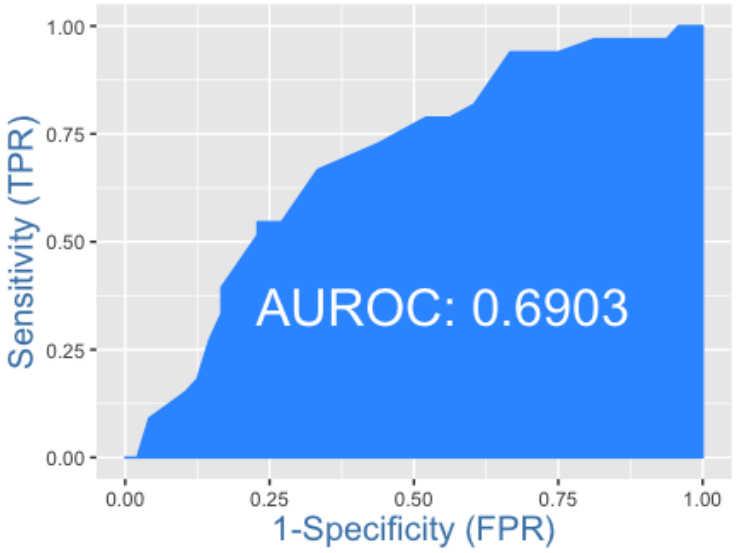


Figure 64 Area under the curve (AUC) analysis for binary logistic regression Model B in differentiating patients with mesothelioma from those non-mesothelioma pleural disease

Note: Received operator characteristics (ROC), true positive rate (TPR), false positive rate (FPR).

5.3.3.3 Survival analysis

The 33 patients found to have mesothelioma were followed up to perform survival analysis with cox-proportional hazard ratios; survival data collection was stopped at three years. It was hypothesised that a greater disease burden would impair movement of the affected hemithorax to a greater degree, as such the $Contribution_{affected}$ was the parameter tested for influence on survival. Exploratory analysis of survival was performed to examine possible trends and determine if future work would be advisable to fully investigate SLP as a tool for use in prognostication. Only four patients fell into Brims group 3; the proportion of patients surviving at 18 months in Brims group 3 (28%) was closer to Brims group 4 (0-11%) than Brims group 2 (47-51%) so these four patients were allocated to Brims group 4 to maintain a reasonable number of patients per group for survival analysis.

5.3.3.3.1 Survival analysis assumptions

Survival analysis assumes continuous variables are linear; fitted lines of Martingale residuals can be used to assess linearity of continuous variables. $Contribution_{affected}$ was clearly non-linear with this method showing a curve with a peak close to 0.425 (Figure 65). This variable was grouped into binary categories, split by the median value of the dataset, to achieve linearity by definition.

Cox proportional hazard ratio analysis assumes that the ratio of the hazard remains constant over time. This can be assessed by inspection of Kaplan Meier curves; curves that overlap or curve that diverge but then one curve falls to zero indicate non-proportional hazards. $Contribution_{affected}$ showed overlapping in the early part of the

Kaplan Meier curve so further testing was performed (Figure 66). Brims decision tree analysis showed a proportional hazard, confirming its applicability to this dataset (Figure 67).

Proportional hazards can also be tested by plotting scaled Schoenfeld residuals against time, proportional hazards should not have a significant relationship. Schoenfield residual test was employed to this end and showed proportional hazards for both Brims group and binary $Contribution_{affected}$ (Figure 68 and Figure 69). The presence of influential variables was tested for by plotting the deviance residual for each patient (Figure 70). The pattern should be symmetrical around zero in the absence of influential variables; this was confirmed to be the case for the survival study cohort.

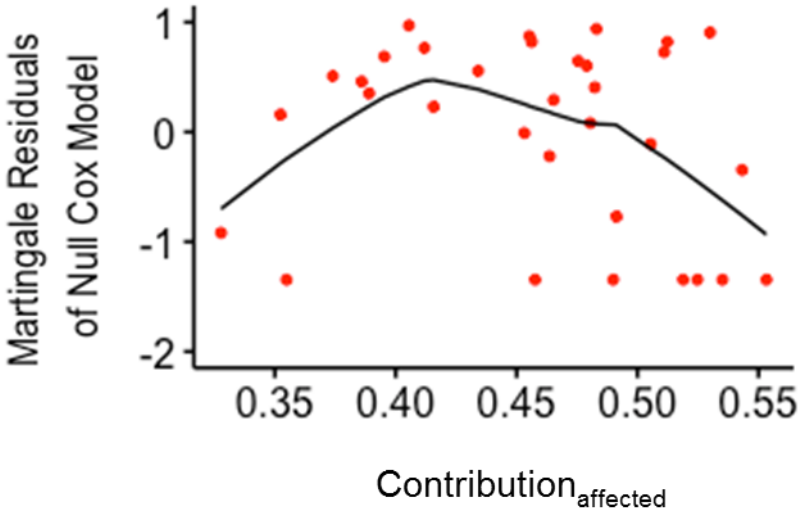


Figure 65 Martingale residuals of Null Cox Model test of linearity for $Contribution_{affected}$

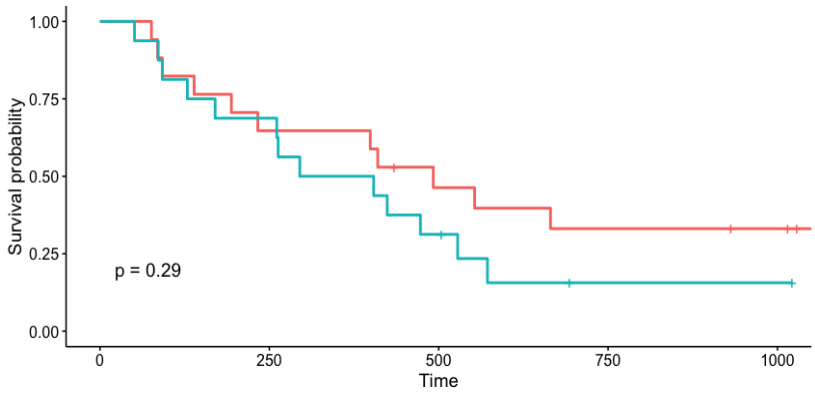


Figure 66 Kaplan Meier curve for Binary $Contribution_{affected}$

Time recorded in days, orange = $Contribution_{affected}$ above the group median, blue = $Contribution_{affected}$ below group median.

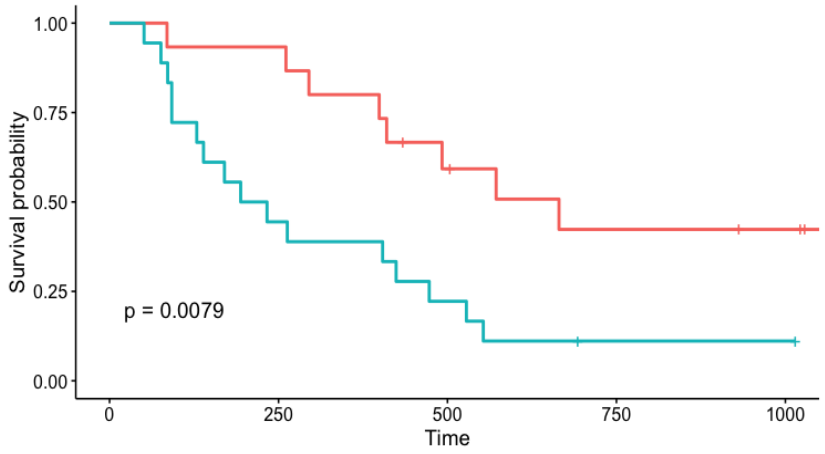


Figure 67 Kaplan Meier curve for Brims decision tree groups 2 and 4

Time recorded in days, orange = Brims group 2, blue = Brims group 4.

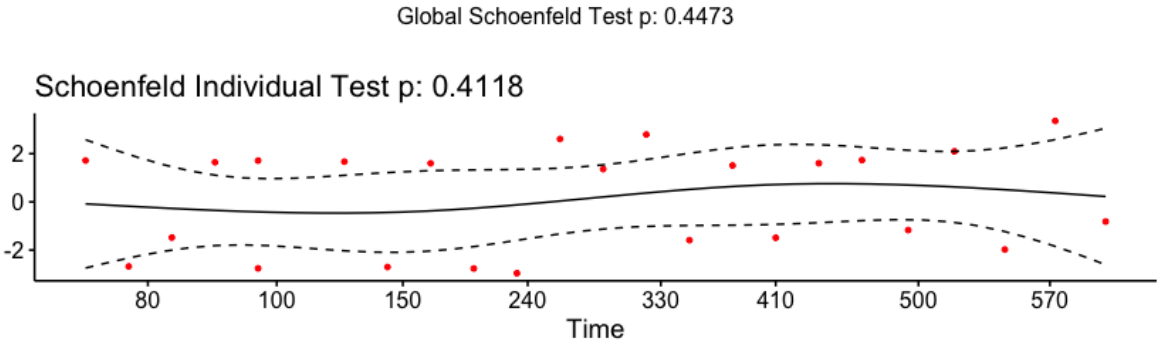


Figure 68 Schoenfeld tests of proportional hazards for $Contribution_{affected}$

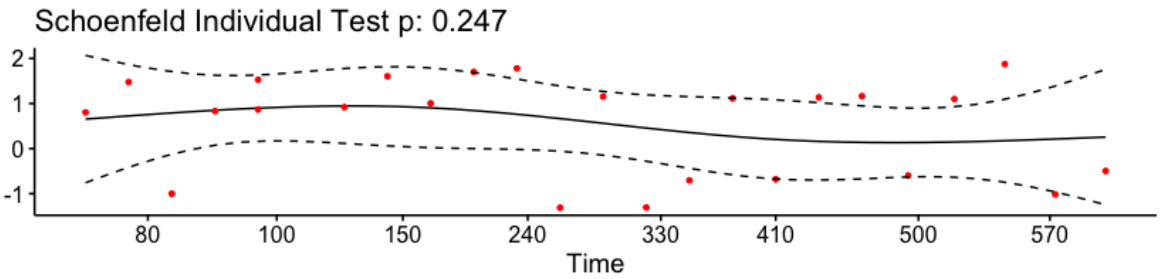


Figure 69 Schoenfeld tests of proportional hazards for Brims decision tree groups

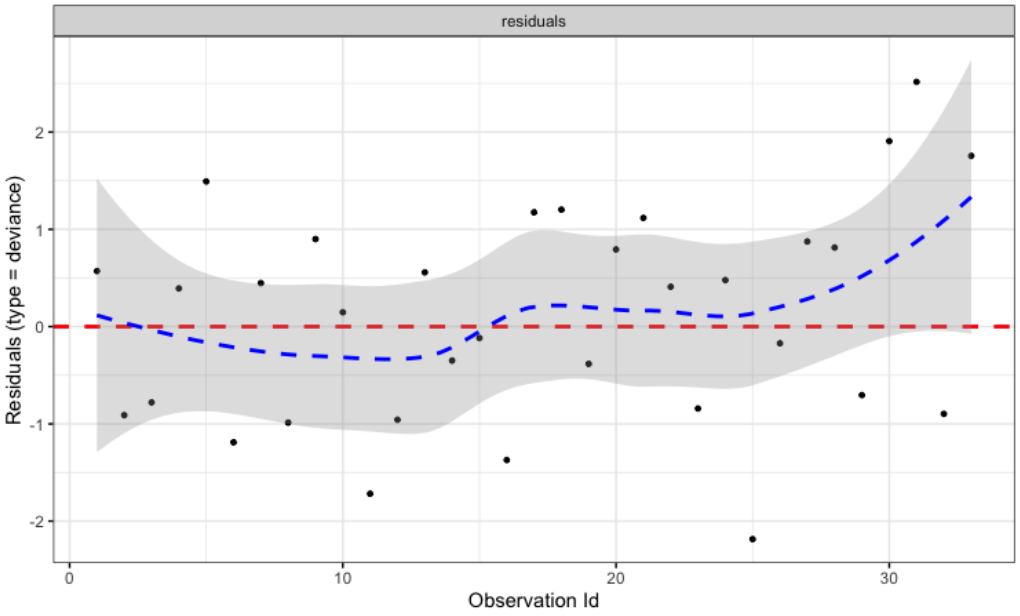


Figure 70 Residuals deviance testing for influential variables in the model

5.3.3.3.2 Cox proportional hazard ratio testing

Cox proportional hazard ratio testing was performed after confirming that the model met the assumptions, results are displayed in Figure 71. There were 24 events and 9 censorships during follow up. The model was significant (global Log Rank test p=0.03) and it was confirmed that decision tree grouping was a significant hazard for death; hazard ratio for Brims group 4 versus Brims group 2 was 1.7 (95%CI 1.1-2.7, p=0.019). This means that at any point in time patients in Brims group 3 or 4 (since the groups were combined for analysis in this study) were 70% more likely to die compared to patients in Brims group 2. Binary $\text{Contribution}_{\text{affected}}$ however did not have a significant effect on the risk of death with a hazard ratio of 1.1 (95%CI 0.49-2.6, p=0.77). Two patients in Brims group 2 were censored prior to 18 months and seven of the remaining 13 were alive at 18 months, giving a survival rate of 54%. Three of the 18 patients in Brims group 4 were alive at 18 months, giving a survival rate of 17%. The survival rates given in the Brims study found 18 month survival rates of 47-51% and 0-11% for Brims group 2 and group 4 respectively; these results provide external validation for the Brims decision tree as a prognostic aid.[349]

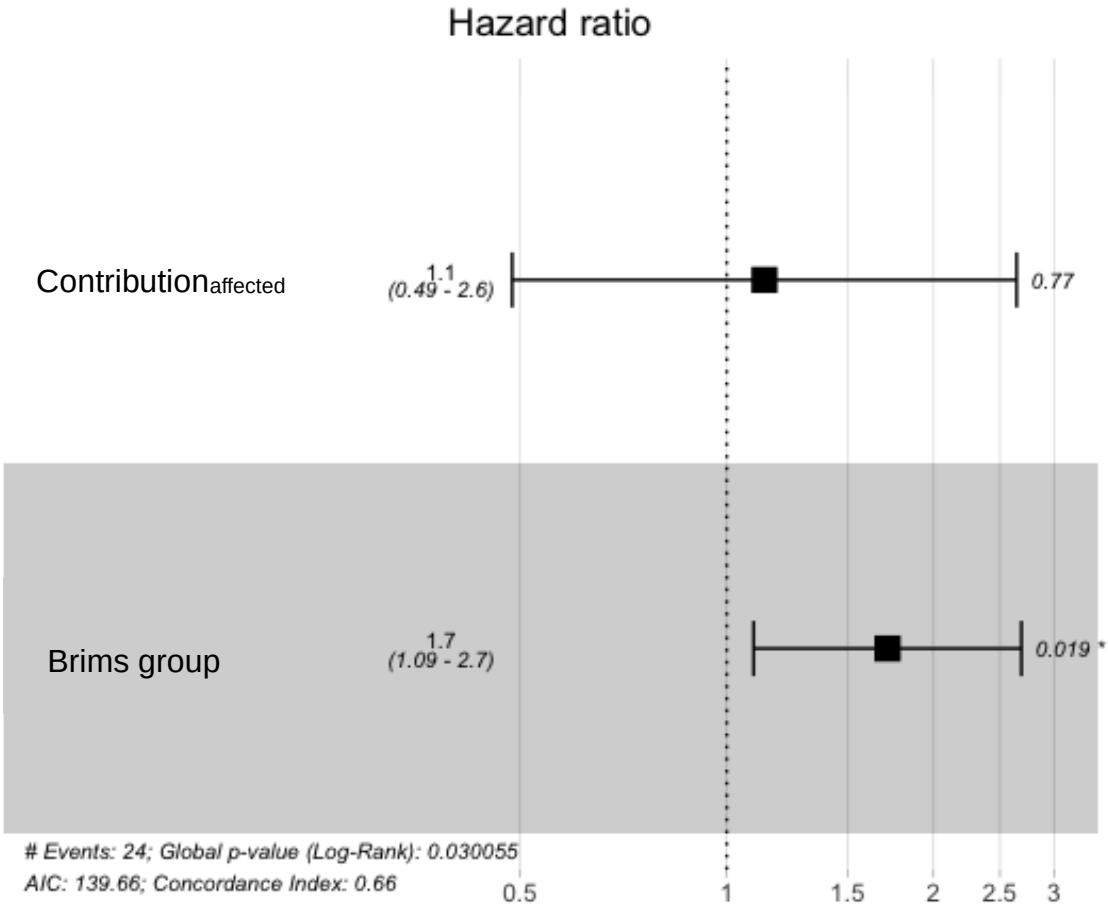


Figure 71 Hazard ratios of variables entered in Cox proportional hazard ratio testing, n=33

5.4 Discussion

5.4.1 Results in context

The primary vision for chest wall motion quantification with SLP in helping patient management was to stratify the risk of mesothelioma in patients presenting for diagnostic surgery. If SLP measures indicated the presence mesothelioma, patients could be managed urgently on cancer pathways for obtaining tissue samples to guide chemotherapeutic options, or they could avoid surgery and opt for supportive care as per patient choice. Alternatively if SLP indicated the pleural disease was likely to be benign in nature, patients could proceed to elective decortication if they were symptomatic or opt to not have any surgical procedure if they were asymptomatic. This vision was not realised by the work in this study since SLP had a sensitivity and specificity of only 39% and 83% respectively; for comparison the sensitivity and specificity of d-dimer testing in assessment of potential pulmonary thromboembolism is 80-100% and 23-63%.[351] Clinicians will be familiar with the limitations of d-dimer testing, and how it does not clearly indicate a diagnosis but may raise further questions if not used judiciously.[352]

The measures that were anticipated to differ between mesothelioma and non-mesothelioma cases, $Phase_{trunk}$ and $Contribution_{affected}$, did not show any difference upon univariable analysis and could not be used in a binary logistic regression in their continuous form due to non-linearity. Analysis when the variables were converted to binary form resulted in a model that was no better than one without any variables. It may be that SLP is most suited to monitoring the pattern of breathing rather than quantifying regional movements of the trunk, since studies in asthma and COPD shown

differences in respiratory cycle timings and IE50 IQR was a significant individual variable in this study.[343,344]

A large difference in $Contribution_{affected}$ between mesothelioma and benign pleural disease has previously been found using OEP, but these findings have not been replicated with SLP. This raised the question as to whether the SLP equipment was not sensitive enough to detect a difference or there was no true difference in physiology with different pathological processes. Simultaneous OEP of the anterior trunk surface with 52 reflective markers and SLP was attempted in one female and one male to compare their measurements, however the hemispherical markers required for OEP produced large artefacts in the SLP tracing. These artefacts could not be resolved with positioning and therefore it was not possible to record the two techniques at the same time to compare recordings.

The secondary question regarding the potential for SLP to aid prognostication also failed to demonstrate any additional information over and above decision tree prognostication. This study provides some external validation for the Brims decision tree analysis.

The trends observed in univariable and multivariable analyses were in the opposite direction to the hypothesised differences. This may indicate that the differences seen in chest wall motion with OEP were not real, or it could indicate that the groups of patients with benign pleural disease in the two studies were different. Empyema takes weeks to months to form a firm fibrous rind around the lung; chest wall motion early in the disease course may show minimal change and these patients may have more normal

chest excursion compared to patients with mesothelioma, but once established fibrosis is present this may restrict chest wall motion more severely than the tumour bulk of mesothelioma. This potential spectrum of effects of benign pleural thickening on chest wall motion would potentially explain the conflicting results of the two studies.

5.4.2 Comparison of results and hypotheses

Four initial hypotheses have been tested, they were:

1. The contribution of the affected hemithorax to total ribcage motion ($Contribution_{affected}$) would be reduced in patients with mesothelioma compared to patients with non-mesothelioma pleural thickening or effusion.
2. The phase angle of the ribcage and abdomen movement ($Phase_{trunk}$) would be increased (more asynchronous) in patients with mesothelioma compared to patients with non-mesothelioma pleural thickening or effusion.
3. A statistical model using $Phase_{trunk}$ and $Contribution_{affected}$, controlled for the presence of respiratory disease, would be able to differentiate patients with mesothelioma from patients with non-mesothelioma pleural thickening or effusion.
4. The extent of the reduction in contribution of the affected hemithorax to total ribcage motion ($Contribution_{affected}$), controlled for known prognostic variables, would be linked to length of survival in mesothelioma.

Contrary to the hypotheses the median $Contribution_{affected}$ value was higher and $Phase_{trunk}$ value was lower in mesothelioma compared to non-mesothelioma, although these comparisons were not statistically significant upon univariable analysis the same trend was evident upon multivariable analysis. Although Kaplan Meier curves did show a separation between the upper half and lower half of $Contribution_{affected}$ results after 250 days, this was not significant and did not add anything over an existing prognostic

tool. Thus there are no grounds to reject the null hypothesis related to any of the four hypotheses.

A true difference in regional chest wall motion could have been missed using SLP if differences predominated in the lateral or superoinferior planes, since the calculation of trunk motion is predominantly in the anteroposterior plane (towards and away from the cameras). This could explain the difference in findings using OEP in a small number of patients, where there was no overlap in the contribution of the affected ribcage to overall chest wall motion between empyema and mesothelioma cases, and the findings using SLP.[85] The $Contribution_{affected}$ was less than one third in all cases of mesothelioma using OEP but only one out of 33 cases (3%) using SLP.

A preliminary analysis using SLP on 15 patients also showed a significant difference in chest wall motion, leading to another possible conclusion that both reports of a small numbers of patients were unrepresentative samples, leading to a type 1 error. [353]

5.4.3 Strengths of the study

Strengths of this study include a high recruitment rate and complete follow up of patients from a wide geographical area, meaning results should be applicable to the patient population presenting for pleural biopsy in the UK. This study also met the pre-specified target sample size on time.

Data quality for SLP tracings was high; where other sites have failed to get good traces in the seated position, the Pneumacare technician provided feedback that local tracings were good quality except for the problems with artefacts in two cases described

above.[348] This study patient group may have been more co-operative during recordings as they did not have a condition causing muscle weakness. The researchers performing SLP in this study may have been more tenacious than others in getting smooth tracings in the seated position; recordings in the supine position were not attempted as this would be uncomfortable, and possibly intolerable, for patients with breathlessness so there was only one opportunity to obtain the recordings.

The patient population was generally keen to contribute to medical research, which is encouraging for those planning studies of pleural disease. The data from this study provides support for possible use of the Brims decision tree in providing prognostic information and this is potentially immediately useful to clinicians.

5.4.4 Weaknesses of the study

Conversion of continuous data to binary categorical data loses detail in the data and limits the ability to define the effects of variables, however this was necessary to meet statistical assumptions. Transformation was attempted but failed to meet the assumption criteria.

Assessment of SLP measures on prognosis was limited by the small number of patients diagnosed with mesothelioma. It is difficult to enrol large numbers of patients with a rare cancer so a multicentre study would likely be needed to fulfil adequate numbers for comprehensive survival analysis, which is not supported but is also not entirely futile based on the results of this study. The data used in prognosis was limited and it would be desirable to collect details of chemotherapy or radiotherapy delivered in addition to

baseline characteristics as these factors could have influenced survival to an unknown extent in this study.

The low incidence of metastatic carcinoma is a limitation since this is a common cause of pleural effusion and more work to assess how SLP measures are distributed in this patient group would be necessary before SLP could be considered for a clinical use. This low incidence indicates the cohort of patients presenting for surgical biopsy once cytology has not identified the cause of an effusion have different characteristics to the wider population of patients with undiagnosed unilateral effusion. Patients presenting for surgery are likely to be of a better functional status and considered able to withstand general anaesthesia with single lung ventilation, thus the results of this study cannot be extrapolated to patients who are unfit for surgery.

The problem of skin contours affecting the SLP trace has been described in Section 5.3.1; refining the technique of chest wall motion measurement to overcome both the issue of skin folds and detection of movement in the lateral or superoinferior planes is desirable and a promising method that has proof of concept established is use of the Microsoft Kinnect apparatus.[354] The additional benefit of Kinnect is the lower purchase cost for hospitals making this more accessible for centres with lower incidence of pleural disease or centres in developing countries.

5.4.5 Implications for clinical practice and future research

At present there is no role for SLP in the stratification or prognostication of patients with pleural disease presenting for diagnostic surgery. It is uncertain whether this is

because of limitations with the technique of SLP or whether there is no true physiological difference between patients groups.

Further areas of research with SLP may yield useful results. Patients with known asbestos exposure and pleural disease may be eligible for compensation, but those who are not fit for surgical biopsy may have a stronger legal case if there is additional evidence for the presence of mesothelioma. Such cases are based on civil law, the standard of proof being *'on the balance of probabilities'*.[355] Testing of SLP in patients unfit for surgery caries a very low risk of harm and could help these patients if a significant model were found, even if it were not sufficiently accurate for clinical use.

Patients with recurrent pleural effusion from any cause may or may not benefit symptomatically from drainage of the effusion; the procedure is not entered into lightly as it can be painful and associated with complications.[356] Examining measures of SLP before drainage and degree of relief of dyspnoea afterwards could help identify the patients that would benefit from intervention for their pleural effusion, which can currently be a therapeutic conundrum.[357]

Finally a more detailed study of prognosis or degree of tumour burden taking into account interventions for mesothelioma, such as chemotherapy, may reveal additional information from SLP. This kind of study would be best run alongside a multicentre trial of chemotherapy to ensure detailed information about treatments are available and also to ensure feasibility for the intended clinical setting is confirmed.

In summary chest wall motion as defined by SLP is not detectably different in the presence of mesothelioma versus non-mesothelioma pleural disease. Measurement

techniques that include lateral and superoinferior movements may be more useful in this patient group. Restrictions in chest wall motion do not aid in prognostication but the Brims decision tree now has external validation for this use. These results indicate that further research into the SLP as a tool for use in managing patients with pleural disease should only proceed with caution, preferably being limited to patients who are not fit for invasive procedures as they have the most to gain from non-invasive assessment.

CHAPTER 6: ASSESSING THE MECHANISM OF ACTION OF ENDOBRONCHIAL COILS USING OPTOELECTRONIC PLETHYSMOGRAPHY

6.1 Introduction

6.1.1 Lung volume reduction procedures

The landmark National Emphysema Treatment Trial (NETT) established symptomatic and prognostic benefits of LVR surgery in patients with severe emphysema compared to best medical therapy, but only for patients with a low exercise capacity and emphysema predominantly in the upper lobes of the lungs.[33] Surgery was not beneficial in patients with lower lobe emphysema, baseline exercise tolerance of 25 watts or higher for women or 40 watts or higher for men, or those considered to have high surgical risk (FEV1 less than 20% expected and homogenous distribution of emphysema, or gas transfer less than 20% expected).[33,358] It is reported that LVR treatment for patients with severe emphysema primarily results in the clinical benefits of reduced dyspnoea and increased exercise tolerance by reducing the lung volume relative to that of the ribcage and by improving the elastic recoil of the lung, however the effects are not consistent or predictable, meaning patient selection is a persistent challenge. [359,360] Surgical excision of lung tissue in patients with significant pulmonary disease is a high risk procedure, therefore less invasive techniques were sought both by patients and clinicians.

EBVs are implantable devices inserted via bronchoscopy to reduce lung volume; the one-way valves are positioned in the segmental bronchi of one lobe of the lung to allow

airflow out of the lobe but not back in to it, thus inducing permanent lobar atelectasis. Successful atelectasis is dependent upon the absence of collateral ventilation between lung lobes, which can be assessed at the time of bronchoscopy by the Chartis system or preoperatively by the quantitative assessment of fissure completeness on CT scans. In the short term EBVs improve quality of life and FEV1.[361] Whilst trials of EBVs versus medical care have shown symptomatic benefits; impact upon prognosis is not yet certain and comparison between LVR surgery and EBVs is underway (CELEB trial).[362] There exists a group of patients that could potentially benefit from LVR but do not meet criteria for either LVR surgery or EBVs; for example patients who are considered too high risk for surgery, have incomplete fissures or proven interlobar collateral ventilation, or patients with a homogenous distribution of emphysema.

EBCs were developed to address the unmet need for palliation of dyspnoea in patients with severe homogenous emphysema. The treating clinician places 10-15 nitinol coils into one lobe under fluoroscopy guidance, the procedure is repeated on another lobe after approximately six weeks to allow time for recovery from the first procedure. Each coil, 100-150mm in length, is passed through the bronchoscope so the tip is placed within 3cm of pleura. Once the coil is released it returns to a predefined folded pattern due and in doing so gathers emphysematous tissue together. [363]

The clinical efficacy of EBCs is uncertain and further scrutiny of both their mechanism of action and long term outcomes is warranted, this study aims to further elaborate on the mechanism of action of EBCs. There are four major clinical trials to date that have studied the short term clinical outcomes of EBCs. The RESET trial was an RCT of 47 patients that had a primary outcome of quality of life in patients treated with EBCs

versus medical care. The trial reported better quality of life with an eight point reduction in the St George's Respiratory Questionnaire (SGRQ) score, 64 metre increase in the 6 minute walk test, 310ml reduction in residual volume, and an 11 percentage point increase in FEV1 at 90 days after treatment. [364] The REVOLENS RCT reported treatment efficacy, cost, and safety for 100 patients treated with EBCs versus medical care with a longer follow up of 12 months. It reported a 21 meter increase in the 6 minute walk test, 11 percentage point increase in FEV1, 370ml reduction in residual volume, and 13 point reduction in SGRQ score at 6 months. [365]

RENEW was a larger multicentre RCT (n=315) that, again, followed patients up for 12 months. Similar benefits in trial endpoints were demonstrated with a 15 meter increase in 6 minute walk and 9 point reduction in SGRQ score, however the authors also investigated the costs of treatment. The EBCs cost $20 000 per side treated and the total healthcare costs at 1 year were $48 000 higher in patients treated with EBCs versus medical care; the results of the 5 year follow up with cross over treatment are awaited.[363]

The high costs and uncertain response to all techniques of LVR have lead clinicians to seek further understanding of how the procedures produce an effect and also how to define the patient subgroup that will respond favourably to the procedures; dynamic measures of lung function may have potential to address both of these issues.

6.1.2 Dynamic hyperinflation

Expiratory flow limitation is a hallmark of COPD and causes a prolonged expiratory phase of the respiratory cycle, thus as the respiratory rate increases during exercise

some patients with COPD may not be able to exhale completely before the drive to inhale is irresistible. One consequence of this incomplete expiration is dynamic hyperinflation (DH); a quantitative definition of DH is lacking but it is empirically defined as an increase in the end expiratory volume (EEV) of the lung during exercise. Changes in EEV can be derived from continuous spirometry during exercise and also by measuring chest wall volume changes using OEP.

6.1.2.1 Spirometry derived dynamic hyperinflation

Previous studies have evaluated change in EEV as a derived measure using spirometry during exercise; the change in EEV of the lung is derived by subtracting serial inspiratory capacity manoeuvres during exercise from total lung capacity measured before exercise. [28] Changes in EEV and end inspiratory volume (EIV) using spirometry have been reported for patient undergoing either bullectomy or LVR surgery. Both EIV and EEV reduced after surgery and this was associated with a reduced sensation of dyspnoea, increased tidal volumes, and lower work of breathing. [28,366] Patients undergoing LVR surgery had an increase in exercise tolerance in association with a reduction in DH; patients undergoing EBV insertion also had an increase in exercise endurance in association with a reduction in DH, this was only in patients who clinically responded to EBV insertion.[367,368] Spirometry derived measures are useful in detailing volume changes for the lungs as a whole, however OEP can provide more detail about contributions of the trunk to breathing movements.

6.1.3 Optoelectronic plethysmography during exercise

The response to exercise in healthy individuals is to reduce EEV predominantly by contracting abdominal muscles in combination with diaphragmatic relaxation and

increase EIVs predominantly by contracting inspiratory muscles that act upon the ribcage, the pattern is variable between individuals but occurs in healthy young and older adults of both male and female sex.[77,369,370]

OEP during exercise has shown two patterns of response in male patients with a range of COPD severity, no patients had completed pulmonary rehabilitation and bronchodilators were not administered.[371] A euvolaemic pattern was defined as EEV at maximum workload being the same or lower than EEV at rest; a DH pattern was defined as EEV at maximum workload being above EEV at rest. OEP was performed simultaneously with spirometry and in all patients the EEVs were mean values over one minute. Euvolaemic patients had a small increase in the EEV of the ribcage by 46ml (SD 148), and a decrease in the EEV of the abdomen whilst EIVs were almost unchanged. Patients with DH had a large increase in the EEV of the ribcage by 494ml (SD 90), no change in the EEV of the abdomen, and EIVs increased. The increase in the EIV of the ribcage occurred prior to loaded exercise in both groups of patients. Both groups had a similar Borg dyspnoea score, oxygen consumption, tidal volumes, and minute ventilation at peak workload however the euvolaemic patients had a higher work of breathing. The euvolaemic patients also had higher FEV1, higher BMI, and higher FEV1/FVC ratios, indicating their COPD was be less severe. These findings together imply that DH is not in itself a detrimental response pattern to exercise in patients with COPD; in fact using more energy to avoid DH may create a situation where a larger proportion of oxygen transferred into the bloodstream is utilised by respiratory muscles instead of by those muscles involved in locomotion.

Two subtypes of DH in response to exercise have been identified using OEP in men and women affected by severe COPD (mean FEV1 35%, FEV1/FVC ratio 35%, RV 216%). [372] Early hyperinflators exhibited a progressive increase in EEV of the chest wall (EEVcw) during exercise reaching 750ml above baseline at exhaustion; this increase occurred predominantly in the ribcage. Early hyperinflators also tended to have higher tidal volumes and higher minute ventilation. The increase in tidal volumes arose from an increased EIV of the ribcage and abdomen. Late hyperinflators maintained a constant EEV until two thirds of their peak exercise in Watts and then exhibited an increase in EEV of around 200ml. Initial avoidance of increased EEV came from a reduction in EEV of the abdomen, whilst some increase in tidal volumes came from increased EIV of the ribcage.

OEP at rest in patients undergoing LVR surgery or EBV treatment has shown that asynchronous movements improve after surgery.[373] It is not known whether different breathing patterns represent a disease continuum and whether they can be altered by external influences.

6.1.4 Accuracy of OEP

Comparisons of physiology need to account for the accuracy of the technique being used to measures the variables of interest. OEP measurements of volume of whole chest wall are highly accurate, being within 12-16ml of the true value for a static model (instrumental error). [374,375] Measurements on patients with respiratory failure over time and with changes in mechanical ventilation settings (positive end expiratory pressure) demonstrated that EEV of the chest wall does not exhibit drift. [373] OEP was compared to volume measurements with helium dilution; the difference in the change in EEV

between the two methods was -24ml. There are additional volume changes due to gas compression and shifts in blood volume that can affect EEV measured by OEP and account for some difference between the two measurement techniques. There is a 0.1% change in the thoracic gas volume per 1cmH_2O change in alveolar pressure, and a 7.2ml shift in blood volume per 1cmH_2O. [375] OEP and spirometry based measures show good agreement; the mean difference between the change in EEV measured by OEP and by spirometry was 35ml (SE 24) during exercise. [372] The equipment accuracy and agreement with a gold standard technique are thus sufficient for OEP to be considered an accurate and appropriate instrument to continuously monitor changes in EEV.

The precision of OEP has also been assessed in normal humans providing intra-observer and inter-observer variation measures (observation error), these are displayed in Table 28 and Table 29.[376]

Table 28 Intra-observer variation of OEP during exercise

	Mean difference	**SD**	**Intra-class Correlation Coefficient**	**Minimum Detectable Change**
Vt cw	30ml	110	0.98	43ml
EEVcw	160ml	460	1.0	40ml
EIVcw	130ml	500	1.0	44ml
Ribcage %	0.12 pp	5.11	0.86	5 pp
Abdomen %	-0.12 pp	5.11	0.86	-5 pp

Note: Vt – tidal volume, cw chest wall, EEV – end expiratory volume, EIV – end inspiratory volume, pp – percentage points, n=20, data reported by Vieira et al [376]

Table 29 Inter-observer variation of OEP during exercise

	Mean difference	**SD**	**Intra-class Correlation Coefficient**	**Minimum Detectable Change**
Vt cw	0ml	60	0.96	33ml
EEVcw	520ml	770	0.98	302ml
EIVcw	520ml	800	0.98	314ml
Ribcage %	0.58 pp	3.81	0.92	3 pp
Abdomen %	-0.58 pp	3.81	0.92	-3 pp

Note: Vt - tidal volume, cw chest wall, EEV – end expiratory volume, EIV – end inspiratory volume, pp – percentage points, n=12, data reported by Vieira et al [376]

6.1.5 Hypotheses

OEP had never been performed on patients undergoing coil insertion, and it had not been reported during exercise for any kind of LVR procedure. Patterns of DH in particular had not been specifically studied in this clinical setting, but it could be highly relevant to either patient selection or understanding the physiological effects of LVR. The hypotheses that were planned for testing were:

- Three types of breathing pattern would be demonstrated in a group of patients with severe emphysema undergoing coil insertion
- DH would be reduced by the insertion of EBCs
- The type of breathing pattern will have an association with presence or absence of clinical response to EBCs

6.2 Methods

6.2.1 Study design & setting

A prospective observational cohort study was conducted at Heartlands Hospital. The study was awarded an Investigator Initiated Study grant from BTG International Ltd, had ethical approval (Research Ethics Committee reference 10/H1202/58), and was pre-registered at clinicaltrials.gov (NCT02958683). All patients that were due to undergo coil insertion were eligible; patients who lacked capacity to give informed consent and patients under 18 years of age were excluded. All LVR candidates are discussed at the Emphysema MDT meetings so these meetings were screened for eligible patients, it was anticipated that 10 patients per year would undergo coil insertion and thus a target of 15 patients over 18 months was set for this study.

Patients were recruited in outpatient clinics after the Emphysema MDT and OEP recordings were performed at the time of the preoperative assessment clinic before coil insertion, and 6 months after the second stage of the procedure to allow time for postoperative recovery.

6.2.2 Variables & sample size

Baseline demographics, lung function, and quality of life (SGRQ) were recorded. Not all patients respond clinically to LVR procedures; responders were defined as patients who had achieved a reduction in SGRQ by 4 or more points, as this change is the reported minimum clinically important difference for patients with COPD.[377] Patients who did not meet this criterion were classed as non-responders and patients who did not return for follow up because they felt unwell were also classed as non-responders. Responder status for this study was determined before processing of OEP results. The primary outcome variable of interest was the change in EEV of the chest wall during exercise compared to EEV at rest; secondary variables included changes in EEV within the ribcage and abdominal compartments. The effects of EBCs on EEV were unknown but they were anticipated to be small; for sample size calculations estimations had to be used. For a two tailed, paired t-test a sample size of 11 would achieve 80% power, with a 5% significance level to detect a mean difference in change in the EEV of the chest wall of 100ml (SD 100ml) when comparing preoperative to postoperative recordings. Synchrony of chest movements can also be assessed using OEP, however the clinical consequences are unclear and therefore this measurement was not planned for analysis.

6.2.3 Data analysis

Paired t-test comparison of the change in EEV of the chest wall from rest to exhaustion at preoperative and postoperative time points was planned as the primary analysis. Descriptive reports of the changes in EEV between the ribcage and abdomen during exercise for each patient were also planned to identify the previously reported patterns in breathing: euvolaemia, late hyperinflation and early hyperinflation. The Freeman-Halton extension of a Fisher's exact test was then planned to compare the prevalence of response to EBCs across the three patterns of breathing during exercise.[378]

6.2.4 Technique of OEP

6.2.4.1 Equipment set up

Eight cameras that both emitted and recorded infrared light were positioned around a static exercise cycle, four cameras were positioned in front of the patient and four were positioned behind the patient (Figure 72). The software used for OEP was the SMARTtracker Motion Capture System, Version 1.10.458.0 on a Windows XP 2002 computer with a 32 bit operating system. The recording system was calibrated prior to each session of OEP recording using a static three dimensional marker (Figure 73) for 60 seconds, the arm with three reflective markers was then manipulated to cover a cuboidal volume of air where the patient would be seated during the recording, this was done for a further 120 seconds.

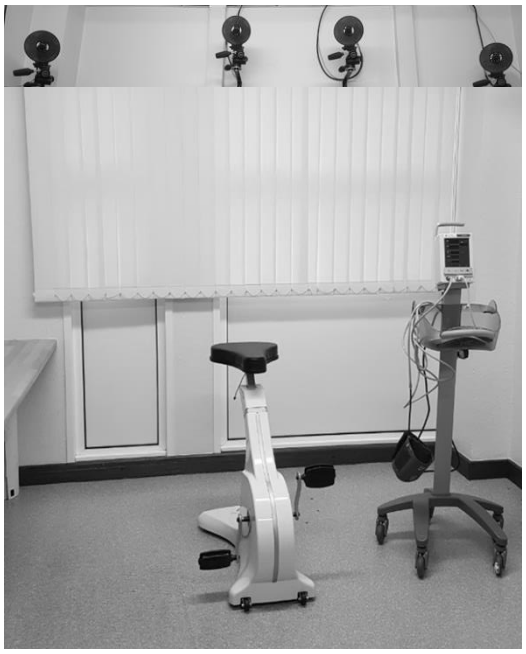


Figure 72 Equipment set up with infrared cameras, bicycle without handlebars and observation monitoring

Figure 73 Wand and axes for calibration of equipment prior to OEP recording

6.2.4.2 Marker placement

Marker placement is defined in a handbook provided by the distributors of the OEP equipment but only briefly described in published literature.[379] Recordings were performed with the patient positioned on the exercise cycle in a seated position, in this position 89 reflective markers were used with 42 markers anteriorly, 37 posteriorly, and 10 laterally. Hemispherical markers were preferred as they follow the movements of the torso more precisely but spherical markers on raised stalks were sometimes necessary to ensure adequate visibility of the marker to the cameras, particularly in the lateral positions and around some body contours, such as breast tissue. All markers were secured with double-sided hypoallergenic tape.

OEP should only be used to measure volume contributions according to two compartments (ribcage and abdomen) rather than three (pulmonary ribcage, diaphragmatic ribcage, and abdomen) in the more difficult recordings with female or obese patients. This study included female patients so volumes were measured for two compartments. The same researcher applied the markers in all patients before and after treatments, minimising bias from inter-observer variation of the technique.

6.2.4.3 Anterior marker placement

The first row of markers sat below the clavicle, the middle marker was positioned at the jugular notch and the lateral markers were medial to the acromion. The middle marker on second row was positioned at the manubriosternal junction and the lateral markers were placed on the anterior axillary line. The third row followed the fifth rib. The fourth row was at the level of the junction between the xiphisternum and body of the sternum.

The fifth row followed the costal margin with the middle marker at the caudal end of the xiphisternum, but a minimum of 2cm away from the marker cranial to it. The sixth row was at the level of the umbilicus. The seventh row joined the anterior superior iliac spines. Extra markers were added to aid definition, two between the second and third rows, and three between the fifth and sixth rows (Figure 74).

6.2.4.4 Lateral marker placement

Five markers were placed on each side in a vertical row following the posterior axillary line; markers were spread along the vertical line to form a continuation of the third to seventh anterior rows of markers.

6.2.4.5 Posterior marker placement

On the lower back, five markers were placed in a vertical line along the spinous processes of the vertebrae; the markers were spread along the vertical line at the same heights as the lateral markers. Four additional markers were placed equidistant between the middle and lateral markers at each level to form a grid pattern of 25 posterior markers. On the upper back, the first row followed the suprascapular line with the middle marker placed on the spinous process of the seventh cervical vertebra and the most lateral markers at the posterior axillary lines. The second row was placed equidistant between the first row and the grid on the lower back. Two extra markers were added below the second row to aid definition (Figure 74).

6.2.4.6 Special considerations for marker placement

Female subjects should wear a well-fitting bra and the researcher should avoid placing markers on bra material or close to material that will move and cover the marker during

exercise. Adhesive tape can be used to adjust the lie of material and improve skin exposure, the markers in the fifth row will need to be placed slightly higher than in males. Use of a spherical marker in the midline between breasts eliminated tracking errors due to reduced marker visibility in this area.

Markers may need to be adjusted in patients with obesity to avoid markers being hidden from the camera view by a skin fold, particularly those over the lower abdomen. Use of spherical markers in place of hemispherical markers should be kept to a minimum due to the increased measurement noise associated with the marker not directly touching the skin, but they may be necessary to ensure good visibility. For example, the most lateral markers on the anterior trunk may have a side on orientation to the camera when the abdomen is larger and as such visibility would be improved with use of a spherical marker.

6.2.4.7 Resting and exercise regimen

Patients were recorded in a seated position at rest with arms holding a supportive pole laterally to aid stability for 120 seconds. They then commenced pedalling without resistance; recordings were intended to continue until patients reached 80% of their predicted maximum heart rate, however all patients except one individual exhibited resting tachycardia that exceeded the target heart rate. Patients were thus asked to pedal until they felt they needed to stop, either due to dyspnoea or muscle fatigue. Observations including pulse, blood pressure, and oxygen saturations were monitored during exercise for patient safety.

6.2.4.8 Marker tracking

A predefined label map was included in the OEP software; the user had to manually assign labels to the track of each marker. The software calculated three-dimensional volumes after labels were assigned (Figure 75). Extraction of data from the volume file was facilitated by a custom software application called Diamov (Version 1.0.0.1, June 2004) provided by Antonella Lo Mauro at Politecnico di Milano. Recordings were analysed by ribcage and abdomen compartments only because many participants were female and some patients had central adiposity.

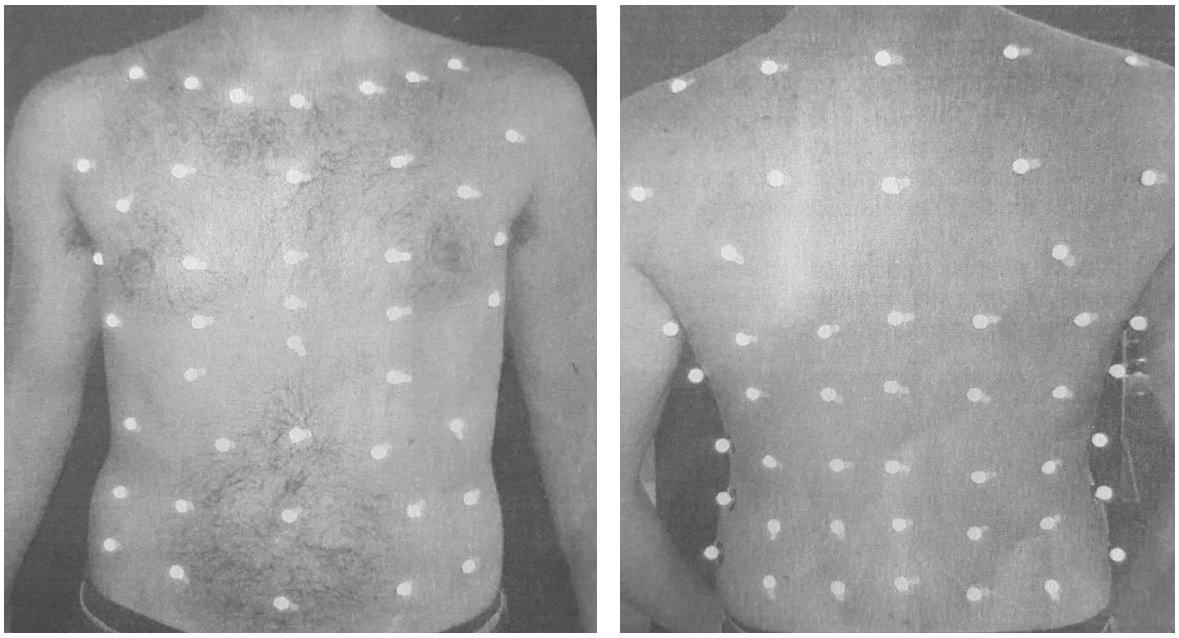


Figure 74 Placement of hemispherical infrared reflective markers on the torso

Note: Adapted from images in the marker placement handbook.[379]

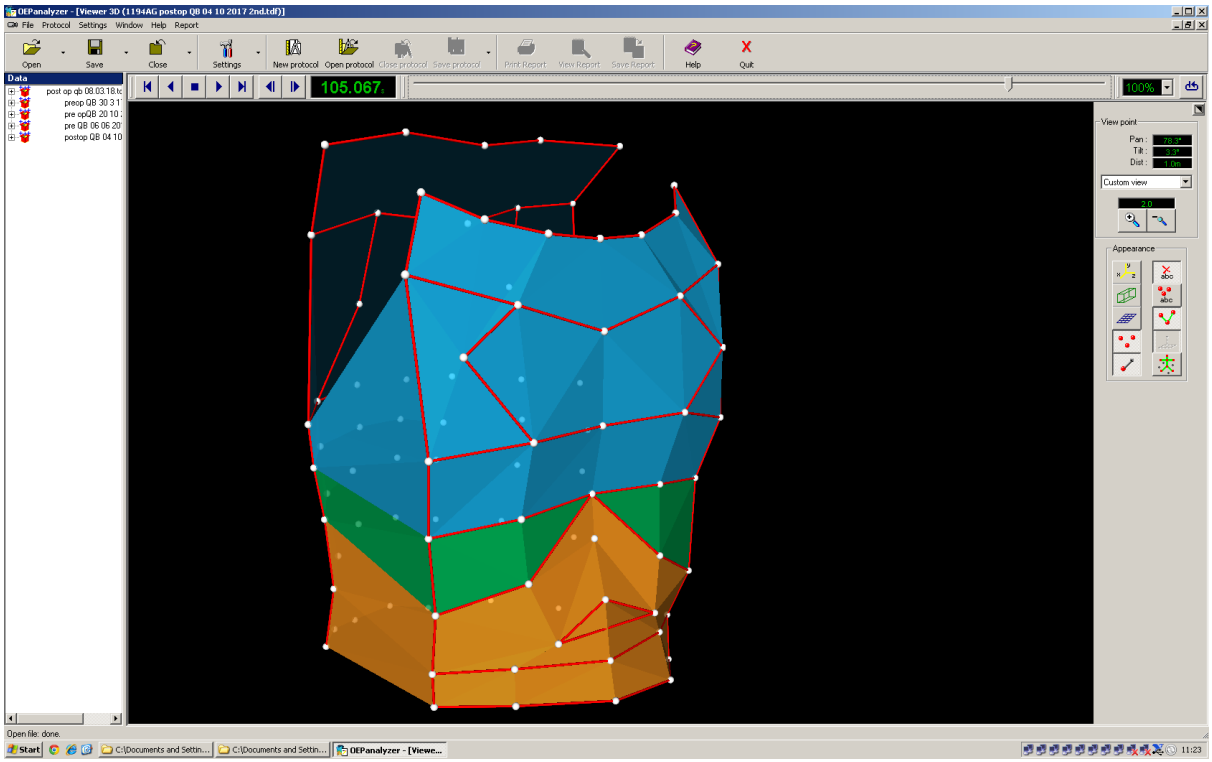


Figure 75 View of SMARTtracker with tracked reconstructed data from 3D co-ordinates

6.3 Results

6.3.1 Patient flow and characteristics

There were fewer patients listed for EBCs than anticipated during the study so recruitment was extended to last 36 months in order to meet the target sample size of 15, patient flow through the study is illustrated in Figure 76. Patient demographics and physiological data at baseline are displayed in Table 30, demographic variables were checked for normality by inspection of density plots and found to be non-normal in their distributions therefore median and IQR values were used to summarise the baseline variables. All patients had severe emphysema with a high residual volume indicating the presence of hyperinflation.

A total of eight patients completed baseline OEP recordings and underwent coil insertion; four of these patients were classed as responders according to SGRQ scores. Unfortunately, only two patients completed postoperative OEP recordings, one was a responder and one was a non-responder. Pairwise analysis of preoperative and postoperative EEV values could not be undertaken to compare the groups of responders and non-responders. Eight patients was also too few to complete Fisher's Exact testing.

Table 30 Patient demographics and clinical information

Variable	**Baseline value**
Age (years)	66 (63-72)
Sex (male:female)	3:5
BMI	24.6 (23.0-25.8)
FEV1 (L)	0.51 (0.43-0.61)
FEV1 (% expected)	23 (20-26)
FVC (L)	1.60 (1.44-1.87)
FVC (% expected)	62 (52-70)
RV (L)	4.86 (4.42-5.51)
RV (% expected)	249 (214-283)
TLC (L)	7.12 (6.54-8.30)
TLC (% expected)	130 (122-151)
St George's Respiratory Questionnaire score	75.3 (52.0-89.4)
6 minute walk test (m)	220 (205-264)
Exercise time during OEP (seconds)	245 (234-270)

Note: Patients who completed baseline tests and underwent endobronchial coil insertion, n=8. Values are median and IQR apart from sex, for which counts are displayed.

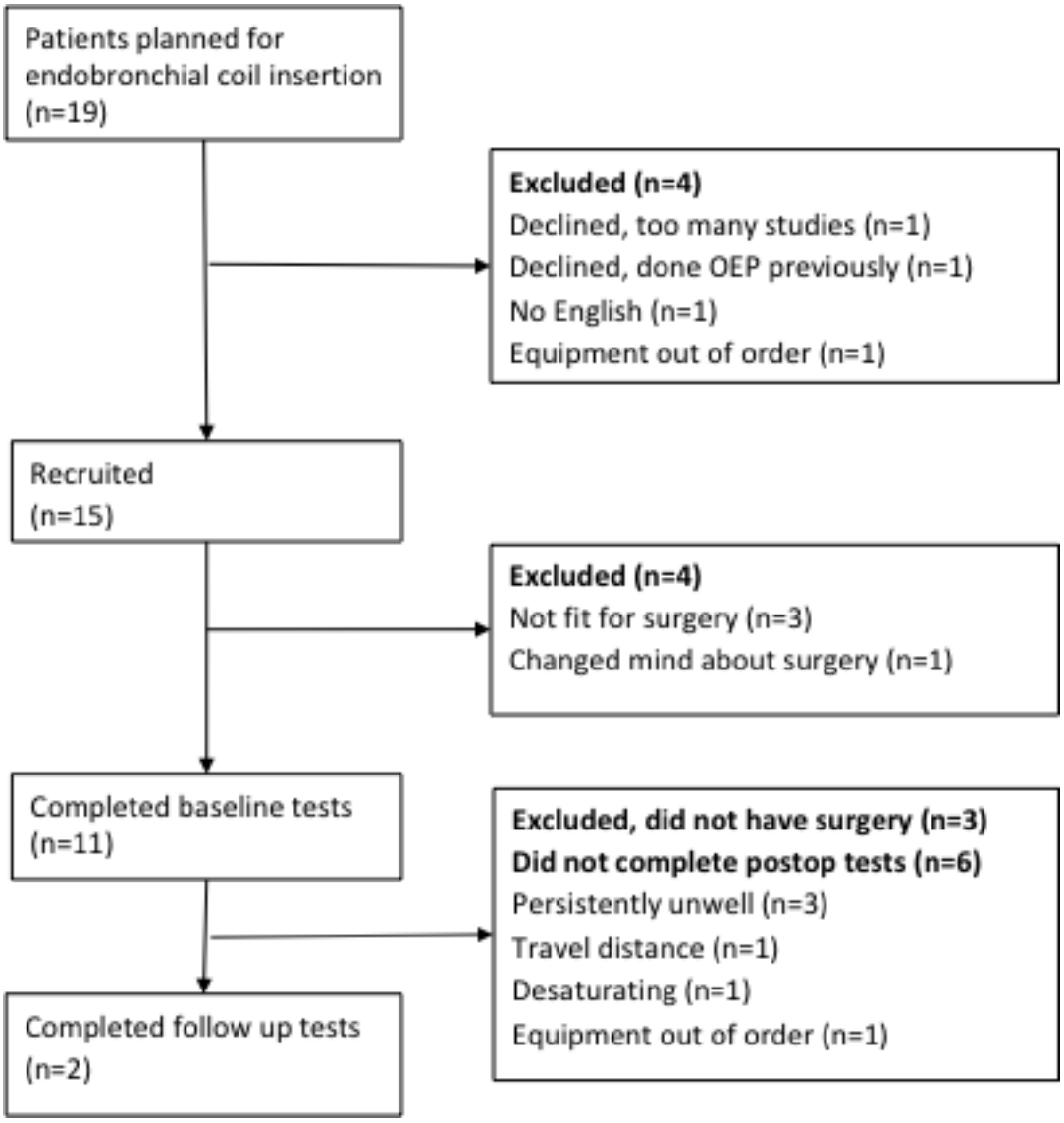


Figure 76 Patient flow through the study

6.3.2 Patterns of dynamic hyperinflation

The changes in EEV for the chest wall, ribcage and abdomen relative to the resting EEV were plotted graphically to identify the patterns of response to exercise reported in existing literature. Resting values were considered time point 0, the period of exercise was divided into thirds and median values were plotted as time points one through to three, akin to the reporting of Vogiatzis et al.[372] Three patterns of EEV response to exercise were demonstrated among the patients; Patient A was euvolaemic, Patients C and D were late hyperinflators, and Patients B, E, F, G, and H were early hyperinflators (Figure 77 and Figure 78). The type of response to exercise did not determine whether patients responded to EBCs clinically with 100% accuracy, however a slightly lower accuracy that may still be clinically helpful cannot be excluded (Table 31).

Patient D, who clinically responded to EBCs by the study definition, demonstrated a shift in their pattern of response to exercise after coil insertion so that DH. Prior to the procedure the onset of DH started during the final third of the exercise time, after the procedure DH started during the middle third of the exercise time (Figure 79). Their exercise time to exhaustion increased from 286 seconds preoperatively to 343 seconds postoperatively (20% increase). Patient F, who did not respond to EBCs clinically, showed no change in the pattern of dynamic hyperinflation (Figure 80). Their exercise time to exhaustion reduced from 246 seconds preoperatively to 184 seconds postoperatively (25% decrease).

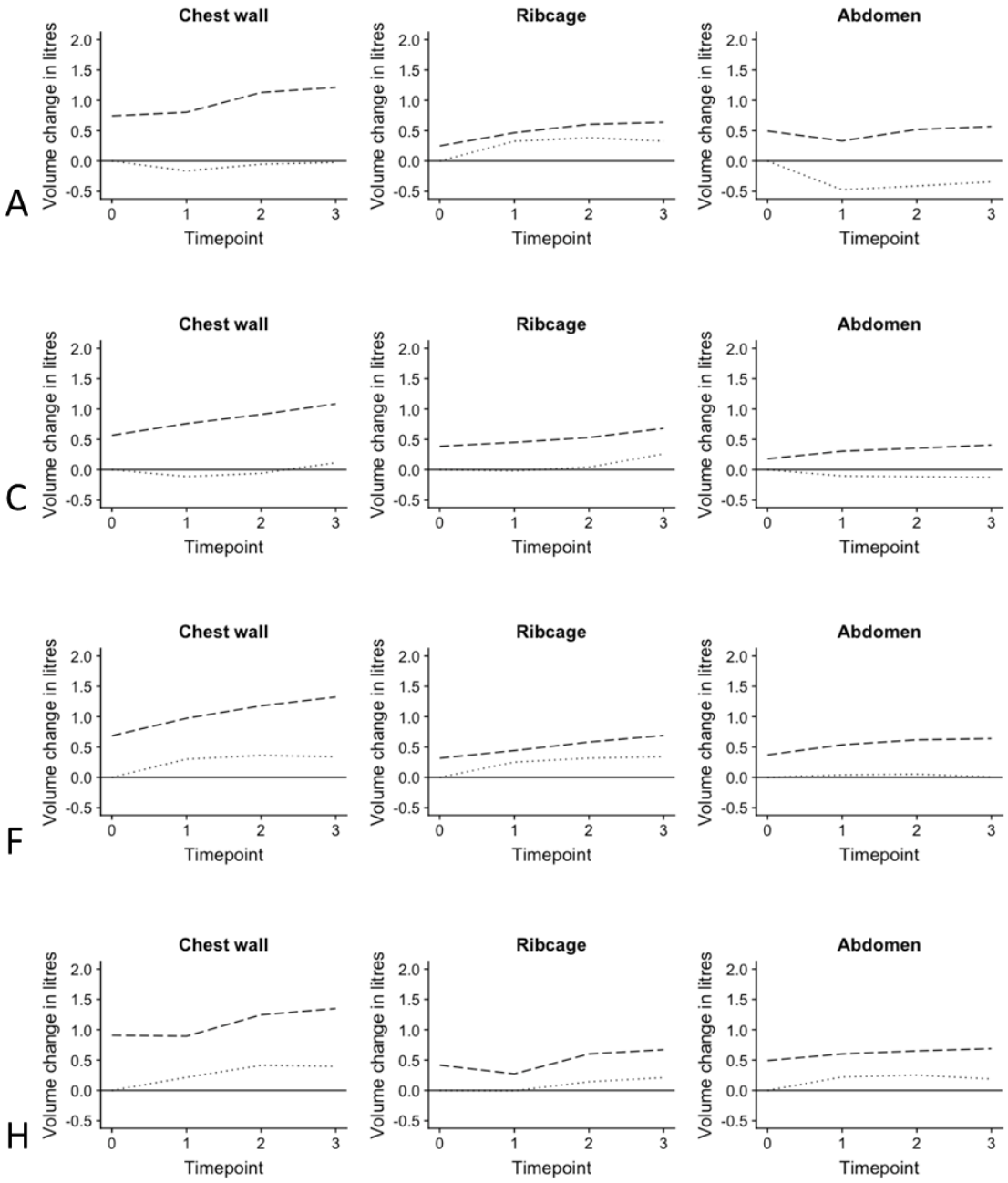


Figure 77 Preoperative graphs of trunk volumes for non-responders to EBCs. Patient A- euvolaemia, patient C – late dynamic hyperinflation, patient F and H – late dynamic hyperinflation.

Note: Dashes - end inspiratory volumes, dots - end expiratory volumes. Time point 0 - resting value, time point 1 - average over the first third of exercise, time point 2 - second third of exercise, time point 3 - final third of exercise.

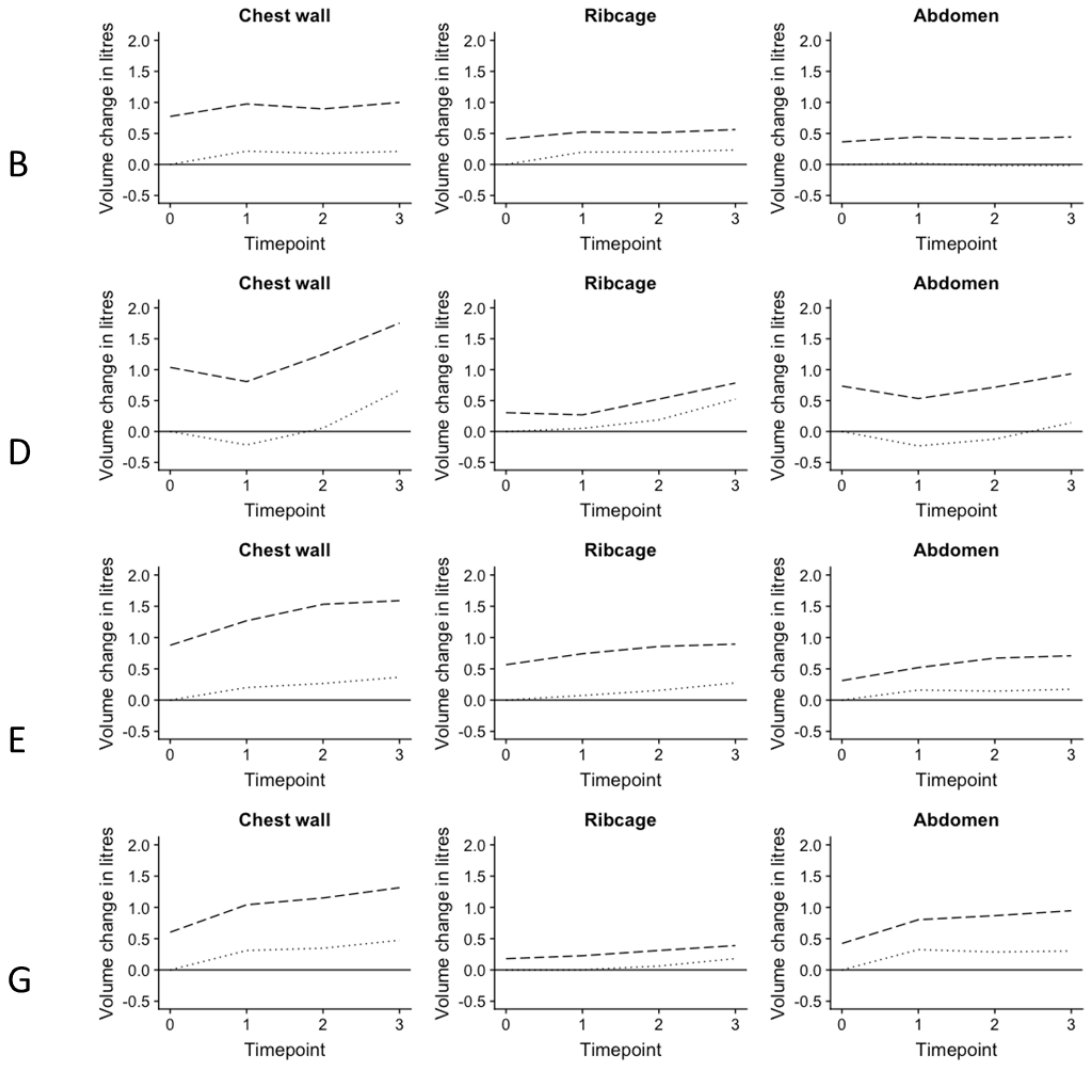


Figure 78 Preoperative graphs of trunk volumes for responders to EBCs. Patients B, E and G – early dynamic hyperinflation, Patient D – late dynamic hyperinflation.

Note: Dashes - end inspiratory volumes, dots - end expiratory volumes. Time point 0 - resting value, time point 1 - average over the first third of exercise, time point 2 - second third of exercise, time point 3 - final third of exercise.

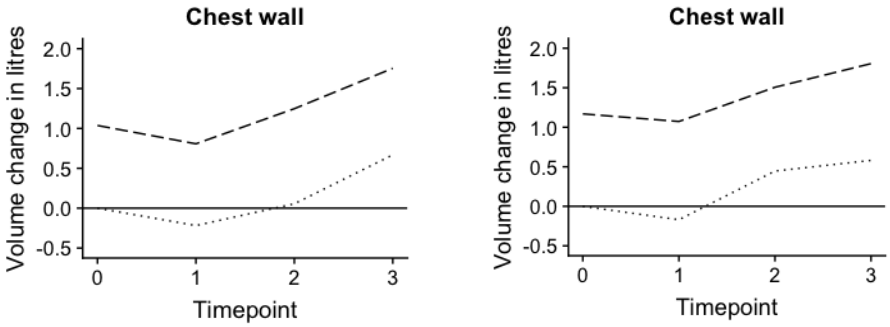


Figure 79 Preoperative (left) and postoperative (right) changes in trunk volumes, Patient D (responder). Late dynamic hyperinflation pattern altered after endobronchial coil insertion.

Note: Dashes - end inspiratory volumes, dots - end expiratory volumes. Time point 0 - resting value, time point 1 - average over the first third of exercise, time point 2 - second third of exercise, time point 3 - final third of exercise.

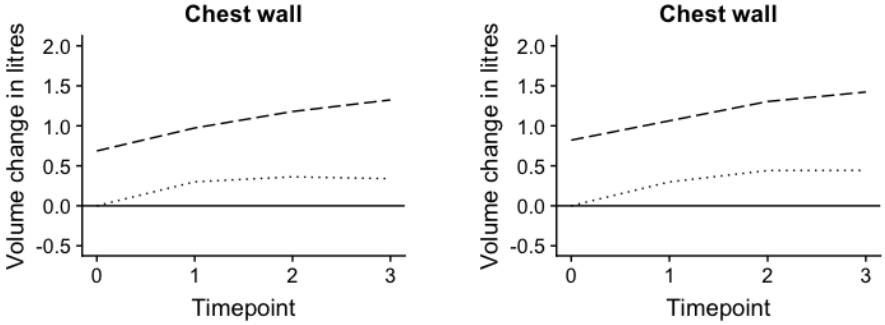


Figure 80 Preoperative (left) and postoperative (right) changes in trunk volumes, Patient F (non-responder). Early dynamic hyperinflation pattern unchanged by endobronchial coil insertion.

Note: Dashes - end inspiratory volumes, dots - end expiratory volumes. Time point 0 - resting value, time point 1 - average over the first third of exercise, time point 2 - second third of exercise, time point 3 - final third of exercise.

6.4 Discussion

6.4.1 Comparison of results and hypotheses

The planned analyses were not possible due to the lower number of coil procedures performed and lack of postoperative data. Consequently, caution must be exercised in interpreting the clinical meaning of the results relative to the pre-stated hypotheses. The findings were:

- Three types of breathing pattern were demonstrated in a group of patients with severe emphysema undergoing coil insertion.
- There is weak evidence to reject the hypothesis that dynamic hyperinflation would be reduced by the insertion of EBCs, with neither patient who completed follow up having a reduced change in EEV of the chest wall.
- The hypothesis that the type of breathing pattern would have an association with the presence or absence of clinical response to EBCs cannot be accepted or rejected.

6.4.3 Strengths of the study

This is the first study to report chest wall motion in patients undergoing coil insertion and the first to report OEP during exercise in patients undergoing any type of LVR. An important strength of measuring breathing parameters using OEP is that patterns should not be altered by the presence of the recording equipment, thus recordings can be considered representative of patient physiology in normal activities. Patients can breathe as they normally would, including pursed lip breathing to provide some autonomous positive end expiratory pressure, as opposed to wearing a nose clip and breathing through a mouth piece of fixed diameter.[380] OEP recordings during exercise

are more difficult to track in the analysis process due to the risk of markers being hidden by moving body parts, thus it is a strength of this work that all of the recordings were fully analysable. Contact with experts in the field revealed that exercise recordings of patients with severe emphysema undergoing LVR surgery or EBV were attempted but not analysable in a different laboratory.[373]

6.4.4 Weaknesses of the study

The cohort was a high risk patient group with heavy disease burden, as is the case for all patients undergoing LVR. The RENEW study included a highly selected group of patients, but 7% of study patients only had unilateral coil placement because of death or deterioration in health and the study achieved a 90% follow up rate.[363] Heartlands Hospital is a tertiary referral centre and as such patients are referred from considerable distances including Hereford and Worcester. The combination of patient ill health and travel distance contributed to the high proportion of patients not completing the study procedures, effectively meaning the study could not be completed as planned. The loss of two potential recordings to equipment difficulties was also disappointing. The preoperative equipment failure was a screen connector port being found broken on the planned day of recording and the patient proceeded to coil insertion before the port could be repaired. OEP recordings are complex and the postoperative equipment failure was the system failed to achieve a satisfactory calibration despite multiple attempts on separate days, the cause of this issue was not identified but resolved without any obvious intervention, however the patient could not attend a third time. It was common for the software to freeze or crash if commands were entered too quickly during marker tracking so updating the processing power of the computer system may be necessary to avoid future equipment failures.

6.4.5 Interpretation of the change in breathing pattern in one responder

The change in DH pattern for Patient D is likely due to confounding factors than a true physiological difference following coil insertion. Two key confounding factors were present; firstly they had undergone a previous LVR procedure, this did not exclude them from the study but may make them unrepresentative of patients being treated with EBCs in general. It would be prudent to specifically exclude patients who have undergone prior LVR from future studies exploring the mechanism of action of a different method of LVR. Secondly, an interesting and important psychological influence of participation in research occurred in Patient D. They gained confidence in their ability to exercise from their experience of using the exercise cycle and proceeded to increase their exercise activities at home after treatment with EBCs. Thus, the prolongation of their time exercising until exhaustion, which was likely due to an increase in fitness from training, prolonged the period of DH that was captured. The improvement in dyspnoea symptoms were also likely to be affected by the exercise training and the patient may not in fact have gained benefit from the EBCs themselves.

6.4.6 Results in context

The commonly reported definition of DH as any increase in EEV with increased respiratory rate is probably correct but represents an oversimplification, since DH itself shows more than one pattern during exercise. There is evidence of at least four EEV change patterns during exercise: reduction, no change, late increase, and early increase. It is not yet certain whether these responses represent a spectrum of disease severity and whether they can be altered by interventions. The presence of three patterns of EEV change during exercise in this study despite a relatively homogenous group of patients

as assessed by standard clinical tests is a new finding and supports the patterns not being part of a continuum that correlates with severity of airway obstruction.

DH has been shown not to be the sole determinant of exercise limitation in all patients with COPD, since patients have equal dyspnoea and endurance on exercise testing when categorised as DH present or absent. [381] Administration of tiotropium does not affect DH and does not increase the amount of time to reach a critical point of impairment in inspiratory reserve volume, it does however lower the operating lung volumes and improve dyspnoea.[380] Patients with COPD most frequently describe inspiratory difficulty as the main sensation of dyspnoea and patients' muscles must adapt to operating at higher lung volumes, this occurs when the change in lung volumes is gradual and chronic. [382,383] An exercise training programme in patients with mild COPD has been reported to increase Functional Residual Capacity, leading the authors to conclude that conditioning of the inspiratory muscles was responsible for increases in exercise capacity after training as opposed to any influential changes within the lungs.[384]

Additional studies were published after commencing this study with two being of particular relevance. Further study of patients undergoing LVR surgery has supported the theory that a favourable length and tension relationship within respiratory muscles following LVR surgery underlies improvement in respiratory function after surgery.[385] Respiratory mechanics in patient who received EBCs as part of an RCT have now been compared to patients who continued with usual medical care.[386] Patients who received EBCs had reduced EEVs across all intensities of exercise as measured using spirometry. The authors did not assess the pattern of DH themselves but inspection of their reported graphs for the patient groups demonstrates early DH both before and after coil

insertion. Interestingly, patients who continued usual medical care showed a late DH pattern, if DH pattern has any association with disease progression or response to coil insertion an important confounding factor could be present in the RCT.

One interpretation of the results of this study in combination with existing evidence is that patients who demonstrate early DH may have individually optimised musculoskeletal and cardiovascular systems, such that their main limitation to increasing exercise tolerance lies in their EEV approaching TLC. Reducing their operating lung volumes via invasive methods can thus benefit the patient symptomatically by improving the mechanical position of the musculoskeletal elements of the respiratory system and relieving the sensation of unsatisfied inspiration. Patients who do not exhibit early EEV may have other factors that limit their exercise tolerance more than EEV, such as respiratory muscle weakness.[387] LVR procedures may not produce any symptomatic or prognostic benefit in these patients because it does not affect these other factors.

6.4.7 Implications for clinical practice and future research

The possible conclusions from this study are limited but in keeping with existing literature and may be a stimulus for further research. Patient D was classed as a responder according to predefined SGRQ criteria (Table 31), if Patient D gained all of their improvement in SGRQ from the confounding factor of increased fitness levels they could in fact be a non-responder to EBCs, in this scenario only patients with early DH responded to EBCs (Table 32). Early DH could thus be a useful test to identify potential responders to LVR, though not all patient with early DH would respond. The pattern of DH warrants further study as a potential test for LVR candidates.

Table 31 Type of response to exercise versus presence or absence of clinical response to endobronchial coils with Patient D as a responder

	Euvolaemia	**Late dynamic hyperinflation**	**Early dynamic hyperinflation**
Responders	0	1	3
Non-responders	1	1	2

Table 32 Type of response to exercise versus presence or absence of clinical response to endobronchial coils with Patient D as a non-responder due to increased exercise as a confounder

	Euvolaemia	**Late dynamic hyperinflation**	**Early dynamic hyperinflation**
Responders	0	0	3
Non-responders	1	2	2

EBCs are not currently the preferred technique for LVR. The United State Food and Drug Administration refused premarket approval for EBCs due to concerns about the risk versus benefit profile and uncertain treatment benefit of the devices; one of their concerns was the potential for confounding factors in defining response to coil treatment.[388] The potential for confounding was demonstrated in this study and it was only apparent due to social interactions between the patient and the researcher during a study procedure that takes time to complete. Healthcare costs are particularly important to consider in procedures of uncertain benefit; EBCs appear to represent poor value for money using the current patient selection criteria.

In conclusion, patient selection for LVR remains a challenge; examination of DH patterns during exercise warrants further investigation, particularly whether early DH indicates a greater chance of significant improvement from LVR.

CHAPTER 7: DISCUSSION

7.1 Summary of results & future directions

This thesis has explored the use of non-invasive tests to quantify regional respiratory function, either through measuring the regional ventilation of lung parenchyma with CT scan analysis or through measuring the regional external movements of the trunk with SLP or OEP. The results of studies using these techniques are considered separately.

7.1.1 Predicting postoperative lung function

The systematic review revealed CT analysis of lung density and volume to be the most accurate and precise method for predicting postoperative FEV1 after lung cancer resection; segment counting appeared to outperform perfusion scintigraphy in predicting postoperative TLCO but data was limited to single studies. Many studies had been conducted around the world from the 1970s to the review date, showing there was ongoing academic interest in this topic and also that it was of international interest. This was the first systematic review and meta-analysis of these studies to be conducted and the authors of more recent articles tended to refer only to a small number of prior studies. This could indicate studies were conducted without all authors having full details about studies from around the globe, possibly due to time and manpower required to gather and assess the large number of studies available.

There is considerable pressure placed upon doctors in training as well as academics to author publications in order to progress and obtain further employment.[389] A potential consequence of this can be that individuals are incentivised to pursue research that is easy to conduct as opposed to researching topics that are time consuming or

challenging, even if the topic is very worthy of that time and effort. Only a little over 10% of the studies identified as addressing the systematic review questions were considered to have a low risk of bias, this could support the possibility of lower quality research being a problem in this topic area. Studies that were assessed as having a low risk of bias in their conduct tended to have small sample sizes, however there was no clear reason as to why this was the case. It simply appeared that exploratory studies had been conducted; no studies had reported feasibility measures.

A refinement of the most accurate predictor of postoperative FEV1 was taken forward in a prospective study but measures of feasibility were recorded. The study reported herein found that integrating another test into the preoperative patient pathway was incredibly difficult and this could be an important reason why prospective studies had small patient numbers. Large savings of time, effort and money could have been made if previous studies had included measures of feasibility. It is therefore important to disseminate the results contained in this thesis regardless of the additional finding of failure to improve upon current prediction of postoperative lung function using lobar deltaSVg.

One aspect of feasibility that would not be apparent from published articles was that it was challenging to predict what operative procedure a patient would actually undergo, due to some inherent uncertainties associated with thoracic surgical practice. Informed consent requires adequate time for an individual to consider participation in a study. Patients should also be approached at an appropriate time and their psychological state during the time pressured cancer treatment pathway should be respected. Patients were approached at the preoperative assessment clinic as this was considered a satisfactory

balance between sufficient time for patients to process their working diagnosis and not being too close to the date of major surgery. However, a number of patients were found to have more advanced cancer or found to have significant co-morbidities after they attended the preoperative assessment clinic and therefore did not proceed to surgery, this lowered the study completion rate. The number of patients who underwent lobectomy was also altered by clinical factors. Decisions had to be made 'on table' in the operating theatre based upon intraoperative findings or intraoperative diagnosis. Some lung lesions were not amenable to preoperative biopsy, or a biopsy may have been inconclusive, in such cases the use of an intraoperative tumour sample for frozen section tissue diagnosis was used to provide a diagnosis of NSCLC, which prompted anatomical resection, or another diagnosis, which required no further action. Conversely a patient may have been listed for lobectomy but intraoperatively there was concern about clearance of tumour and a more extensive operation was necessary. A small number of patients that had been listed for lobectomy in this study only underwent wedge resection because frozen section revealed they did not have NSCLC, others underwent a more extensive procedure to obtain clear margins around the tumour.

Other aspects that influenced feasibility were related to personal circumstances prior to surgery or after surgery; patients frequently had difficulties with travelling to multiple hospital appointments. Centralisation of services has been implemented so adequate caseloads could be maintained and service quality could be improved, however it has made access to treatment more difficult for patients and carers.[390,391] Difficulties with access were reported by patients and some participants were unwilling to complete follow up because of travel difficulties. Finally, some patients were lost to follow up

because they were too unwell to perform lung function testing after surgery or had experienced early recurrence of their NSCLC.

A driving force behind the desire of surgeons to assess patients more thoroughly and accurately before surgery is the aim of providing safe surgery for every patient possible, there is also pressure within the healthcare systems to increase the resection rate in NSCLC in an attempt to improve survival outcomes. Departments can face scrutiny if their resection rate of NSCLC is considered too low, but surgery may not always represent the best care plan for an individual. Healthy life expectancy at birth in the UK is just over 60 years and 44% of incident lung cancer cases are diagnosed in those aged over 75 years. There should be consideration of the fact that some patients may opt for a treatment that is not considered to be gold standard if it has fewer side effects and they are frail or have significant comorbidities. A spotlight audit in the UK revealed almost one third of patients with resectable NSCLC who did not receive surgery had declined surgery by patient choice, and the factor associated with receiving best supportive care rather than treatment with curative intent was an age over 75 years, even when comorbidities were accounted for.[86] The range of anti-cancer treatments available for early NSCLC was outlined in the introduction to this thesis and the National Lung Cancer Audit has added a new outcome to their standards, which is the proportion of patients who are of good performance status, have stage I or II NSCLC, and receive treatment with curative intent. This change represents progress in defining good care from 'surgery for all' towards 'the right treatment for the right patient'. However, clinicians and patients may not share the same view of what the right treatment is, and patient preconceptions may be too pessimistic about potential survival in early NSCLC. The

difficulties noted in the feasibility of the study highlight the fact that there are some unique challenges faced by this diverse patient group and a key consideration is the psychosocial impact of a diagnosis of lung cancer. Patients want more support and information in the postoperative period and they have identified priorities of well-being, both physical and mental, after surgery.[392,393] They experience a range of concerns, often about the impact of the disease upon their family, including the need for care form family members and the inability to perform the activities they did before surgery.[394] Not only do patients have to face a cancer diagnosis with its associated mortality risk but up to one in five patients experience anxiety and depression, they also experience significant stigma and self blame, all of which have the potential for adverse effects on quality of life, treatment outcomes, and behavior.[395,396] These psychosocial aspects of care may need research and interventions more urgently than further studies of operative risk assessment.

Quantitative analysis of CT scans may still have potential for use in the assessment of thoracic surgical patients, but scans must be streamlined into the existing tests that patients undergo and future research should incorporate patient priorities.

7.1.2 Reliability of CIP open access software

This work has shown CIP not to be an acceptably reliable tool for researchers to analyse the lungs if they do not have radiology training, it may yet be a useful tool for those seeking to generate hypotheses in further studies if they have experienced radiologists in the research team. A smaller number of scans were affected by wide variation in lobar density or volume which lead to unacceptably wide LOAs despite excellent agreement as measured by ICCs. These scans were mostly affected by difficulty marking incomplete

horizontal fissures, so analyses performed by radiologists are likely to show better agreement. The lung volumes and densities obtained were affected by the use of a smooth filter, thus publications using of analyses with CIP should describe which filters were used. This work has demonstrated that CIP and the analysis provided commercially by Thirona are not equivalent for calculating lung volumes or density.

7.1.3 Diagnosis of ILD subtype

Scientific understanding of the aetiology of many subtypes of ILD is incomplete and the diagnostic process remains challenging. Therefore biomarkers that can aid the in diagnosis are still needed and several imaging techniques continue to be investigated.[298] Assessment of deltaSVg in this study did not reveal a difference in heterogeneity of regional ventilation between patients with UIP and non-UIP ILD, but it did show more heterogeneous deltaSVg in ILD compared to published values for healthy lungs. Confident conclusions about deltaSVg in subtyping ILD could not be made because difficulties were encountered with the technique used to analyse deltaSVg in this study. Differences in the expansion properties of healthy lungs versus those affected by ILD were found by other authors after the commencement of the study described in this thesis and assessment of lung expansion, including deltaSVg, may yet be found to be clinically useful in subtyping ILD.[307]

Segmentation can be particularly challenging in cases of severe ILD because the cellular or fibrotic lung tissue approaches the same density as the normal soft tissues of the chest wall, thus segmentation based upon a density threshold is liable to underestimate the volume of lung tissue present and exclude it from further analysis. The similarity in density of lung tissue to the chest wall tissues is particularly prominent on expiratory

phase scans. Matching of expiratory and inspiratory CT slices is time consuming and adds a source of human error. It is also problematic because the lungs do not undergo linear movements during expansion, meaning it is not always possible to perfectly match portions of lung tissue on axial cross sections. The ability to analyse deltaSVg in 3D would be essential to continue further study of the expansion of lung parenchyma.

The study cohort was smaller than desirable and included patients with very advanced ILD. Whilst the current study has not shown a difference between UIP and non-UIP ILD, this could be due to the time course of the scanning in addition to the technological limitations. It could be that deltaSVg becomes increasingly similar between types of ILD as the disease progresses and differences that would have been apparent around the time of diagnosis are not identifiable after a period of time. Analysis to aid diagnosis in clinical practice would be performed earlier in the course of the disease, however it was not considered practical to recruit every patient undergoing respiratory assessment, very few of which would be confirmed to have ILD, in order to do this exploratory evaluation of deltaSVg in ILD.

Quantitative CT analysis of deltaSVg may still have a role in subtyping ILD, but if it is to be used then refinements in the analysis will be required. Analysis in 3D is particularly important as well as the study of a larger number of patients around the time of diagnosis. It should be possible to perform assessment of analysis with newly developed software more rapidly if scans from databases can be used, thus removing the constraint of recruiting further patient cohorts. CT is readily available, and provides higher resolution than modalities such as MRI or PET, and therefore it remains the foremost candidate to become the best imaging for quantitative as well as qualitative assessment

of lung structure, but the optimal quantitative assessment for subtyping or disease monitoring in ILD is yet to be determined.

7.1.4 Chest wall motion and pleural disease

A diagnostic and prognostic biomarker in mesothelioma is lacking and however the promising results of a small study of chest wall motion using OEP did not translate into a clinical use for SLP in this larger patient group. The test could not discriminate between mesothelioma and other pleural diseases with sufficient accuracy to be useful in practice, though the test was better than allocation of diagnosis by chance. This may be due to the small sample size of the initial study leading to a false positive result because the first set of results using SLP also showed a difference in chest wall movement between malignant and benign pleural disease, but that disappeared with a larger sample. Another important reason may be that SLP does not measure chest wall movements outside of the anteroposterior plane as much as it measures breathing patterns, thus the differences in chest wall motion detected using OEP may be present but undetected by SLP. The developers of the Thora3Di are aware of OEP but have not published a direct comparison of SLP and OEP; validation of the device has been against pneumotachography. SLP cannot capture lateral movements of the ribcage and the rigid grid of light that is projected does not provide regional data informed by anatomical landmarks and thus some movement within the abdomen may be included in ribcage movements and vice versa. Whilst SLP may be useful for assessing breathing patterns it may have too many technical limitations to detect subtle differences in regional respiratory movements.

A non-contact tool that does capture lateral chest movements was developed four years ago and validated against OEP.[354] This technology progressed to the finals of the European Health Catapult competition with startup company Evolyst, however the key concern by potential investors was that results of initial phases of testing had been published and there was a lack of a patent granted or pending.[397] This is an important illustration of the competing interests of rapid dissemination of results desired within academia, and the calculated financial risks taken by individuals who invest in early phase startup companies. Even if a new technology has great potential for patient benefit it will not be developed further than the proof of scientific concept phase without financial support and the sums involved can be prohibitively large before a company begins to make a profit. This problem is well recognised and many new technologies do not make it out of the so called 'valley of death'.[398] Further development of a device that is simpler to use than OEP but captures more detail about respiratory movement than SLP may yield clinically useful information about pleural diseases, both in terms of diagnosis and disease progression. Additional testing of SLP for assessment of pleural disease is not supported.

Assessment of survival of patients found to have mesothelioma during the study did allow for comparison between their survival and that predicted by the Brims Decision tree; the comparison found the predictions held true in this cohort and serves as an external validation of the decision tree.

7.1.5 Dynamic hyperinflation and lung volume reduction procedures

Three patterns of DH were observed in clinically similar patients with severe emphysema during exercise; this finding replicates previous reports of trunk volume

changes in response to exercise. The study could not be completed as intended but the data gathered from this small number of patients indicates a physiological parameter could potentially identify patients with the best chance of clinical benefit from LVR. DH is not currently measured as part of the range of assessments used in the care pathway prior to LVR and other tests used are not known to be surrogate markers of DH. There is a suggestion that early DH may be a prerequisite for response to LVR and further study of DH pattern is warranted. Further study is likely to involve EBVs and LVR surgery as opposed to EBCs. The loss to follow up due to the poor clinical condition of patients is important to report as it contributes to a picture where the benefits of EBCs that were found in RCTs do not seem to translate into real world clinical practice. A European registry study of EBCs examining quality of life outcomes, cost effectiveness, and safety has now been halted, in addition to the FDA not approving the coil device. [399] Assessment of the reported patterns of trunk volumes during exercise shows different patterns in patients who were treated with EBCs and those not receiving EBCs in a reported RCT, this unaccounted for confounding factor difference may explain why the RCT reported a benefit but this has not translated into usual practice as expected. [386] It is possible that the clinical difficulties encountered in the OEP study are representative of a procedure that is not as beneficial as the developers of the device had thought. If further assessment demonstrated that all LVR responders exhibit early DH then preoperative assessment could be streamlined and patients that would not benefit could avoid the risks of surgical intervention.

The tools to assess chest wall motion are currently limited too severely by their properties for routine clinical use – OEP is too time consuming to perform, SLP does not

provide measurements during exercise and does not provide a 360 degree view of the trunk. A better tool to assess chest wall motion could reveal clinical uses for this aspect of respiratory physiology, which is yet to find be fully explored. An important aspect that would need to be established for researchers to provide interpretation of results to clinicians is thorough assessment of normal values. Comparisons of a small number of patients with a specific disease to an equally sized cohort of healthy individuals is not sufficient as the respiratory system is known to have variations in function with different demographic factors such as age, gender, ethnicity, height, and weight. The creation of population level data as part of the Global Lung Initiative provides an example of the kind of data needed for clinicians to interpret what is truly normal.[59]

Measuring chest wall motion once the normal variation has been established may yet be useful in the management of patients with pleural disease or emphysema. Further assessment of measuring DH patterns prior to LVR is warranted, the pattern of DH may also have relevance to non-invasive strategies used to manage emphysema. Measuring changes in inspiratory capacity would be more practical in the short term, though using chest wall motion has the advantage of not altering the upper airway, as it does not require a mouthpiece or nose clip. Measuring chest wall motion in patients with pleural disease does not appear to be useful for diagnostic purposes; there is however unexplored potential for monitoring of patients with mesothelioma for progression or response to anti-cancer therapies.

7.2 Collaborations in research

Collaboration between institutions provides fertile ground for developing new technology and reaching research goals faster or more effectively. Managing expectations and ensuring all collaborators can both contribute to the work and appreciate the potential and limitations contributions of others can be challenging. Geography, language, culture, and priorities will vary between teams and indeed this is a strength that can bring different perspectives to a problem. The CT analysis work included collaboration between the disciplines of bioengineering, surgery, and radiology across three institutions and two countries. The working relationships were good, however the clinical requirements and the bounds of the custom software were mismatched due to the clinical need for 3D lobar analysis of deltaSVg and the current technological ability to quantify it in 2D axial CT sections. Without a large amount of additional funding the further development of the software could not be made a priority for the collaborators with the correct expertise to do so. The essential clinical requirements were not intuitive to the engineers, and the engineering complexities of the clinical requirements were not intuitive to the clinicians. Whilst the potential benefits of collaboration are worth pursuing, the additional complexity needs to be heeded.

7.3 Software developments in surgery

The systematic review identified multiple studies that utilised custom software to analyse CT scans and custom software was used for analysis of ILD scans in this work; these kinds of software face significant practical hurdles before they can used clinically.

One issue is how the software can access the scans and produce results in a suitable format for clinicians. Using custom software frequently involves downloading and transferring scan data from the patient imaging system for processing in a separate program, results are then often written into spreadsheets, image files, or text files. An institution might need to have access to multiple programs, with their associated costs, if it were to allow clinicians to use custom software. These difficulties are in addition to any regulatory assessments that would need to be completed prior to the results of analysis being approved for clinical use. It is therefore unsurprising that studies using custom software often do not lead to their analysis being widely used. One commercial solution to the practicalities of trying new software has been proposed whereby a user friendly interface between conventional patient imaging software and the analyses provided by software developers is provided.[400] Clinicians can then trial novel software without the need to download DICOM files and learn to use the programming language that custom software is often written in; if results are found to be clinically helpful the software can be developed further to meet regulations and then enter clinical use.

7.4 Conclusion

Thoracic surgeons are faced with different challenges from patients with different conditions; non-invasive technologies to assess regional respiratory function were applied to these difficult scenarios. CT analysis using the method described was shown not to be clinically feasible and there was no trend for improvement over existing techniques for predicting postoperative FEV1 or TLCO after surgery for early NSCLC. The lobar segmentation and parenchyma analysis modules of CIP were found not to give reproducible results when used by non-radiologists, but this software may yet be used

by researchers with radiology experience to generate hypotheses without any costs associated with CT analysis. CT analysis did not aid in subtyping ILD but deltaSVg was found to be more heterogeneous than reported values in health lungs; the custom software limitations were a significant problem during scan processing. SLP did not aid in diagnosis of pleural disease but potential limitations of the way the device measures volume changes were noted. The prognostic information provided by the Brims decision tree was externally validated with the SLP data. OEP confirmed the presence of different patterns of DH in severe emphysema and identified that early DH may possibly be a prerequisite for response to LVR; this warrants further investigation.

LIST OF REFERENCES

1. West D, Walton P, Kinsman R. Third National Thoracic Surgery Activity & Outcomes Report [Internet]. The Society for Cardiothoracic Surgery in Great Britain & Ireland and Dendrite Clinical Systems Limited; 2018. Available from: https://scts.org/wp-content/uploads/2019/06/Third-thoracic-blue-book-FINAL.pdf

2. Cancer Research UK. Lung Cancer Statistics [Internet]. [cited 2020 May 20]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer

3. Trueman D, Woodcock F, Hancock E. Estimating the economic burden of respiratory illness in the UK. British Lung Foundation; 2017.

4. Lim E, Baldwin D, Beckles M, Duffy J, Entwisle J, Faivre-Finn C, et al. Guidelines on the Radical Management of Patients with Lung Cancer. Thorax. 2010;65:Supplement III.

5. Riquet M, Hidden G, Debesse B. Direct lymphatic drainage of lung segments to the mediastinal nodes. An anatomic study on 260 adults. J Thorac Cardiovasc Surg. 1989 Apr;97(4):623–32.

6. Poghosyan H, Sheldon LK, Leveille SG, Cooley ME. Health-related quality of life after surgical treatment in patients with non-small cell lung cancer: A systematic review. Lung Cancer. 2013 Jul 1;81(1):11–26.

7. Franks K, Mcparland L, Webster J, Baldwin D, Sebag-Montefiore D, Evison M, et al. P2.16-16 SABRTOOTH: A Fasibility Study of SABR Versus Surgery in Patients with Peripheral Stage I NSCLC Considered to be at Higher Risk for Surgery. J Thorac Oncol. 2018 Oct 1;13(10):S837.

8. Chen H, Laba JM, Boldt RG, Goodman CD, Palma DA, Senan S, et al. Stereotactic Ablative Radiation Therapy Versus Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score Studies. Int J Radiat Oncol Biol Phys. 2018 01;101(1):186–94.

9. Li M, Yang X, Chen Y, Yang X, Dai X, Sun F, et al. Stereotactic body radiotherapy or stereotactic ablative radiotherapy versus surgery for patients with T1-3N0M0 non-small cell lung cancer: a systematic review and meta-analysis. OncoTargets Ther. 2017 Jun 7;10:2885–92.

10. D'Andrilli A, Rendina EA. POINT: Should Segmentectomy Rather Than Lobectomy Be the Operation of Choice for Early-Stage Non-small Cell Lung Cancer? Yes. CHEST. 2018 Mar 1;153(3):590–2.

11. Bertolaccini L, Solli P. COUNTERPOINT: Should Segmentectomy Rather Than Lobectomy Be the Operation of Choice for Early-Stage Non-small Cell Lung Cancer? No. CHEST. 2018 Mar 1;153(3):592–5.

12. Sienel W, Dango S, Kirschbaum A, Cucuruz B, Hörth W, Stremmel C, et al. Sublobar Resections in Stage IA Non-Small Cell Lung Cancer: Segmentectomies Result in Significantly Better Cancer-Related Survival Than Wedge Resections. Eur J Cardiothorac Surg [Internet]. 2008 Apr [cited 2020 May 24];33(4). Available from: https://pubmed.ncbi.nlm.nih.gov/18261918/

13. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg. 1995 Sep;60(3):615–22; discussion 622-623.

14. Altorki N. Comparison of Different Types of Surgery in Treating Patients With Stage IA Non-Small Cell Lung Cancer [Internet]. ClinicalTrials.gov. 2007 [cited 2020 May 24]. Available from: https://clinicaltrials.gov/ct2/show/NCT00499330

15. Nakamura K, Saji H, Nakajima R, Okada M, Asamura H, Shibata T, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol. 2010 Mar;40(3):271–4.

16. Zhang Y, Yuan C, Zhang Y, Sun Y, Chen H. Survival following segmentectomy or lobectomy in elderly patients with early-stage lung cancer. Oncotarget. 2016 Apr 5;7(14):19081–6.

17. Lim E, Baldwin D, Duffy J, Entwisle J, Faivre-Finn C, Kerr K, et al. Guidelines on the Radical Management of Patients with Lung Cancer. Thorax. 2010 Oct;65:Supplement III.

18. Young RP, Hopkins RJ, Christmas T, Black PN, Metcalf P, Gamble GD. COPD prevalence is increased in lung cancer, independent of age, sex and smoking history. Eur Respir J. 2009 Aug 1;34(2):380–6.

19. Global Surveillance, Prevention and Control of Chronic Respiratory Diseases: A Comprehensive Approach. World Health Organization; 2007. 156 p.

20. Soriano JB, Zielinski J, Price D. Screening for and early detection of chronic obstructive pulmonary disease. The Lancet. 2009 Aug 29;374(9691):721–32.

21. Mathers CD, Loncar D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. PLOS Med. 2006 Nov 28;3(11):e442.

22. Martinez CH, Diaz AA, Parulekar AD, Rennard SI, Kanner RE, Hansel NN, et al. Age-Related Differences in Health-Related Quality of Life in COPD: An Analysis of the COPDGene and SPIROMICS Cohorts. Chest. 2016 Apr 1;149(4):927–35.

23. Celli BR, MacNee W, Agusti A, Anzueto A, Berg B, Buist AS, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004 Jun 1;23(6):932–46.

24. Hogg JC, Senior RM. Chronic obstructive pulmonary disease c 2: Pathology and biochemistry of emphysema. Thorax. 2002 Sep 1;57(9):830–4.

25. McDonough JE, Yuan R, Suzuki M, Seyednejad N, Elliott WM, Sanchez PG, et al. Small-Airway Obstruction and Emphysema in Chronic Obstructive Pulmonary Disease. N Engl J Med. 2011 Oct 27;365(17):1567–75.

26. Tschernko EM, Wisser W, Wanke T, Rajek MA, Kritzinger M, Lahrmann H, et al. Changes in ventilatory mechanics and diaphragmatic function after lung volume reduction surgery in patients with COPD. Thorax. 1997 Jun;52(6):545–50.

27. Bon J, Liao S, Tseng G, Sciurba FC. Considerations and pitfalls in phenotyping and reclassification of chronic obstructive pulmonary disease. Transl Res J Lab Clin Med. 2013 Oct;162(4):252–7.

28. O'Donnell DE, Webb KA, Bertley JC, Chau LK, Conlan AA. Mechanisms of relief of exertional breathlessness following unilateral bullectomy and lung volume reduction surgery in emphysema. Chest. 1996 Jul;110(1):18–27.

29. Bellemare F, Cordeau M-P, Couture J, Lafontaine E, Leblanc P, Passerini L. Effects of emphysema and lung volume reduction surgery on transdiaphragmatic pressure and diaphragm length. Chest. 2002 Jun;121(6):1898–910.

30. Criner G, Cordova FC, Leyenson V, Roy B, Travaline J, Sudarshan S, et al. Effect of Lung Volume Reduction Surgery on Diaphragm Strength. Am J Respir Crit Care Med. 1998 May 1;157(5):1578–85.

31. NICE COPD guideline [Internet]. Guidelines. 2019 [cited 2020 May 25]. Available from: https://www.guidelines.co.uk/respiratory/nice-copd-guideline/454912.article

32. Glaspole IN, Gabbay E, Smith JA, Rabinov M, Snell GI. Predictors of perioperative morbidity and mortality in lung volume reduction surgery. Ann Thorac Surg. 2000 Jun;69(6):1711–6.

33. National Emphysema Treatment Trial Research Group. A Randomized Trial Comparing Lung-Volume–Reduction Surgery with Medical Therapy for Severe Emphysema. N Engl J Med. 2003 May 22;348(21):2059–73.

34. Goldstein R, Todd T, Guyatt G, Keshavjee S, Dolmage T, van Rooy S, et al. Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. Thorax. 2003 May;58(5):405–10.

35. Fowler PBS, Sloper JC, Warner EC. Exposure to Asbestos and Mesothelioma of the Pleura. Br Med J. 1964 Jul 25;2(5403):211–3.

36. Chapman A, Mulrennan S, Ladd B, Muers MF. Population based epidemiology and prognosis of mesothelioma in Leeds, UK. Thorax. 2008 May;63(5):435–9.

37. Zamboni MM, da Silva CT, Baretta R, Cunha ET, Cardoso GP. Important prognostic factors for survival in patients with malignant pleural effusion. BMC Pulm Med. 2015 Mar 28;15.

38. Office for National Statistics. Hospital Episode Statistics [Internet]. Admitted Patient Care - England 2014-2015. 2015 [cited 2017 May 15]. Available from: http://content.digital.nhs.uk/searchcatalogue?productid=19420&q=title%3a%22Hospital+Episode+Statistics%2c+Admitted+patient+care+-+England%22&sort=Relevance&size=10&page=1#top

39. Hooper C, Lee YCG, Maskell N. Investigation of a unilateral pleural effusion in adults: British Thoracic Society pleural disease guideline 2010. Thorax. 2010 Aug 1;65(Suppl 2):ii4–17.

40. Bielsa S, Panadés MJ, Egido R, Rue M, Salud A, Matías-Guiu X, et al. [Accuracy of pleural fluid cytology in malignant effusions]. An Med Interna Madr Spain 1984. 2008 Apr;25(4):173–7.

41. Motherby H, Nadjari B, Friegel P, Kohaus J, Ramp U, Böcking A. Diagnostic accuracy of effusion cytology. Diagn Cytopathol. 1999 Jun;20(6):350–7.

42. Khan SL, Haris M, Munavvar M. Diagnostic accuracy of pleural fluid cytology compared to pleural biopsy histology obtained via thoracoscopy. Eur Respir J. 2014 Sep 1;44(Suppl 58):P2775.

43. Fassina A, Fedeli U, Corradin M, Da Frè M, Fabbris L. Accuracy and reproducibility of pleural effusion cytology. Leg Med. 2008 Jan;10(1):20–5.

44. Dipper A, Jones HE, Bhatnagar R, Preston NJ, Maskell N, Clive AO. Interventions for the management of malignant pleural effusions: a network meta-analysis. Cochrane Database Syst Rev. 2020 21;4:CD010529.

45. Gokce M, Okur E, Baysungur V, Ergene G, Sevilgen G, Halezeroglu S. Lung decortication for chronic empyaema: effects on pulmonary function and thoracic asymmetry in the late period. Eur J Cardiothorac Surg. 2009 Oct 1;36(4):754–8.

46. Macroscopic Features of Mesotheliomas. In: Pathology of Malignant Mesothelioma [Internet]. Springer, London; 2006 [cited 2018 Aug 8]. p. 57–67. Available from: https://doi.org/10.1007/978-1-84628-012-2_7

47. Leslie KO. Pathology of interstitial lung disease. Clin Chest Med. 2004 Dec;25(4):657–703, vi.

48. European Respiratory Society. Chapter 22: Interstitial lung diseases. In: The European Lung White Book [Internet]. [cited 2019 Jul 1]. p. 256–69. Available from: https://www.erswhitebook.org/chapters/interstitial-lung-diseases/

49. Belkin A, Albright K, Swigris JJ. A qualitative study of informal caregivers' perspectives on the effects of idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2014 Jan 1;1(1):e000007.

50. Green FHY. Overview of Pulmonary Fibrosis. CHEST. 2002 Dec 1;122(6):334S-339S.

51. Leslie KO. My approach to interstitial lung disease using clinical, radiological and histopathological patterns. J Clin Pathol. 2009 May 1;62(5):387–401.

52. Meyer KC. Diagnosis and management of interstitial lung disease. Transl Respir Med. 2014 Feb 13;2.

53. Haynes JM. Basic spirometry testing and interpretation for the primary care provider. Can J Respir Ther CJRT Rev Can Thérapie Respir RCTR. 2018;54(4).

54. Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med. 2003 Sep 1;168(5):538–42.

55. Travis WD, Costabel U, Hansell DM, King TE, Lynch DA, Nicholson AG, et al. An Official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med. 2013 Sep 15;188(6):733–48.

56. Wells AU, Hirani N. Interstitial lung disease guideline: the British Thoracic Society in collaboration with the Thoracic Society of Australia and New Zealand and the Irish Thoracic Society. Thorax. 2008 Sep 1;63(Suppl 5):v1–58.

57. Hutchinson JP, McKeever TM, Fogarty AW, Navaratnam V, Hubbard RB. Surgical lung biopsy for the diagnosis of interstitial lung disease in England: 1997–2008. Eur Respir J. 2016 Nov 1;48(5):1453–61.

58. Collard HR, Ryerson CJ, Corte TJ, Jenkins G, Kondoh Y, Lederer DJ, et al. Acute Exacerbation of Idiopathic Pulmonary Fibrosis. An International Working Group Report. Am J Respir Crit Care Med. 2016 01;194(3):265–75.

59. Cooper BG, Stocks J, Hall GL, Culver B, Steenbruggen I, Carter KW, et al. The Global Lung Function Initiative (GLI) Network: bringing the world's respiratory reference values together. Breathe. 2017 Sep 1;13(3):e56–64.

60. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005 Aug 1;26(2):319–38.

61. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardisation of the measurement of lung volumes. Eur Respir J. 2005 Sep 1;26(3):511–22.

62. Stanojevic S, Graham BL, Cooper BG, Thompson BR, Carter KW, Francis RW, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. Eur Respir J. 2017;50(3).

63. Graham BL, Brusasco V, Burgos F, Cooper BG, Jensen R, Kendrick A, et al. 2017 ERS/ATS standards for single-breath carbon monoxide uptake in the lung. Eur Respir J. 2017;49(1).

64. Flohr TG, Stierstorfer K, Ulzheimer S, Bruder H, Primak AN, McCollough CH. Image reconstruction and image quality evaluation for a 64-slice CT scanner with z-flying focal spot. Med Phys. 2005 Aug;32(8):2536–47.

65. Bergin C, Roggli V, Coblentz C, Chiles C. The secondary pulmonary lobule: normal and abnormal CT appearances. Am J Roentgenol. 1988 Jul 1;151(1):21–5.

66. Gattinoni L, Pesenti A, Bombino M, Baglioni S, Rivolta M, Rossi F, et al. Relationships between lung computed tomographic density, gas exchange, and PEEP in acute respiratory failure. Anesthesiology. 1988 Dec;69(6):824–32.

67. Hogg JC, Nepszy S. Regional lung volume and pleural pressure gradient estimated from lung density in dogs. J Appl Physiol. 1969 Aug;27(2):198–203.

68. Aliverti A, Pennati F, Salito C, Woods JC. Regional lung function and heterogeneity of specific gas volume in healthy and emphysematous subjects. Eur Respir J. 2013 May;41(5):1179–88.

69. Coxson HO, Mayo JR, Behzad H, Moore BJ, Verburgt LM, Staples CA, et al. Measurement of lung expansion with computed tomography and comparison with quantitative histology. J Appl Physiol Bethesda Md 1985. 1995 Nov;79(5):1525–30.

70. Coxson HO, Hogg JC, Mayo JR, Behzad H, Whittall KP, Schwartz DA, et al. Quantification of idiopathic pulmonary fibrosis using computed tomography and histology. Am J Respir Crit Care Med. 1997 May 1;155(5):1649–56.

71. Coxson HO, Rogers RM, Whittall KP, D'yachkova Y, Paré PD, Sciurba FC, et al. A Quantification of the Lung Surface Area in Emphysema Using Computed Tomography. Am J Respir Crit Care Med. 1999 Mar 1;159(3):851–6.

72. Konno K, Mead J. Measurement of the separate volume changes of rib cage and abdomen during breathing. J Appl Physiol. 1967 Mar;22(3):407–22.

73. Clarenbach CF, Senn O, Brack T, Kohler M, Bloch KE. Monitoring of ventilation during exercise by a portable respiratory inductive plethysmograph. Chest. 2005 Sep;128(3):1282–90.

74. Pennock BE. Rib cage and abdominal piezoelectric film belts to measure ventilatory airflow. J Clin Monit. 1990 Oct 1;6(4):276–83.

75. Vaughn CM, Clemmons P. Piezoelectric belts as a method for measuring chest and abdominal movement for obstructive sleep apnea diagnosis. Neurodiagnostic J. 2012 Sep;52(3):275–80.

76. Kenyon CM, Cala SJ, Yan S, Aliverti A, Scano G, Duranti R, et al. Rib cage mechanics during quiet breathing and exercise in humans. J Appl Physiol Bethesda Md 1985. 1997 Oct;83(4):1242–55.

77. Aliverti A, Cala SJ, Duranti R, Ferrigno G, Kenyon CM, Pedotti A, et al. Human respiratory muscle actions and control during exercise. J Appl Physiol. 1997 Oct 1;83(4):1256–69.

78. Massaroni C, Schena E, Saccomandi P, Morrone M, Sterzi S, Silvestri S. Evaluation of optoelectronic Plethysmography accuracy and precision in recording displacements during quiet breathing simulation. In: 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC). 2015. p. 1291–4.

79. De Boer W, Lasenby J, Cameron J, Wareham R, Ahmad S, Roach C, et al. SLP:A zero-contact non-invasive method for pulmonary function testing [Internet]. British Machine Vision Conference; 2010. Available from: https://pdfs.semanticscholar.org/8e64/bb0fc07ed1f052748fd36b248761f0dab76a.pdf

80. Iles R, Khalid A, Kimber K, Wilson R, De Boer W. Non Invasive Measurement Of Respiratory Rate: Comparison Between The Embletta? (GOLD) Respiband Device And Thora3Di, PneumaCare Ltd. In: B41 QUANTUM OF SPIROMETRY: ADVANCES IN PULMONARY FUNCTION TESTING [Internet]. 2014. p. A2935–A2935. (American Thoracic Society International Conference Abstracts). Available from: DOI: 10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A2935

81. Motamedi-Fakhr S, Iles R, Barney A, de Boer W, Conlon J, Khalid A, et al. Evaluation of the agreement of tidal breathing parameters measured simultaneously using pneumotachography and structured light plethysmography. Physiol Rep [Internet]. 2017 Feb 13 [cited 2020 Sep 3];5(3). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5309576/

82. Organ CH. The Impact of Technology on Surgery. Arch Surg. 1999 Nov 1;134(11):1175–7.

83. Jungebluth P, Macchiarini P. Airway transplantation. Thorac Surg Clin. 2014 Feb;24(1):97–106.

84. Slebos D-J, Ten Hacken NH, Hetzel M, Herth FJF, Shah PL. Endobronchial Coils for Endoscopic Lung Volume Reduction: Best Practice Recommendations from an Expert Panel. Respir Int Rev Thorac Dis. 2018;96(1):1–11.

85. Elshafie G, Kumar P, Djearaman M, Aliverti A, Naidu B. The Effect of Benign and Malignant Pleural Disease on Chest Wall Mechanics. Am J Respir Crit Care Med. 2017 Jul 14;196(2):241–2.

86. Royal College of Physicians. National Lung Cancer Audit annual report 2017 (for the period 2016) [Internet]. London: Royal College of Physicians; 2018 [cited 2019 May 5]. Available from: https://www.rcplondon.ac.uk/file/8986/download

87. Riaz SP, Lüchtenborg M, Jack RH, Coupland VH, Linklater KM, Peake MD, et al. Variation in surgical resection for lung cancer in relation to survival: population-based study in England 2004-2006. Eur J Cancer Oxf Engl 1990. 2012 Jan;48(1):54–60.

88. Brunelli A, Charloux A, Bolliger CT, Rocco G, Sculier J-P, Varela G, et al. ERS/ESTS clinical guidelines on fitness for radical therapy in lung cancer patients (surgery and chemo-radiotherapy). Eur Respir J. 2009 Jul 1;34(1):17–41.

89. Brunelli A, Kim WK, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery. Chest. 2013 May;143(5):e166S-e190S.

90. Subotic D, Mandaric D, Radosavljevic G, Stojsic J, Gajic M. Lung function changes and complications after lobectomy for lung cancer in septuagenarians. Ann Thorac Med. 2009;4(2):54–9.

91. Wang J, Olak J, Ferguson MK. Diffusing capacity predicts operative mortality but not long-term survival after resection for lung cancer. J Thorac Cardiovasc Surg. 1999 Mar;117(3):581–6; discussion 586-587.

92. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

93. Wolff R, Moons K, Riley R, Whiting P, Westwood M, Collins G, et al. PROBAST – A risk-of-bias tool for prediction-modelling studies | Colloquium Abstracts [Internet]. 2017 [cited 2018 May 29]. Available from: /2017-global-evidence-summit/probast-%E2%80%93-risk-bias-tool-prediction-modelling-studies

94. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019 Jan 1;170(1):W1–33.

95. Nagamatsu Y, Maeshiro K, Kimura NY, Nishi T, Shima I, Yamana H, et al. Long-term recovery of exercise capacity and pulmonary function after lobectomy. J Thorac Cardiovasc Surg. 2007 Nov;134(5):1273–8.

96. Brunelli A, Xiumé F, Refai M, Salati M, Marasco R, Sciarra V, et al. Evaluation of expiratory volume, diffusion capacity, and exercise tolerance following major lung resection: a prospective follow-up analysis. Chest. 2007 Jan;131(1):141–7.

97. Brunelli A, Sabbatini A, Xiume' F, Al Refai M, Borri A, Salati M, et al. A model to predict the decline of the forced expiratory volume in one second and the carbon monoxide lung diffusion capacity early after major lung resection. Interact Cardiovasc Thorac Surg. 2005 Feb 1;4(1):61–5.

98. The Cochrane Collaboration. Review Manager (Revman) Version 5.3 [Internet]. Copenhagen: The Nordic Cochrane Centre; 2014. Available from: https://training.cochrane.org/online-learning/core-software-cochrane-reviews/revman/revman-5-download

99. Senior AM, Gosby AK, Lu J, Simpson SJ, Raubenheimer D. Meta-analysis of variance: an illustration comparing the effects of two dietary interventions on variability in weight. Evol Med Public Health. 2016;1:244–55.

100. RStudio: Integrated development environment for R [Internet]. Boston, MA; Available from: www.rstudio.org

101. Rohatgi A. WebPlotDigitizer [Internet]. Austin, Texas, USA; 2018. Available from: https://automeris.io/WebPlotDigitizer

102. Juhl B, Frost N. A comparison between measured and calculated changes in the lung function after operation for pulmonary cancer. Acta Anaesthesiol Scand Suppl. 1975;57:39–45.

103. Nakahara K, Monden Y, Ohno K, Miyoshi S, Maeda H, Kawashima Y. A method for predicting postoperative lung function and its relation to postoperative complications in patients with lung cancer. Ann Thorac Surg. 1985 Mar;39(3):260–5.

104. Maestre UJ, N M Malanda, L H Perez, N U E Lugariza-Ares, M L Martin, J C R Sanchez, et al. Evaluation of VRI (vibration response imaging) utility in the prediction of postoperative function after lung resection surgery. Interact Cardiovasc Thorac Surg. 2009 Jul;(SUPPL. 1):S11.

105. Yabuuchi H, Kawanami S, Kamitani T, Yonezawa M, Yamasaki Y, Yamanouchi T, et al. Prediction of post-operative pulmonary function after lobectomy for primary lung cancer: A comparison among counting method, effective lobar volume, and lobar collapsibility using inspiratory/expiratory CT. Eur J Radiol. 2016 Nov;85(11):1956–62.

106. Ohno Y, Seki S, Koyama H, Yoshikawa T, Matsumoto S, Takenaka D, et al. 3D ECG- and respiratory-gated non-contrast-enhanced (CE) perfusion MRI for postoperative lung function prediction in non-small-cell lung cancer patients: A comparison with thin-section quantitative computed tomography, dynamic CE-perfusion MRI, and perfusion scan. J Magn Reson Imaging JMRI. 2015 Aug;42(2):340–53.

107. Yoshimoto K, Nomori H, Mori T, Kobayashi H, Ohba Y, Shibata H, et al. Prediction of pulmonary function after lung lobectomy by subsegments counting, computed

tomography, single photon emission computed tomography and computed tomography: a comparative study. Eur J Cardiothorac Surg. 2009 Mar;35(3):408–13.

108. Wu M-T, Pan H-B, Chiang AA, Hsu H-K, Chang H-C, Peng N-J, et al. Prediction of postoperative lung function in patients with lung cancer: comparison of quantitative CT with perfusion scintigraphy. AJR Am J Roentgenol. 2002 Mar;178(3):667–72.

109. Wu MT, Chang JM, Chiang AA, Lu JY, Hsu HK, Hsu WH, et al. Use of quantitative CT to predict postoperative lung function in patients with lung cancer. Radiology. 1994 Apr;191(1):257–62.

110. Fourdrain A, De Dominicis F, Lafitte S, Iquille J, Prevot F, Lorne E, et al. Quantitative computed tomography to predict postoperative FEV1 after lung cancer surgery. J Thorac Dis. 2017 Aug;9(8):2413–8.

111. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. J Clin Epidemiol. 2005 Sep 1;58(9):894–901.

112. Comce F, Bingol Z, Kiyan E, Tanju S, Toker A, Cagatay P, et al. Vibration-response imaging versus quantitative perfusion scintigraphy in the selection of patients for lung-resection surgery. Respir Care. 2011 Dec;56(12):1936–41.

113. Şimşek Veske N, Sökücü SN, Günlüoğlu G, Seyhan EC, Dalar L, Altın S. Place of vibration response imaging in preoperative lung cancer patients. Tuberk Ve Toraks. 2014;62(4):279–85.

114. Sekine Y, Iwata T, Chiyo M, Yasufuku K, Motohashi S, Yoshida S, et al. Minimal alteration of pulmonary function after lobectomy in lung cancer patients with chronic obstructive pulmonary disease. Ann Thorac Surg. 2003 Aug;76(2):356–61; discussion 362.

115. Zeiher BG, Gross TJ, Kern JA, Lanza LA, Peterson MW. Predicting postoperative pulmonary function in patients undergoing lung resection. Chest. 1995 Jul;108(1):68–72.

116. Bria WF, Kanarek DJ, Kazemi H. Prediction of postoperative pulmonary function following thoracic operations. Value of ventilation-perfusion scanning. J Thorac Cardiovasc Surg. 1983 Aug;86(2):186–92.

117. Kikuchi K, Ishii Y, Kitamura S. Prediction of Postoperative Lung Function in Patients with Lung Cancer and Chronic Obstructive Pulmonary Disease. Jpn J Thorac Dis. 1996 Oct 25;34(10):1071–6.

118. Ueda K, Murakami J, Sano F, Hayashi M, Kobayashi T, Kunihiro Y, et al. Assessment of volume reduction effect after lung lobectomy for cancer. J Surg Res. 2015 Jul;197(1):176–82.

119. Khargi K, Duurkens VA, Verzijlbergen FF, Huysmans HA, Knaepen PJ. Pulmonary function after sleeve lobectomy. Ann Thorac Surg. 1994 May;57(5):1302–4.

120. Sangalli M, Spiliopoulos A, Mégevand R. Predictability of FEV1 after pulmonary resection for bronchogenic carcinoma. Eur J Cardiothorac Surg. 1992;6(5):242–5.

121. Yasukawa M, K Nakagawa, M Sakaguchi, T Iwasaki, Sasaki N. Prediction of postoperative pulmonary function after pneumonectomy for lung cancer. [Japanese]. J Lung Cancer. 2004 Oct;(6):683–7.

122. Mizobuchi T, Wada H, Sakairi Y, Suzuki H, Nakajima T, Tagawa T, et al. Spirometric and radiological evaluation of the remnant lung long after major pulmonary resection: can compensatory phenomena be recognized in clinical cases? Surg Today. 2014 Sep;44(9):1735–43.

123. Murakami J, Ueda K, Sano F, Hayashi M, Tanaka N, Hamano K. Prediction of postoperative dyspnea and chronic respiratory failure. J Surg Res. 2015 May 1;195(1):303–10.

124. Smulders SA, Smeenk FWJM, Janssen-Heijnen MLG, Postmus PE. Actual and predicted postoperative changes in lung function after pneumonectomy: a retrospective analysis. Chest. 2004 May;125(5):1735–41.

125. Imaeda T, Kanematsu M, Asada S, Seki M, Matsui E, Doi H, et al. Prediction of pulmonary function after resection of primary lung cancer. Utility of inhalation-perfusion SPECT imaging. Clin Nucl Med. 1995 Sep;20(9):792–9.

126. Detterbeck F, Gat M, Miller D, Force S, Chin C, Fernando H, et al. A new method to predict postoperative lung function: quantitative breath sound measurements. Ann Thorac Surg. 2013 Mar;95(3):968–75.

127. Lipscomb DJ, Pride NB. Ventilation and perfusion scans in the preoperative assessment of bronchial carcinoma. Thorax. 1977 Dec;32(6):720–5.

128. Suh M, Kang Y-K, Ha S, Kim Y-I, Paeng JC, Cheon GJ, et al. Comparison of Two Different Segmentation Methods on Planar Lung Perfusion Scan with Reference to Quantitative Value on SPECT/CT. Nucl Med Mol Imaging. 2017 Jun;51(2):161–8.

129. Chae EJ, Kim N, Seo JB, Park J-Y, Song J-W, Lee HJ, et al. Prediction of postoperative lung function in patients undergoing lung resection: dual-energy perfusion computed tomography versus perfusion scintigraphy. Invest Radiol. 2013 Aug;48(8):622–7.

130. Larsen KR, Lund JO, Svendsen UG, Milman N, Petersen BN. Prediction of post-operative cardiopulmonary function using perfusion scintigraphy in patients with bronchogenic carcinoma. Clin Physiol Oxf Engl. 1997 May;17(3):257–67.

131. Hara K, Izumi N, Tsukioka T, Chung K, Komatsu H, Toda M, et al. P3.16-032 Prediction of Postoperative Lung Function in Patients with Lung Cancer by Lung Lobe. J Thorac Oncol. 2017 Nov 1;12(11):S2355.

132. Usuda K, Maeda S, Motomo N, Tanaka M, Ueno M, Machida Y, et al. Pulmonary Function After Lobectomy: Video-Assisted Thoracoscopic Surgery Versus Muscle-Sparing Mini-thoracotomy. Indian J Surg. 2017 Dec;79(6):504–9.

133. Yoo ID, Im JJ, Chung Y-A, Choi EK, Oh JK, Lee S-H. Prediction of postoperative lung function in lung cancer patients using perfusion scintigraphy: Acta Radiol [Internet]. 2018 Jul 30 [cited 2020 Sep 3]; Available from: https://journals.sagepub.com/doi/10.1177/0284185118787355

134. Nomori H, Cong Y, Sugimura H. Systemic and regional pulmonary function after segmentectomy. J Thorac Cardiovasc Surg. 2016 Sep;152(3):747–53.

135. Kovacević-Kuśmierek K, Kozak J, Pryt Ł, Bieńkiewicz M, Cichocki P, Kuśmierek J, et al. Perfusion lung scintigraphy for the prediction of postoperative residual pulmonary function in patients with lung cancer. Nucl Med Rev. 2015;18(2):70–7.

136. Hashimoto M, J Hanaoka, K Teramoto, T Igarashi. Prediction of postoperative pulmonary function using CT volumetry. J Thorac Oncol. 2015 Sep;(9 SUPPL. 2):S558.

137. Choi H, D Teeters, D Raymond, X Wang, P Mazzone. The accuracy of quantitative CT scan based prediction of post-lung resection FEV1. Chest. 2015 Oct;(4 Meeting Abstract).

138. Edvardsen E, S A Anderssen, F Borchsenius, OH Skjonsberg. Predicted versus observed pulmonary function and peak oxygen uptake after lung cancer surgery. Eur Respir J. 2015 Sep;(Suppl. 59).

139. Rangarajan V, Purandare N, Agrawal A, Shah S, Nag S, Ranganathan P, et al. Comparison of predicted FEV1 and observed FEV1 post lung surgery Using lung Perfusion scintigraphy. J Nucl Med Mol Imaging. 2015 Oct;(1 Suppl. 1):S63–4.

140. Saito H, Nakagawa T, Ito M, Imai K, Ono T, Minamiya Y. Pulmonary function after lobectomy versus segmentectomy in patients with stage I non-small cell lung cancer. World J Surg. 2014 Aug;38(8):2025–31.

141. Seok Y, Jheon S, Cho S. Serial changes in pulmonary function after video-assisted thoracic surgery lobectomy in lung cancer patients. Thorac Cardiovasc Surg. 2014 Mar;62(2):133–9.

142. Takahashi N. Assessment of predicted post-lobectomy lung function by means of a new method of anatomical residual lung volume ratio. [Japanese]. Respir Circ. 2014 Dec;(12):1213–9.

143. Vos W, Janssens A, Van Holsbeke C, Leemans G, De Backer J, De Backer W, et al. Functional Respiratory Imaging To Predict Post-Operative Forced Expiratory Volume In 1 Second After Lobectomy/Pneumonectomy. In: C38 LICENSE TO CALL A SURGEON: INVASIVE MANAGEMENT OF LUNG DISEASE [Internet]. 2014. p. A4362–A4362. (American Thoracic Society International Conference Abstracts). Available from: DOI: 10.1164/ajrccm-conference.2014.189.1_MeetingAbstracts.A4362

144. Marinov B, Chapkanov A, Todorova M, Paskalev G, Kostianev S. Smoking status affects VRI assissted prediction of postoperative FEV1 and DL,CO in patients with lung cancer. Eur Respir J. 2014 Sep 1;44(Suppl 58):P3257.

145. Franchi P, Larici A.r, Devicienti E, Occhipinti M, Inchingolo R, Calvello M.r, et al. Role of MDCT-virtual lobectomy in the prediction of post-operative lung function in patients undergoing surgical lobectomy. J Thorac Imaging. 2014 May;(3):W27.

146. Li M, Liang C, Guo J, Ma Y, Zhou L, Yang P, et al. [The clinical application value of dual source CT quantification volume imaging to forecast lung cancer patients' postoperative pulmonary function changing: a prospective study]. Zhonghua Wai Ke Za Zhi. 2014 Oct;52(10):734–8.

147. Yanagita H, Honda N, Nakayama M, Watanabe W, Shimizu Y, Osada H, et al. Prediction of postoperative pulmonary function: preliminary comparison of single-breath dual-energy xenon CT with three conventional methods. Jpn J Radiol. 2013 Jun;31(6):377–85.

148. Westhoff M, Herth F, Albert M, Dienemann H, Eberhardt R. A new method to predict values for postoperative lung function and surgical risk of lung resection by quantitative breath sound measurements. Am J Clin Oncol. 2013 Jun;36(3):273–8.

149. Marinov B, Chapkanov A, Todorova M, Paskalev G, Kostianev S. The utility of vibration response imaging for calculation of ppoFEV1 and ppoDL,CO in patients with lung cancer referred for resection - The influence of coexisting COPD. Eur Respir J. 2013 Sep 1;42(Suppl 57):196.

150. Janssens A, C Van Holsbeke, W Vos W, P Van Schil P, L Carp L, E Oostveen E, et al. Is postoperative fev1 (poFEV1) more accurately estimated by functional respiratory imaging (FRI) than by conventional methods? J Thorac Oncol. 2013 Nov;(SUPPL. 2):S828.

151. Cukic V. Preoperative prediction of lung function in pneumonectomy by spirometry and lung perfusion scintigraphy. Acta Inform Medica AIM J Soc Med Inform Bosnia Herzeg Cas Drustva Za Med Inform BiH. 2012 Dec;20(4):221–5.

152. Kim HK, Yoo D, Sung HK, Lee HJ, Choi YH. Vibration Response Imaging in Prediction of Pulmonary Function After Pulmonary Resection. Ann Thorac Surg. 2012 Nov 1;94(5):1680–6.

153. Comce F, Bingol Z, Kiyan E, Tanju S, Toker A, Cagatay P, et al. The Role of a Vibration Response Imaging Device in the Selection of Patients for Lung Resection Surgery. Respir Care. 2011 Jun 17;

154. Zhu X, Zhao M, Liu C, Zhou J. Prediction of the postoperative pulmonary function in lung cancer patients with borderline function using ventilation-perfusion scintigraphy. Nucl Med Commun. 2012 Mar;33(3):283–7.

155. Ohno Y, Koyama H, Nogami M, Takenaka D, Onishi Y, Matsumoto K, et al. State-of-the-art radiological techniques improve the assessment of postoperative lung function in patients with non-small cell lung cancer. Eur J Radiol. 2011 Jan;77(1):97–104.

156. Holvoet T, van Meerbeeck JP, Van De Wiele C, Salhi B, Derom E. Quantitative Perfusion Scintigraphy or Anatomic Segment Method in lung cancer resection. Lung Cancer Amst Neth. 2011 Nov;74(2):212–8.

157. Papageorgiou CV, Kaltsakas G, Misthos P, Tsangaridou I, Chaimala D, Koulouris NG. Prediction of postoperative FEV1 and chronic dyspnoea using quantitative computed tomography (CT) in lung resection candidates. Eur Respir J. 2011 Sep 1;38(Suppl 55):1913.

158. Kovacevic-Kusmierek K, J Kozak, M Bienkiewicz, P Cichocki, J Kusmierek, Plachcinska A. Accuracy of radionuclide methods predicting postoperative residual lung function. Nucl Med Rev. 2014;(Supplement A):A7–8.

159. Pancieri MVC, Cataneo DC, Montovani JC, Cataneo AJM. Comparison between actual and predicted postoperative stair-climbing test, walk test and spirometric values in patients undergoing lung resection. Acta Cir Bras. 2010 Dec;25(6):535–40.

160. Morice RC, Jimenez CA, Eapen GA, Mehran RJ, Keus L, Ost D. Using quantitative breath sound measurements to predict lung function following resection. J Cardiothorac Surg. 2010 Oct 12;5:81.

161. Jimenez U, Marina N, de Santamaria EL, Pac JJ, Galdiz JB. Evaluation of the utility of vibration response imaging device and Operation Planning Software in the assessment of patients before lung resection surgery. Eur J Cardiothorac Surg. 2010 May;37(5):1185–90.

162. Caglar M, Kara M, Aksoy T, Kiratli PO, Karabulut E, Dogan R. Is the predicted postoperative FEV1 estimated by planar lung perfusion scintigraphy accurate in patients undergoing pulmonary resection? Comparison of two processing methods. Ann Nucl Med. 2010 Jul;24(6):447–53.

163. Yamashita CM, Langridge J, Hergott CA, Inculet RI, Malthaner RA, Lefcoe MS, et al. Predicting postoperative FEV1 using spiral computed tomography. Acad Radiol. 2010 May;17(5):607–13.

164. Eberhardt R, Gompelmann D, Gruenewald C, Dienemann H, Herth FJ. Using a novel lung sound software to estimate pulmonary function after lung resection surgery. In: D42 INTERVENTIONAL PULMONOLOGY AND THORACIC SURGERY [Internet]. 2010. p. A5840–A5840. (American Thoracic Society International Conference Abstracts). Available from: DOI: 10.1164/ajrccm-conference.2010.181.1_MeetingAbstracts.A5840

165. Lian MCS, W H Sudin, K M Nor, L Mathews, Fui C.c. Prediction of post-operative pulmonary function after pulmonary lobectomy using quantitative ct volumetric analysis derived equation. Heart Surg Forum. 2010 Oct;(Suppl. 2):S94.

166. Ueda K, Tanaka T, Li T-S, Tanaka N, Hamano K. Quantitative computed tomography for the prediction of pulmonary function after lung cancer surgery: a simple method using simulation software. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2009 Mar;35(3):414–8.

167. Brunelli A, Refai M, Salati M, Xiumé F, Sabbatini A. Predicted versus observed FEV1 and DLCO after major lung resection: a prospective evaluation at different postoperative periods. Ann Thorac Surg. 2007 Mar;83(3):1134–9.

168. Ohno Y, Koyama H, Takenaka D, Nogami M, Kotani Y, Nishimura Y, et al. Coregistered ventilation and perfusion SPECT using krypton-81m and Tc-99m-labeled macroaggregated albumin with multislice CT utility for prediction of postoperative lung function in non-small cell lung cancer patients. Acad Radiol. 2007 Jul;14(7):830–8.

169. Beyer F, Heindel W, Hoffknecht P, Kuhnigk J, Dicken V, Lange T, et al. [CT-based software-supported prediction of the postoperative lung function after partial resection of the lung]. RöFo Fortschritte Auf Dem Geb Röntgenstrahlen Nukl. 2006 Sep;178(9):872–9.

170. Mineo TC, Schillaci O, Pompeo E, Mineo D, Simonetti G. Usefulness of lung perfusion scintigraphy before lung cancer resection in patients with ventilatory obstruction. Ann Thorac Surg. 2006 Nov;82(5):1828–34.

171. Win T, Tasker AD, Groves AM, White C, Ritchie AJ, Wells FC, et al. Ventilation-perfusion scintigraphy to predict postoperative pulmonary function in lung cancer patients undergoing pneumonectomy. AJR Am J Roentgenol. 2006 Nov;187(5):1260–5.

172. Varela G, Brunelli A, Rocco G, Marasco R, Jiménez MF, Sciarra V, et al. Predicted versus observed FEV1 in the immediate postoperative period after pulmonary lobectomy. Eur J Cardio-Thorac Surg Off J Eur Assoc Cardio-Thorac Surg. 2006 Oct;30(4):644–8.

173. Wang J-S, Abboud RT, Wang L-M. Effect of lung resection on exercise capacity and on carbon monoxide diffusing capacity during exercise. Chest. 2006 Apr;129(4):863–72.

174. Sudoh M, Ueda K, Kaneda Y, Mitsutaka J, Li T-S, Suga K, et al. Breath-hold single-photon emission tomography and computed tomography for predicting residual pulmonary function in patients with lung cancer. J Thorac Cardiovasc Surg. 2006 May;131(5):994–1001.

175. Sverzellati N, Chetta A, Calabrò E, Carbognani P, Internullo E, Olivieri D, et al. Reliability of quantitative computed tomography to predict postoperative lung function in patients with chronic obstructive pulmonary disease having a lobectomy. J Comput Assist Tomogr. 2005 Dec;29(6):819–24.

176. Sekine Y, Chiyo M, Iwata T, Yasufuku K, Furukawa S, Amada Y, et al. Perioperative rehabilitation and physiotherapy for lung cancer patients with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg Off Publ Jpn Assoc Thorac Surg Nihon Kyobu Geka Gakkai Zasshi. 2005 May;53(5):237–43.

177. Liu F, Han P, Feng G, Liang B, Xiao J, Tian Z, et al. Using quantitative CT to predict postoperative pulmonary function in patients with lung cancer. Chin Med J (Engl). 2005 May 5;118(9):742–6.

178. Win T, Laroche CM, Groves AM, White C, Wells FC, Ritchie AJ, et al. Use of quantitative lung scintigraphy to predict postoperative pulmonary function in lung cancer patients undergoing lobectomy. Ann Thorac Surg. 2004 Oct;78(4):1215–8.

179. Piai DB, Quagliatto R, Toro I, Cunha Neto C, Etchbehere E, Camargo E. The use of SPECT in preoperative assessment of patients with lung cancer. Eur Respir J. 2004 Aug;24(2):258–62.

180. Ohno Y, Hatabu H, Higashino T, Takenaka D, Watanabe H, Nishimura Y, et al. Dynamic perfusion MRI versus perfusion scintigraphy: prediction of postoperative lung function in patients with lung cancer. AJR Am J Roentgenol. 2004 Jan;182(1):73–8.

181. Koizumi K, Haraguchi S, Hirata T, Hirai K, Mikami I, Fukushima M, et al. Video-assisted lobectomy for a lung cancer patient with chronic obstructive pulmonary disease. Jpn J Thorac Cardiovasc Surg Off Publ Jpn Assoc Thorac Surg Nihon Kyobu Geka Gakkai Zasshi. 2003 Nov;51(11):569–76.

182. Bolliger CT, Gückel C, Engel H, Stöhr S, Wyser CP, Schoetzau A, et al. Prediction of functional reserves after lung resection: comparison between quantitative computed tomography, scintigraphy, and anatomy. Respir Int Rev Thorac Dis. 2002;69(6):482–9.

183. Foroulis CN, Kotoulas C, Konstantinou M, Lioulias A. Is the reduction of forced expiratory lung volumes proportional to the lung parenchyma resection, 6 months after pneumonectomy? Eur J Cardiothorac Surg. 2002 May;21(5):901–5.

184. Edwards JG, Duthie DJ, Waller DA. Lobar volume reduction surgery: a method of increasing the lung cancer resection rate in patients with emphysema. Thorax. 2001 Oct;56(10):791–5.

185. Beccaria M, Corsico A, Fulgoni P, Zoia MC, Casali L, Orlandoni G, et al. Lung cancer resection: the prediction of postsurgical outcomes should include long-term functional results. Chest. 2001 Jul;120(1):37–42.

186. Koh YM, Park SJ, Suh GY, Chung MP, Kim K, Kwon O, et al. Preservation of pulmonary function after sleeve lobectomy in patients with lung cancer. [Korean]. Tuberc Respir Dis. 1999;(1):35–41.

187. Furrer M, Rechsteiner R, Eigenmann V, Signer C, Althaus U, Ris HB. Thoracotomy and thoracoscopy: postoperative pulmonary function, pain and chest wall complaints. Eur J Cardiothorac Surg. 1997 Jul;12(1):82–7.

188. Giordano A, Calcagni ML, Meduri G, Valente S, Galli G. Perfusion lung scintigraphy for the prediction of postlobectomy residual pulmonary function. Chest. 1997 Jun;111(6):1542–7.

189. Leone G, Volpino P, Galati G, Fiori E, Baccarini A, Boccuzzi M, et al. [Evaluation of the respiratory function by lung scintigraphy in patients candidates for pulmonary resection]. Il G Chir. 1997 May;18(5):301–7.

190. Weiner P, Man A, Weiner M, Rabner M, Waizman J, Magadle R, et al. The effect of incentive spirometry and inspiratory muscle training on pulmonary function after lung resection. J Thorac Cardiovasc Surg. 1997 Mar;113(3):552–7.

191. Bolliger CT, Wyser C, Roser H, Stulz P, Solèr M, Perruchoud AP. [Lung scintigraphy and ergospirometry in prediction of postoperative course in lung resection candidates with increased risk of postoperative complications]. Pneumol Stuttg Ger. 1996 May;50(5):334–41.

192. Gaissert HA, Mathisen DJ, Moncure AC, Hilgenberg AD, Grillo HC, Wain JC. Survival and function after sleeve lobectomy for lung cancer. J Thorac Cardiovasc Surg. 1996 May;111(5):948–53.

193. Izquierdo JM, Pac JJ, Casanova J, Vara F, Cortés J, Fombellida J, et al. [Lung resection surgery in patients with functional limits]. Arch Bronconeumol. 1995 Sep;31(7):328–32.

194. Hosokawa N, Tanabe M, Satoh K, Takashima H, Ohkawa M, Maeda M, et al. [Prediction of postoperative pulmonary function using 99mTc-MAA perfusion lung SPECT]. Nihon Igaku Hoshasen Gakkai Zasshi Nippon Acta Radiol. 1995 May;55(6):414–22.

195. Giordano A, Calcagni ML, Rossi B, D'Ugo D, Corbo GM, Fumagalli G, et al. [The scintigraphic prediction of residual lung function after lobectomy in patients with bronchial carcinoma]. Radiol Med (Torino). 1995 Apr;89(4):501–5.

196. Bolliger CT, Wyser C, Roser H, Solèr M, Perruchoud AP. Lung scanning and exercise testing for the prediction of postoperative performance in lung resection candidates at increased risk for complications. Chest. 1995 Aug;108(2):341–8.

197. Romessis M, F Mucilli, G Bruni, R Massari. The predicting residual pulmonary function after pulmonary resection. [Italian]. Chirurgia (Bucur). 1995;(5–6):218–21.

198. Cheon Y K, Kwak Y I, Yun J G, Zo J I, Shim Y M, Lim S M, et al. Comparison of inhalation scan and perfusion scan for the prediction of postoperative pulmonary function. Tuberc Respir Dis. 1994;(2):111–9.

199. Hirose Y, Imaeda T, Doi H, Kokubo M, Sakai S, Hirose H. Lung perfusion SPECT in predicting postoperative pulmonary function in lung cancer. Ann Nucl Med. 1993 May;7(2):123–6.

200. Omote Y, Maeda T, Ikeda K, Kubo Y. [Examination of post operative split lung function using quantitative xenon 133 (133Xe) inhalation scan]. Zasshi J Nihon Kyobu Geka Gakkai. 1992 Dec;40(12):2205–11.

201. Cangemi V, Volpino P, Caputo V, D'Andrea N, R T, E G, et al. Quantitative and qualitative regional ventilation-perfusion scanning to predict postsurgical lung function and postoperative morbidity and mortality in patients submitted to polmonary resectional surgery. [Italian]. Chirurgia (Bucur). 1992;(12):731–7.

202. Cordiner A, De Carlo F, De Gennaro R, Pau F, Flore F. Prediction of postoperative pulmonary function following thoracic surgery for bronchial carcinoma. Angiology. 1991 Dec;42(12):985–9.

203. Koizumi K, Tanaka S, Shioda M, Haraguchi S, Masaki Y, Morota T, et al. [Simplified prediction of postoperative lung function by plain chest roentgenogram in patients with primary lung cancer--in correlation to postoperative respiratory complications]. Zasshi J Nihon Kyobu Geka Gakkai. 1991 Sep;39(9):1758–64.

204. Ashino Y, Chida M, Suzuki S, Nasu G, Isogami K, Kubo H, et al. [Lung function after lobectomy in chronic pulmonary emphysema]. Zasshi J Nihon Kyobu Geka Gakkai. 1991 Sep;39(9):1752–7.

205. Wang J. [Clinical value of perfusion lung scanning in the surgical treatment of lung cancer]. Zhonghua Yi Xue Za Zhi. 1991 Nov;71(11):620–2, 44.

206. Mende T, Orlick M, Fischbeck O, Neef H. [Risk assessment of bronchial cancer surgery using quantitative lung perfusion scintigraphy]. Nukl Nucl Med. 1990 Dec;29(6):274–7.

207. Markos J, Mullan BP, Hillman DR, Musk AW, Antico VF, Lovegrove FT, et al. Preoperative assessment as a predictor of mortality and morbidity after lung resection. Am Rev Respir Dis. 1989 Apr;139(4):902–10.

208. Huang WL, Chiang CD, King SL, Yiin KT, Jih KS, Lin TM, et al. [Prediction of postoperative pulmonary function in the patient undergoing pneumonectomy using combined pulmonary function test and ventilation/perfusion scintiphotography]. Zhonghua Yi Xue Za Zhi Chin Med J Free China Ed. 1989 Mar;43(3):185–90.

209. Nonoyama A, Saito Y, Ohmoto K, Umemoto M, Sakurai Y, Tanaka K, et al. [Pneumonectomy in lung cancer in patients over 70 years old--prediction of postpneumonectomy pulmonary function]. Zasshi J Nihon Kyobu Geka Gakkai. 1988 Jul;36(7):1096–105.

210. Yoshikawa K. Prediction of postoperative lung function after pulmonary resection. Nippon Kyobu Geka Gakkai Zasshi. 1988;36(11):2437–46.

211. Nonoyama A, Saito Y, Tanaka K, Ohmoto K, Umemoto M, Sakurai Y, et al. [Prediction of postpneumonectomy pulmonary function using perfusion lung scanning]. Zasshi J Nihon Kyobu Geka Gakkai. 1988 Oct;36(10):2221–8.

212. Julius AJ, de Jong D, van Deutekom H, Heidendal GA, den Otter G, Kester AD. The value of 99mTc macroaggregated albumin lung perfusion scanning in the prediction of postpneumonectomy function and pulmonary artery pressure. Scand J Thorac Cardiovasc Surg. 1987;21(1):81–5.

213. Veneskoski T, Sovijärvi AR. Prediction of ventilatory function after subtotal lung resection using preoperative dynamic spirometry and radiospirometry. Eur J Respir Dis. 1986 Mar;68(3):167–72.

214. Egeblad K, Aunsholt NA, Funder V, Nielsen PH. A Simple method for predicting pulmonary function after lung resection. Scand J Thorac Cardiovasc Surg. 1986 Jan 1;20(2):103–7.

215. Ladurie ML, Ranson-Bitker B. Uncertainties in the expected value for forced expiratory volume in one second after surgery. Chest. 1986 Aug;90(2):222–8.

216. Veneskoski T, Sovijärvi A. 133Xe radiospirometry in prediction of ventilatory function and vital capacity after pneumonectomy in patients with an endobronchial tumour. Ann Chir Gynaecol. 1985;74(6):256–60.

217. Nakahara K, Monden Y, Ohno K, Fujii Y, Maeda H, Fujimoto Y, et al. Prediction of lung cancer spread and functional resectability by 133Xe radiospirometry. Jpn J Surg. 1985 Jul;15(4):254–9.

218. Hara F. Prediction of postoperative pulmonary function in lung cancer patient using corrected lateral radionuclide lung image. Nippon Kyobu Geka Gakkai Zasshi. 1985;33(6):889–95.

219. Williams AJ, Cayton RM, Harding LK, Mostafa AB, Matthews HR. Quantitative lung scintigrams and lung function in the selection of patients for pneumonectomy. Br J Dis Chest. 1984 Apr;78(2):105–12.

220. Bins MC, Wever AM, Pauwels EK, van der Velde EA. Krypton-81m ventilation studies as a parameter for lung capacity after lobectomy. Eur J Nucl Med. 1984;9(7):312–5.

221. Ali MK, Ewer MS, Atallah MR, Mountain CF, Dixon CL, Johnston DA, et al. Regional and overall pulmonary function changes in lung cancer. Correlations with tumor stage, extent of pulmonary resection, and patient survival. J Thorac Cardiovasc Surg. 1983 Jul;86(1):1–8.

222. Nakahara K, Fujimoto Y, Ikeda M, Maeda H, Miyoshi S, Kitagawa Y, et al. [Analysis of the correlation between predicted and measured post- operative respiratory function in primary lung cancer]. Kyobu Geka. 1983 Dec;36(11):863–6.

223. Loddenkemper R, Gabler A, Göbel D. Criteria of functional operability in patients with bronchial carcinoma: preoperative assessment of risk and prediction of postoperative function. Thorac Cardiovasc Surg. 1983 Dec;31(6):334–7.

224. Nakahara K, S Miyoshi, T Kido. Prediction of the postoperative lung function in patients with primary lung cancer. [Japanese]. J Lung Cancer. 1982;(4):429–34.

225. Konishi H. Prediction of postoperative respiratory function of lung cancer patients using quantitative lung scans. Nippon Kyobu Geka Gakkai Zasshi. 1982;30(11):1784–95.

226. Ali MK, Mountain CF, Ewer MS, Johnston D, Haynie TP. Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. Chest. 1980 Mar;77(3):337–42.

227. Taube K, Konietzko N. [Can the effect of pneumonectomy on cardiopulmonary function be anticipated? (author's transl)]. Prax Klin Pneumol. 1980 Sep;34(9):548–54.

228. Taube K, Konietzko N. Prediction of postoperative cardiopulmonary function in patients undergoing pneumonectomy. Thorac Cardiovasc Surg. 1980 Oct;28(5):348–51.

229. Walkup RH, Vossel LF, Griffin JP, Proctor RJ. Prediction of postoperative pulmonary function with the lateral position test. A prospective study. Chest. 1980 Jan;77(1):24–7.

230. Cooper WR, Guerrant JL, Teates CD. Prediction of postoperative respiratory function in patients undergoing lung resection. Va Med. 1980 Apr;107(4):264–8.

231. Wernly JA, DeMeester TR, Kirchner PT, Myerowitz PD, Oxford DE, Golomb HM. Clinical value of quantitative ventilation-perfusion lung scans in the surgical management of bronchogenic carcinoma. J Thorac Cardiovasc Surg. 1980 Oct;80(4):535–43.

232. Nicoli MM, Jammes Y, Fornaris E, Giacchero G, Coutant P. [133 Xe radiospirometry: prediction of VC and FEV1 (author's transl)]. Respir Int Rev Thorac Dis. 1979;37(4):208–14.

233. Malm A, Arborelius M, Kristersson S. [Pathophysiology after resections of the lung (author's transl)]. Zentralbl Chir. 1977;102(10):585–91.

234. Wever AMJ, J J Klein, H Beekhuis. Prediction by means of regional ^{133}Xe radiospirometry of the spirometric pulmonary function after pneumonectomy (Dutch). [Dutch]. Ned Tijdschr Geneeskd. 1975;(21):825–9.

235. Kristersson S, Arborelius M, Jungquist G, Lilja B, Svanberg L. Prediction of ventilatory capacity after lobectomy. Scand J Respir Dis. 1973;54(6):315–25.

236. Kristersson S, Lindell S-E, Svanberg L. Prediction of Pulmonary Function Loss Due to Pneumonectomy Using 133Xe-Radiospirometry. CHEST. 1972 Dec 1;62(6):694–8.

237. Donohue JF. Minimal clinically important differences in COPD lung function. COPD. 2005;2(1):111–24.

238. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003 Sep 4;327(7414):557–60.

239. Diagnosis of diseases of chronic airflow limitation: 2015 asthma, COPD and asthma-COPD overlap syndrome (ACOS) [Internet]. Global Initiative for Asthma & Global Initiative for Chronic Obstructive Lung Disease; 2015 [cited 2019 Mar 6]. Available from: https://goldcopd.org/wp-content/uploads/2016/04/GOLD_ACOS_2015.pdf

240. Surgical research: the reality and the IDEAL [Editorial]. The Lancet. 2009 Sep 26;374(9695):1037.

241. Ueda K, Kaneda Y, Sudo M, Mitsutaka J, Li T-S, Suga K, et al. Quantitative Computed Tomography Versus Spirometry in Predicting Air Leak Duration After Major Lung Resection for Cancer. Ann Thorac Surg. 2005 Nov 1;80(5):1853–8.

242. Kaplan T, Atac GK, Gunal N, Kocer B, Alhan A, Cubuk S, et al. Quantative computerized tomography assessment of lung density as a predictor of postoperative pulmonary morbidity in patients with lung cancer. J Thorac Dis. 2015 Aug;7(8):1391–7.

243. Green CE, Parr DG, Edgar RG, Stockley RA, Turner AM. Lung density associates with survival in alpha 1 antitrypsin deficient patients. Respir Med. 2016 Mar;112:81–7.

244. Crossley D, Renton M, Khan M, Low EV, Turner AM. CT densitometry in emphysema: a systematic review of its clinical utility. Int J Chron Obstruct Pulmon Dis. 2018 Feb 7;13:547–63.

245. Chapman KR, Burdon JGW, Piitulainen E, Sandhaus RA, Seersholm N, Stocks JM, et al. Intravenous augmentation treatment and lung density in severe α1 antitrypsin deficiency (RAPID): a randomised, double-blind, placebo-controlled trial. Lancet Lond Engl. 2015 Jul 25;386(9991):360–8.

246. Fintelmann FJ, Troschel FM, Mario J, Chretien YR, Knoll SJ, Muniappan A, et al. Thoracic Skeletal Muscle Is Associated With Adverse Outcomes After Lobectomy for Lung Cancer. Ann Thorac Surg. 2018;105(5):1507–15.

247. Sepesi B, Gold KA, Correa AM, Heymach JV, Vaporciyan AA, Roszik J, et al. The Influence of Body Mass Index on Overall Survival Following Surgical Resection of Non-Small Cell Lung Cancer. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2017;12(8):1280–7.

248. Ha D, Ries AL, Mazzone PJ, Lippman SM, Fuster MM. Exercise capacity and cancer-specific quality of life following curative intent treatment of stage I-IIIA lung cancer. Support Care Cancer Off J Multinatl Assoc Support Care Cancer. 2018 Jul;26(7):2459–69.

249. Farkhooy A, Janson C, Arnardóttir RH, Malinovschi A, Emtner M, Hedenström H. Impaired Carbon Monoxide Diffusing Capacity is the Strongest Predictor of Exercise Intolerance in COPD. COPD J Chronic Obstr Pulm Dis. 2013 Mar 21;10(2):180–5.

250. Pompili C, Brunelli A, Refai M, Xiumè F, Sabbatini A. Does chronic obstructive pulmonary disease affect postoperative quality of life in patients undergoing lobectomy for lung cancer? A case-matched study. Eur J Cardiothorac Surg. 2010 Mar;37(3):525–30.

251. Kim H, Goo JM, Ohno Y, Kauczor H-U, Hoffman EA, Gee JC, et al. Effect of Reconstruction Parameters on the Quantitative Analysis of Chest Computed Tomography. J Thorac Imaging. 2019 Mar 1;34(2):92–102.

252. Gallardo-Estrella L, Lynch DA, Prokop M, Stinson D, Zach J, Judy PF, et al. Normalizing computed tomography data reconstructed with different filter kernels: effect on emphysema quantification. Eur Radiol. 2016 Feb 1;26(2):478–86.

253. Gierada DS, Bierhals AJ, Choong CK, Bartel ST, Ritter JH, Das NA, et al. Effects of CT Section Thickness and Reconstruction Kernel on Emphysema Quantification: Relationship to the Magnitude of the CT Emphysema Index. Acad Radiol. 2010 Feb;17(2):146.

254. Martin CJ, Young AC. Lobar ventilation in man. Am Rev Tuberc. 1956 Mar;73(3):330–7.

255. Mattson SB, Carlens E. Lobar ventilation and oxygen uptake in man; influence of body position. J Thorac Surg. 1955 Dec;30(6):676–82.

256. Rodarte JR, Chaniotakis M, Wilson TA. Variability of parenchymal expansion measured by computed tomography. J Appl Physiol Bethesda Md 1985. 1989 Jul;67(1):226–31.

257. Altemeier WA, McKinney S, Glenny RW. Fractal nature of regional ventilation distribution. J Appl Physiol Bethesda Md 1985. 2000 May;88(5):1551–7.

258. Glenny RW, Lamm WJ, Bernard SL, An D, Chornuk M, Pool SL, et al. Selected contribution: redistribution of pulmonary perfusion during weightlessness and increased gravity. J Appl Physiol Bethesda Md 1985. 2000 Sep;89(3):1239–48.

259. Koshiol J, Rotunno M, Consonni D, Pesatori AC, De Matteis S, Goldstein AM, et al. Chronic Obstructive Pulmonary Disease and Altered Risk of Lung Cancer in a Population-Based Case-Control Study. PLoS ONE. 2009 Oct 8;4(10).

260. Li Y, Lu L, Xiao M, Dercle L, Huang Y, Zhang Z, et al. CT Slice Thickness and Convolution Kernel Affect Performance of a Radiomic Model for Predicting EGFR Status in Non-Small Cell Lung Cancer: A Preliminary Study. Sci Rep. 2018 Dec 17;8(1):1–10.

261. Wiemker R, Rogalla P, Zwartkruis A, Blaffert T. Computer-aided lung nodule detection on high-resolution CT data. Proc SPIE 4684 Med Imaging 2002 Image Process. 2002 May 9;677–88.

262. Reconstruction FC Guide Aquilion series, V7.0 software or above. Toshiba Medical Systems Corporation; 2015.

263. National Institute for Health Research. Guidance on applying for feasibility studies [Internet]. 2017 [cited 2019 Nov 24]. Available from: https://www.nihr.ac.uk/documents/nihr-research-for-patient-benefit-rfpb-programme-guidance-%20%20on-applying-for-feasibility-studies/20474

264. Browne RH. On the use of a pilot sample for sample size determination. Stat Med. 1995 Sep 15;14(17):1933–40.

265. Kieser M, Wassmer G. On the Use of the Upper Confidence Limit for the Variance from a Pilot Sample for Sample Size Determination. Biom J. 1996 Jan 1;38(8):941–9.

266. Ranganathan P, Pramesh CS, Aggarwal R. Common pitfalls in statistical analysis: Measures of agreement. Perspect Clin Res. 2017;8(4):187–91.

267. Harvard University. Chest Imaging Platform (CIP) [Internet]. [cited 2019 Nov 24]. Available from: https://chestimagingplatform.org/

268. Thirona – Automated Medical Image Analysis [Internet]. [cited 2019 Nov 24]. Available from: https://thirona.eu/

269. Ross JC, Estépar RSJ, Díaz A, Westin C-F, Kikinis R, Silverman EK, et al. Lung Extraction, Lobe Segmentation and Hierarchical Region Assessment for Quantitative Analysis on High Resolution Computed Tomography Images. Med Image Comput Comput-Assist Interv MICCAI Int Conf Med Image Comput Comput-Assist Interv. 2009;12(Pt 2):690–8.

270. Estepar R, Washko GR, Silverman EK, Reilly JJ, Kikinis R, Westin C-F. Airway Inspector: an Open Source Application for Lung Morphometry [Internet]. First International Workshop on Pulmonary Image Processing; 293-302; 2008. Available from: https://acil.med.harvard.edu/files/acil/files/first_international_workshop_on_pulmonary_image_processing_2008_san_jose_estepar.pdf

271. van Rikxoort EM, de Hoop B, Viergever MA, Prokop M, van Ginneken B. Automatic lung segmentation from thoracic computed tomography scans using a hybrid approach with error detection. Med Phys. 2009 Jul;36(7):2934–47.

272. Lassen B, Rikxoort EM van, Schmidt M, Kerkstra S, Ginneken B van, Kuhnigk JM. Automatic Segmentation of the Pulmonary Lobes From Chest CT Scans Based on Fissures, Vessels, and Bronchi. IEEE Trans Med Imaging. 2013 Feb;32(2):210–22.

273. Lassen-Schmidt BC, Kuhnigk J-M, Konrad O, van Ginneken B, van Rikxoort EM. Fast interactive segmentation of the pulmonary lobes from thoracic computed tomography data. Phys Med Biol. 2017 Jul 31;62(16):6649–65.

274. Koo TK, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. J Chiropr Med. 2016 Jun;15(2):155–63.

275. Karimi R, Tornling G, Forsslund H, Mikko M, Wheelock ÅM, Nyrén S, et al. Lung density on high resolution computer tomography (HRCT) reflects degree of inflammation in smokers. Respir Res. 2014;15(1):23.

276. Oswald NK, Halle-Smith J, Mehdi R, Nightingale P, Naidu B, Turner AM. Predicting Postoperative Lung Function Following Lung Cancer Resection: A Systematic Review and Meta-analysis. EClinicalMedicine. 2019 Oct;15:7–13.

277. Wielpütz MO, Bardarova D, Weinheimer O, Kauczor H-U, Eichinger M, Jobst BJ, et al. Variation of densitometry on computed tomography in COPD--influence of different software tools. PloS One. 2014;9(11):e112898.

278. Batchelor TJP, Rasburn NJ, Abdelnour-Berchtold E, Brunelli A, Cerfolio RJ, Gonzalez M, et al. Guidelines for enhanced recovery after lung surgery: recommendations of the Enhanced Recovery After Surgery (ERAS®) Society and the European Society of Thoracic Surgeons (ESTS). Eur J Cardiothorac Surg. 2019 Jan 1;55(1):91–115.

279. Pennati F, Salito C, Baroni G, Woods J, Aliverti A. Comparison Between Multivolume CT-Based Surrogates of Regional Ventilation in Healthy Subjects. Acad Radiol. 2014 Oct 1;21(10):1268–75.

280. Eslick EM, Kipritidis J, Gradinscak D, Stevens MJ, Bailey DL, Harris B, et al. CT ventilation imaging derived from breath hold CT exhibits good regional accuracy with Galligas PET. Radiother Oncol. 2018 May 1;127(2):267–73.

281. Kipritidis J, Woodruff H, Keall P. VESPIR (VEntilation via Scripted Pulmonary Image Registration). Australia: University of Sydney; 2015.

282. Parr DG, Stoel BC, Stolk J, Nightingale PG, Stockley RA. Influence of calibration on densitometric studies of emphysema progression using computed tomography. Am J Respir Crit Care Med. 2004 Oct 15;170(8):883–90.

283. Schwartz DA, Helmers RA, Galvin JR, Van Fossen DS, Frees KL, Dayton CS, et al. Determinants of survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1994 Feb 1;149(2):450–4.

284. Skandamis A, Kani C, Markantonis SL, Souliotis K. Systematic review and network meta-analysis of approved medicines for the treatment of idiopathic pulmonary fibrosis. J Drug Assess. 2019;8(1):55–61.

285. Gribbin J, Hubbard RB, Jeune IL, Smith CJP, West J, Tata LJ. Incidence and mortality of idiopathic pulmonary fibrosis and sarcoidosis in the UK. Thorax. 2006 Nov 1;61(11):980–5.

286. Paramothayan NS, Lasserson TJ, Jones P. Corticosteroids for pulmonary sarcoidosis. Cochrane Database Syst Rev. 2005 Apr 20;2005(2).

287. Kreider ME, Hansen-Flaschen J, Ahmad NN, Rossman MD, Kaiser LR, Kucharczuk JC, et al. Complications of Video-Assisted Thoracoscopic Lung Biopsy in Patients with Interstitial Lung Disease. Ann Thorac Surg. 2007 Mar 1;83(3):1140–4.

288. Fibla JJ, Brunelli A, Cassivi SD, Deschamps C. Aggregate risk score for predicting mortality after surgical biopsy for interstitial lung disease. Interact Cardiovasc Thorac Surg. 2012 Aug 1;15(2):276–9.

289. Bayman EO, Parekh KR, Keech J, Selte A, Brennan TJ. A Prospective Study of Chronic Pain after Thoracic Surgery. Anesthesiology. 2017 May;126(5):938–51.

290. The Effectiveness of ThOracic Epidural and Paravertebral Blockade In Reducing Chronic Post- Thoracotomy Pain: 2 - Full Text View - ClinicalTrials.gov [Internet]. [cited 2019 Sep 16]. Available from: https://clinicaltrials.gov/ct2/show/NCT03677856

291. Higashi M, Shigematsu K, Nakamori E, Sakurai S, Yamaura K. Efficacy of programmed intermittent bolus epidural analgesia in thoracic surgery: a randomized controlled trial. BMC Anesthesiol. 2019 Jun 15;19(1):107.

292. Knudsen L, Ochs M. The micromechanics of lung alveoli: structure and function of surfactant and tissue components. Histochem Cell Biol. 2018 Dec;150(6):661–76.

293. Do K-H, Lee JS, Colby TV, Kitaichi M, Kim DS. Nonspecific interstitial pneumonia versus usual interstitial pneumonia: differences in the density histogram of high-resolution CT. J Comput Assist Tomogr. 2005 Aug;29(4):544–8.

294. Ariani A, Imperatori A, Castiglioni M, Daffrè E, Aiello M, Bertorelli G, et al. Quantitative computed tomography detects interstitial lung diseases proven by biopsy. Sarcoidosis Vasc Diffuse Lung Dis. 2018 Apr 1;35(1):16–20.

295. Sverzellati N, Calabrò E, Chetta A, Concari G, Larici AR, Mereu M, et al. Visual score and quantitative CT indices in pulmonary fibrosis: Relationship with physiologic impairment. Radiol Med (Torino). 2007 Dec 1;112(8):1160–72.

296. Park SO, Seo JB, Kim N, Lee YK, Lee J, Kim DS. Comparison of Usual Interstitial Pneumonia and Nonspecific Interstitial Pneumonia: Quantification of Disease Severity and Discrimination between Two Diseases on HRCT Using a Texture-Based Automated System. Korean J Radiol. 2011;12(3):297–307.

297. Bartholmai BJ, Raghunath S, Karwoski RA, Moua T, Rajagopalan S, Maldonado F, et al. Quantitative CT Imaging of Interstitial Lung Diseases. J Thorac Imaging. 2013 Sep;28(5).

298. Weatherley ND, Eaden JA, Stewart NJ, Bartholmai BJ, Swift AJ, Bianchi SM, et al. Experimental and quantitative imaging techniques in interstitial lung disease. Thorax. 2019 Jun;74(6):611–9.

299. Galbán CJ, Boes JL, Bule M, Kitko CL, Couriel DR, Johnson TD, et al. Parametric Response Mapping as an Indicator of Bronchiolitis Obliterans Syndrome after Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2014 Oct 1;20(10):1592–8.

300. Smith M, Dalurzo M, Panse P, Parish J, Leslie K. Usual interstitial pneumonia-pattern fibrosis in surgical lung biopsies. Clinical, radiological and histopathological clues to aetiology. J Clin Pathol. 2013 Oct;66(10):896–903.

301. Pennati F, Salito C, Aliverti A. Registration of lung CT images acquired in different respiratory ranges with 4DCT and HRCT. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2015 Aug;2015:2936–9.

302. Hu S, Hoffman EA, Reinhardt JM. Automatic lung segmentation for accurate quantitation of volumetric X-ray CT images. IEEE Trans Med Imaging. 2001 Jun;20(6):490–8.

303. Lucas B, Kanade T. An iterative image registration technique with an application to stereo vision. Proc 7th Intl Jt Conf Artif Intell. 1981;674–9.

304. Hackshaw A. Small studies: strengths and limitations. Eur Respir J. 2008 Nov 1;32(5):1141–3.

305. Ryerson C, Vittinghoff E, Ley B, Lee J, Mooney J, Jones K, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest. 2014;145(4):723–8.

306. Ritman EL. Micro-Computed Tomography of the Lungs and Pulmonary-Vascular System. Proc Am Thorac Soc. 2005 Dec;2(6):477–80.

307. Park J, Jung J, Yoon SH, Goo JM, Hong H, Yoon J-H. Inspiratory Lung Expansion in Patients with Interstitial Lung Disease: CT Histogram Analyses. Sci Rep. 2018 Oct 15;8.

308. Hegi-Johnson F, de Ruysscher D, Keall P, Hendriks L, Vinogradskiy Y, Yamamoto T, et al. Imaging of regional ventilation: Is CT ventilation imaging the answer? A systematic review of the validation data. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2019 Aug;137:175–85.

309. Pennati F, Salito C, Quirk J, Castro M, Woods J, Aliverti A. Regional ventilation quantified by multi-volume computed tomography (CT): Comparison with 3-helium magnetic resonance imaging (3He-MRI). Eur Respir J. 2014 Sep 1;44(Suppl 58):P538.

310. Pennati F, Salito C, Roach D, Clancy JP, Woods J, Aliverti A. Regional ventilation in infants quantified by multi-volume high resolution computed tomography (HRCT) and multi-volume proton magnetic resonance imaging (MRI). Eur Respir J. 2015 Sep 1;46(suppl 59):OA2949.

311. Murphy K, Pluim JPW, van Rikxoort EM, de Jong PA, de Hoop B, Gietema HA, et al. Toward automatic regional analysis of pulmonary function using inspiration and expiration thoracic CT. Med Phys. 2012 Mar;39(3):1650–62.

312. Ritt P, Sanders J, Kuwert T. SPECT/CT technology. Clin Transl Imaging. 2014 Dec 1;2(6):445–57.

313. Mansoor A, Bagci U, Foster B, Xu Z, Papadakis GZ, Folio LR, et al. Segmentation and Image Analysis of Abnormal Lungs at CT: Current Approaches, Challenges, and Future Trends. Radiogr Rev Publ Radiol Soc N Am Inc. 2015 Aug;35(4):1056–76.

314. National Heart, Lung, and Blood Institute. Lung Tissue Research Consortium [Internet]. [cited 2019 Oct 17]. Available from: https://ltrcpublic.com/content/about-0

315. Suzawa N, Ichikawa Y, Ishida M, Tomita Y, Nakayama R, Sakuma H. Respiratory-gated time-of-flight PET/CT during whole-body scan for lung lesions: feasibility in a routine clinical setting and quantitative analysis. Ann Nucl Med. 2016 Dec 1;30(10):722–30.

316. The Asbestos (Prohibitions) (Amendment) Regulations 1999 [Internet]. Nov 24, 1999. Available from: http://www.legislation.gov.uk/uksi/1999/2373/made

317. Health and Safety Executive. Mesothelioma mortality by occupation [Internet]. 2017 [cited 2019 May 5]. Available from: http://www.hse.gov.uk/statistics/causdis/mesothelioma/mesothelioma-mortality-by-occupation-2002-2015.pdf

318. Mesothelioma incidence statistics [Internet]. Cancer Research UK. 2015 [cited 2019 Jun 20]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/mesothelioma/incidence

319. Zalcman G, Mazieres J, Margery J, Greillier L, Audigier-Valette C, Moro-Sibilot D, et al. Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial. Lancet Lond Engl. 2016 Apr 2;387(10026):1405–14.

320. Patel SC, Dowell JE. Modern management of malignant pleural mesothelioma. Lung Cancer Targets Ther. 2016 May 3;7:63–72.

321. Prakash UB, Reiman HM. Comparison of needle biopsy with cytologic analysis for the evaluation of pleural effusion: analysis of 414 cases. Mayo Clin Proc. 1985 Mar;60(3):158–64.

322. Robinson BM. Malignant pleural mesothelioma: an epidemiological perspective. Ann Cardiothorac Surg. 2012 Nov;1(4):491–6.

323. Stephens RJ, Whiting C, Cowan K, James Lind Alliance Mesothelioma Priority Setting Partnership Steering Committee. Research priorities in mesothelioma: A James Lind Alliance Priority Setting Partnership. Lung Cancer Amst Neth. 2015 Aug;89(2):175–80.

324. Corris PA, Best JJ, Gibson GJ. Effects of diffuse pleural thickening on respiratory mechanics. Eur Respir J. 1988 Mar;1(3):248–52.

325. Elshafie G, Aliverti A, Kumar P, Rajesh P, Steyn R, Kalkat M, et al. Diagnosing mesothelioma via its effect on chest wall mechanics. In: C110 MESOTHELIOMA AND MALIGNANT PLEURAL DISEASE: FROM BENCH TO BEDSIDE TO COMMUNITY [Internet]. 2016. p. A6402–A6402. (American Thoracic Society International Conference Abstracts). Available from: DOI: 10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A6402

326. Cagle PT, Churg A. Differential diagnosis of benign and malignant mesothelial proliferations on pleural biopsies. Arch Pathol Lab Med. 2005 Nov;129(11):1421–7.

327. Elshafie G, Kumar P, Steyn R, Wilson R, Kalkat M, Bishay E, et al. The Effect of Thoracic Nerve Blocks on Chest Wall Mechanics. In: C76 VENTILATORY CONTROL: GETTING ON MY NERVES [Internet]. 2016. p. A5969–A5969. (American Thoracic Society International Conference Abstracts). Available from: DOI: 10.1164/ajrccm-conference.2016.193.1_MeetingAbstracts.A5969

328. Stanford F. Sympathetic nerve involvement with mesothelioma of the pleura. Br J Dis Chest. 1976 Jan 1;70:134–7.

329. Pleet DL, Mandel S, Neilan B. Paroxysmal Unilateral Hyperhidrosis and Malignant Mesothelioma. Arch Neurol. 1983 Apr 1;40(4):256–256.

330. Fiorelli A, D'Aponte A, Canonico R, Palladino A, Vicidomini G, Limongelli F, et al. T2–T3 sympathectomy versus sympathicotomy for essential palmar hyperhidrosis: comparison of effects on cardio-respiratory function. Eur J Cardiothorac Surg. 2012 Sep 1;42(3):454–61.

331. Hillard VH, Liu JK, Kwok A, Schmidt MH. Perineural spread of malignant mesothelioma resulting in an intradural spinal cord mass: case report. J Neurooncol. 2007 Jan;81(2):185–9.

332. Kato K, Gemba K, Fujimoto N, Aoe K, Takeshima Y, Inai K, et al. Pleural irregularities and mediastinal pleural involvement in early stages of malignant pleural mesothelioma and benign asbestos pleural effusion. Eur J Radiol. 2016 Sep;85(9):1594–600.

333. Elshafie G, Acosta J, Aliverti A, Bradley A, Kumar P, Rajesh P, et al. Chest wall mechanics before and after diaphragm plication. J Cardiothorac Surg [Internet]. 2016 Feb 2 [cited 2017 May 17];11. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4736549/

334. Hasan SU, Rigaux A. Effect of bilateral vagotomy on oxygenation, arousal, and breathing movements in fetal sheep. J Appl Physiol Bethesda Md 1985. 1992 Oct;73(4):1402–12.

335. Davies A, Jones H. The Influence of Vagotomy on the Respiratory Effects of Injected Phenyl Diguanide in Anaesthetized Rabbits. Q J Exp Physiol. 1986 Oct 10;71(4):649–56.

336. Takaishi S, Isono K, Nishibayashi Y, Tanaka Y, Morikawa T, Masuda A, et al. Effect of unilateral pulmonary vagotomy on respiratory control in man. Respir Int Rev Thorac Dis. 1990;57(5):293–8.

337. Wang ZJ, Reddy GP, Gotway MB, Higgins CB, Jablons DM, Ramaswamy M, et al. Malignant pleural mesothelioma: evaluation with CT, MR imaging, and PET. Radiogr Rev Publ Radiol Soc N Am Inc. 2004 Feb;24(1):105–19.

338. Toshima M, Ohtani Y, Ohtani O. Three-dimensional architecture of elastin and collagen fiber networks in the human and rat lung. Arch Histol Cytol. 2004 Mar;67(1):31–40.

339. Kang D, Kunugi S, Masuda Y, Ishizaki M, Koizumi K, Fukuda Y. Ultrastructural and immunohistochemical analysis of fibrous long-spacing collagen fibrils in malignant mesothelioma. Ultrastruct Pathol. 2009 Apr;33(2):52–60.

340. Kataoka H, Wikström B, Klominek J, Gay RE, Gay S, Hjerpe A. Immunocytochemical demonstration of collagen types I and IV in cells isolated from malignant mesothelioma and in lung cancer cell lines. Lung Cancer. 1990 May 1;6(1):16–27.

341. Lodish H, Berk A, Zipursky SL, Matsudaira P, Baltimore D, Darnell J. Collagen: The Fibrous Proteins of the Matrix. In: Molecular Cell Biology [Internet]. 4th Edition. 2000 [cited 2019 Jun 25]. p. Section 22.3. Available from: https://www.ncbi.nlm.nih.gov/books/NBK21582/

342. Peacock A, Gourlay A, Denison D. Optical measurement of the change in trunk volume with breathing. Bull Eur Physiopathol Respir. 1985 Apr;21(2):125–9.

343. Hmeidi H, Motamedi-Fakhr S, Chadwick E, Gilchrist FJ, Lenney W, Iles R, et al. Tidal breathing parameters measured using structured light plethysmography in healthy children and those with asthma before and after bronchodilator. Physiol Rep. 2017 Mar;5(5).

344. Motamedi-Fakhr S, Wilson RC, Iles R. Tidal breathing patterns derived from structured light plethysmography in COPD patients compared with healthy subjects. Med Devices Auckl NZ. 2016 Dec 29;10:1–9.

345. Elshafie G, Naidu B. The use of structured light plethysmography in assessing the outcome of lung reduction. J Cardiothorac Surg. 2015 Dec 16;10(Suppl 1):A359.

346. Elshafie G, Kumar P, Motamedi-Fakhr S, Iles R, Wilson RC, Naidu B. Measuring changes in chest wall motion after lung resection using structured light plethysmography: a feasibility study. Interact Cardiovasc Thorac Surg. 2016 Oct;23(4):544–7.

347. Ghezzi M, Tenero L, Piazza M, Bodini A, Piacentini G. Structured Light Plethysmography (SLP): Management and follow up of a paediatric patient with pneumonia. Respir Med Case Rep. 2017 Jun 7;22:67–9.

348. Stockley J, O'Reilly L, Cooper B. Assessment of ventilatory mechanics in respiratory muscle weakness using structured light plethysmography. Eur Respir J. 2018 Sep 15;52(suppl 62):PA2416.

349. Brims FJH, Meniawy TM, Duffus I, de Fonseka D, Segal A, Creaney J, et al. A Novel Clinical Prediction Model for Prognosis in Malignant Pleural Mesothelioma Using Decision Tree Analysis. J Thorac Oncol Off Publ Int Assoc Study Lung Cancer. 2016 Apr;11(4):573–82.

350. Wilson Van Voorhis CR, Morgan BL. Understanding Power and Rules of Thumb for Determining Sample Sizes. Tutor Quant Methods Psychol. 2007 Sep 1;3(2):43–50.

351. Crawford F, Andras A, Welch K, Sheares K, Keeling D, Chappell FM. D-dimer test for excluding the diagnosis of pulmonary embolism. Cochrane Database Syst Rev. 2016 Aug 5;2016(8).

352. Glober N, Tainter CR, Brennan J, Darocki M, Klingfus M, Choi M, et al. Use of the d-dimer for Detecting Pulmonary Embolism in the Emergency Department. J Emerg Med. 2018;54(5):585–92.

353. Oswald NK, Robertson A, Rajesh P, Steyn R, Bishay E, Kalkat M, et al. P10 Light may be used to differentiate mesothelioma from benign pleural disease at the bedside. Thorax. 2016 Dec 1;71(Suppl 3):A88–A88.

354. Harte JM, Golby CK, Acosta J, Nash EF, Kiraci E, Williams MA, et al. Chest wall motion analysis in healthy volunteers and adults with cystic fibrosis using a novel Kinect-based motion tracking system. Med Biol Eng Comput. 2016 Nov;54(11):1631–40.

355. Phillips N, Rodger A, Hale B, Brown S, Mance J, Kerr B, et al. Sienkiewicz (Administratrix of the Estate of Enid Costello Deceased) (Respondent) v Greif (UK) Limited (Appellant) [Internet]. 2011. Available from: https://www.supremecourt.uk/cases/docs/uksc-2009-0219-judgment.pdf

356. Corcoran JP, Psallidas I, Wrightson JM, Hallifax RJ, Rahman NM. Pleural procedural complications: prevention and management. J Thorac Dis. 2015 Jun;7(6):1058–67.

357. Beyea A, Winzelberg G, Stafford RE. To Drain or Not to Drain: An Evidence-Based Approach to Palliative Procedures for the Management of Malignant Pleural Effusions. J Pain Symptom Manage. 2012 Aug;44(2):301–6.

358. Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, et al. Long-Term Follow-Up of Patients Receiving Lung-Volume-Reduction Surgery Versus Medical Therapy for Severe Emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg. 2006 Aug 1;82(2):431-443.e19.

359. Sciurba FC, Rogers RM, Keenan RJ, Slivka WA, Gorcsan J, Ferson PF, et al. Improvement in Pulmonary Function and Elastic Recoil after Lung-Reduction Surgery for Diffuse Emphysema. N Engl J Med. 1996;334:1095–9.

360. Henderson AC, Ingenito EP, Salcedo ES, Moy ML, Reilly JJ, Lutchen KR. Dynamic lung mechanics in late-stage emphysema before and after lung volume reduction surgery. Respir Physiol Neurobiol. 2007 Mar 15;155(3):234–42.

361. Low S-W, Lee JZ, Desai H, Hsu C-H, Sam AR, Knepler JL. Endobronchial Valves Therapy for Advanced Emphysema: A Meta-Analysis of Randomized Trials. J Bronchol Interv Pulmonol. 2019 Apr;26(2):81–9.

362. Buttery S. CELEB: Lung volume reduction in COPD - surgery vs endobronchial valves, ISRCTN19684749 [Internet]. ISRCTN registry. 2016 [cited 2019 Jul 6]. Available from: https://www.isrctn.com/ISRCTN19684749

363. Sciurba FC, Criner GJ, Strange C, Shah PL, Michaud G, Connolly TA, et al. Effect of Endobronchial Coils vs Usual Care on Exercise Tolerance in Patients With Severe

Emphysema: The RENEW Randomized Clinical Trial. JAMA. 2016 May 24;315(20):2178–89.

364. Shah PL, Zoumot Z, Singh S, Bicknell SR, Ross ET, Quiring J, et al. Endobronchial coils for the treatment of severe emphysema with hyperinflation (RESET): a randomised controlled trial. Lancet Respir Med. 2013 May;1(3):233–40.

365. Deslée G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, et al. Lung Volume Reduction Coil Treatment vs Usual Care in Patients With Severe Emphysema: The REVOLENS Randomized Clinical Trial. JAMA. 2016 Jan 12;315(2):175–84.

366. Martinez FJ, de Oca MM, Whyte RI, Stetz J, Gay SE, Celli BR. Lung-volume reduction improves dyspnea, dynamic hyperinflation, and respiratory muscle function. Am J Respir Crit Care Med. 1997 Jun;155(6):1984–90.

367. Lammi MR, Marchetti N, Criner GJ. Reduced dynamic hyperinflation after LVRS is associated with improved exercise tolerance. Respir Med. 2014 Oct;108(10):1491–7.

368. Hopkinson NS, Toma TP, Hansell DM, Goldstraw P, Moxham J, Geddes DM, et al. Effect of bronchoscopic lung volume reduction on dynamic hyperinflation and exercise in emphysema. Am J Respir Crit Care Med. 2005 Mar 1;171(5):453–60.

369. McClaran SR, Babcock MA, Pegelow DF, Reddan WG, Dempsey JA. Longitudinal effects of aging on lung function at rest and exercise in healthy active fit elderly adults. J Appl Physiol Bethesda Md 1985. 1995 May;78(5):1957–68.

370. Vogiatzis I, Aliverti A, Golemati S, Georgiadou O, Lomauro A, Kosmas E, et al. Respiratory kinematics by optoelectronic plethysmography during exercise in men and women. Eur J Appl Physiol. 2005 Mar;93(5–6):581–7.

371. Aliverti A, Stevenson N, Dellacà RL, Mauro AL, Pedotti A, Calverley PMA. Regional chest wall volumes during exercise in chronic obstructive pulmonary disease. Thorax. 2004 Mar 1;59(3):210–6.

372. Vogiatzis I, Georgiadou O, Golemati S, Aliverti A, Kosmas E, Kastanakis E, et al. Patterns of dynamic hyperinflation during exercise and recovery in patients with severe chronic obstructive pulmonary disease. Thorax. 2005 Jan 9;60(9):723–9.

373. Zoumot Z, LoMauro A, Aliverti A, Nelson C, Ward S, Jordan S, et al. LUng volume reduction in emphysema improves chest wall asynchrony. Chest. 2015 Jul 1;148(1):185–95.

374. Massaroni C, Schena E, Saccomandi P, Morrone M, Sterzi S, Silvestri S. Evaluation of optoelectronic Plethysmography accuracy and precision in recording displacements during quiet breathing simulation. Conf Proc Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf. 2015;2015:1291–4.

375. Dellacà RL, Aliverti A, Pelosi P, Carlesso E, Chiumello D, Pedotti A, et al. Estimation of end-expiratory lung volume variations by optoelectronic plethysmography. Crit Care Med. 2001 Sep;29(9):1807–11.

376. Vieira DSR, Hoffman M, Pereira DAG, Britto RR, Parreira VF. Optoelectronic plethysmography: Intra-rater and inter-rater reliability in healthy subjects. Respir Physiol Neurobiol. 2013 Dec 1;189(3):473–6.

377. Jones PW, Beeh KM, Chapman KR, Decramer M, Mahler DA, Wedzicha JA. Minimal clinically important differences in pharmacological trials. Am J Respir Crit Care Med. 2014 Feb 1;189(3):250–5.

378. Lydersen S, Pradhan V, Senchaudhuri P, Laake P. Choice of test for association in small sample unordered r x c tables. Stat Med. 2007 Oct 15;26(23):4328–43.

379. Fermi E, Aliverti A. Optoelectronic plethysmography compendium marker set up - a handbook about marker positioning on subjects in standing and supine positions. BTS S.p.a, Rev 3.0, pages 2-20;

380. O'Donnell DE, Hamilton AL, Webb KA. Sensory-mechanical relationships during high-intensity, constant-work-rate exercise in COPD. J Appl Physiol. 2006 Oct 1;101(4):1025–35.

381. Guenette JA, Webb KA, O'Donnell DE. Does dynamic hyperinflation contribute to dyspnoea during exercise in patients with COPD? Eur Respir J. 2012 Aug;40(2):322–9.

382. O'Donnell DE, Revill SM, Webb KA. Dynamic hyperinflation and exercise intolerance in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001 Sep 1;164(5):770–7.

383. Similowski T, Yan S, Gauthier AP, Macklem PT, Bellemare F. Contractile properties of the human diaphragm during chronic hyperinflation. N Engl J Med. 1991 Sep 26;325(13):917–23.

384. Pellegrino R, Villosio C, Milanese U, Garelli G, Rodarte JR, Brusasco V. Breathing during exercise in subjects with mild-to-moderate airflow obstruction: effects of physical training. J Appl Physiol Bethesda Md 1985. 1999 Nov;87(5):1697–704.

385. Criner RN, Yu D, Jacobs MR, Criner GJ. Effect of Lung Volume Reduction Surgery on Respiratory Muscle Strength in Advanced Emphysema. Chronic Obstr Pulm Dis Miami Fla. 2018 Oct 12;6(1):40–50.

386. Makris D, Leroy S, Pradelli J, Benzaquen J, Guenard H, Perotin J-M, et al. Changes in dynamic lung mechanics after lung volume reduction coil treatment of severe emphysema. Thorax. 2018 Jun 1;73(6):584–6.

387. Kim NS, Seo JH, Ko MH, Park SH, Kang SW, Won YH. Respiratory Muscle Strength in Patients With Chronic Obstructive Pulmonary Disease. Ann Rehabil Med. 2017 Aug;41(4):659–66.

388. Burrill S. Anesthesiology and Respiratory Therapy Devices Panel transcript [Internet]. United States of America Department of Health and Human Services Food and Drug Administration; 2018. Available from: https://www.fda.gov/media/114418/download

389. Rawat S, Meena S. Publish or perish: Where are we heading? J Res Med Sci Off J Isfahan Univ Med Sci. 2014 Feb;19(2):87–9.

390. Darzi A. Healthcare for London: a framework for action, 2nd edition. NHS London; 2007.

391. Darzi A. The Lord Darzi review of health and care - interim report. Inst Public Policy Res. 2018;64.

392. Schwartz RM, Gorbenko K, Kerath SM, Flores R, Ross S, Taylor TN, et al. Thoracic surgeon and patient focus groups on decision-making in early-stage lung cancer surgery. Future Oncol. 2018 Jan;14(2):151–63.

393. Oswald N, Hardman J, Kerr A, Bishay E, Steyn R, Rajesh P, et al. Patients want more information after surgery: a prospective audit of satisfaction with perioperative information in lung cancer surgery. J Cardiothorac Surg. 2018 Feb 1;13(1):18.

394. Looijmans M, van Manen AS, Traa MJ, Kloover JS, Kessels BLJ, de Vries J. Psychosocial consequences of diagnosis and treatment of lung cancer and evaluation of the need for a lung cancer specific instrument using focus group methodology. Support Care Cancer. 2018 Dec 1;26(12):4177–85.

395. Park S, Kang CH, Hwang Y, Seong YW, Lee HJ, Park IK, et al. Risk factors for postoperative anxiety and depression after surgical treatment for lung cancer. Eur J Cardiothorac Surg. 2016 Jan 1;49(1):e16–21.

396. Rose S, Paul C, Boyes A, Kelly B, Roach D. Stigma-related experiences in non-communicable respiratory diseases: A systematic review. Chron Respir Dis. 2017 Aug;14(3):199–216.

397. 21 finalists named for European Health Catapult competition [Internet]. European Institute of Innovation & Technology (EIT). 2017 [cited 2020 Jul 18]. Available from: https://eit.europa.eu/news-events/news/21-finalists-named-european-health-catapult-competition

398. Understanding differences in startup financing stages [Internet]. Startupxplore Blog. 2014 [cited 2020 Jul 24]. Available from: https://startupxplore.com/en/blog/types-startup-investing/

399. Donet V. RePneu European Registry Protocol SNCTP 000000917 [Internet]. Kofam Studienregister. 2017 [cited 2020 Jul 24]. Available from: https://www.kofam.ch/it/portale-snctp/studio/116/

400. TeraRecon. TeraRecon | Medical Image Viewing Solutions [Internet]. [cited 2020 Jul 24]. Available from: https://www.terarecon.com/?locale=en

APPENDICES

Appendix 1: PROBAST Tool

Indicator questions rated: Yes, probably yes, probably no, no or no information Y, PY, PN, N, NI. Next risk of bias and concerns about applicability are scored.

Type of evaluation	
Model development without testing in other individuals (internal or no validation) =dev Model development with testing in other individuals (external validation) = dev & val Testing an existing model in other individuals = val	
Participant selection	
Were appropriate data sources used? (Cohort study)	
Were inclusions and exclusions clearly defined and appropriate? Inclusion criteria should be kept wide to keep the model applicable to all surgical candidates coming through clinic. Exclusions should not be common in patient with lung cancer (eg. COPD, chest infections, common comorbidities). Exclusions should not be related to postoperative information (such as perioperative death, findings during surgery, perioperative complications).	
Were patients enrolled in similar states of health or was lung function the main factor that varied?	
Risk of bias by patient selection (high, unclear, low)	
Concern that patients and setting do not match review question (high, unclear low)	
Predictors	
Were predictors defined and assessed in a similar way for all patients? Spirometry should be performed post bronchodilator by ATS guidelines	
Were predictors defined and assessed in a similar way to those in the development model? (val only)	
Were predictors assessed without knowledge of the outcome data?	
Are all predictors available preoperatively?	
Were all relevant predictors analysed?	

Risk of bias by predictors and their assessment (high, unclear, low)	
Concern that definition, assessment or timing of assessment of predictors do not match review question (high, unclear, low)	
Outcome	
Was a pre-specified outcome definition used? Should be FEV1, FVC and /or gas transfer	
Was the outcome defined and determined in a similar way for all patients?	
Was the outcome defined and determined in a similar way to the development model? (val only)	
Was the outcome determined without knowledge of predictor information?	
Risk of bias by outcome or determination (high, unclear, low)	
Was the outcome measured at an appropriate timepoint? Lung function recovers rapidly up to 3 months and declines after 12 months, postop assessment should be 3-12 months	
Concern outcome does not match review question (high, unclear, low)	

Sample size and flow	
Were there a reasonable number of patients? <8 classed as case series and excluded from review.	
Were all recruited patients included in the analysis?	
Were missing data and excluded patients described?	
Risk of bias by sample size and flow (high, unclear, low)	
Analysis (if multivariable model development used refer to page 8 of original PROBAST document)	
Is the formula for predicting postop lung function clearly stated/referenced?	
Were non-functional segments defined and the definition appropriate?	
Were lobes delineated in an accurate and reproducible fashion?	
Were data assessed for normality and handled appropriately if non-normal?	

Mean differences should be checked for normality	
Was the model assessed correctly with statistical measures of agreement? Studies should include mean difference with a measure of uncertainty (95%CI, SD or similar) either reported as numbers or Bland Altmann charts. Bland Altman charts should plot the difference between actual and predicted postop lung function on the y-axis and actual postop lung function on the x-axis. Studies should not just report correlation or T tests.	
Risk of bias by analysis (high, unclear, low)	
Overall risk of bias of model evaluation	
Any high risk, or model has not had external validation = high risk. Any unclear risk but no high risk = unclear. All low risk = low risk.	
Overall applicability of model evaluation	
Any high concern = high. Any unclear concern but no high concern = unclear. All low concern = low.	
Overall usability of model	
Is the model presented with sufficient detail to be used in the intended context and patient population? (Y/N)	

Appendix 2: CURVE study patient information sheet

CURVE Patient Information Sheet Version 3 28.09.2016

An invitation to take part in research

CT assessment of Regional Ventilation of the lung (CURVE)

You are being invited to take part in a clinical research study. Before you decide whether or not you wish to take part, you should read the information provided below carefully. You may wish to discuss it with your family, friends or GP. Please take time to ask questions about the study. You are not obliged to take part and refusal to participate will have no effect on your medical care. You should clearly understand the risks and benefits of taking part so that you can make a decision that is right for you.

Why have I been chosen?

You have been chosen because you are being assessed for a lung condition. We are following patients with lung conditions and studying how the function of individual parts of the lung relates to patient symptoms of breathlessness. We are also studying how the function of individual parts of the lung can help us plan treatments (including surgery) or diagnose lung conditions.

What is the purpose of the study?

Breathing tests can give us information about the overall function of the lungs. However, detailed information about the function of individual parts of the lung is difficult to gather. This type of information may be very helpful in managing your lung condition. Researchers have worked out how to calculate the function of specific areas of the lung using the same kind of CT scan that is used in routine assessment of lung conditions.

What will happen to me if I take part?

This study requires 2 CT scans of your chest, one with you breathing in and one with you breathing out. If you already have an appointment for a CT scan you will have 1 additional scan at the same appointment. If you do not have an appointment to have a CT scan, we will book you in for 2 CT scans at one appointment. If you have already had a suitable scan this will be used instead.

During your visit to hospital we will ask you to complete a short questionnaire about your breathing. Everyone being assessed for lung diseases has routine breathing tests (spirometry and gas transfer). We will use these as part of the study data. You will be asked to repeat the routine breathing tests and questionnaire after 3-6 months. No injections or blood tests are required for the study.

What are the possible benefits of taking part in the study?

Taking part in this study means that you may help suffers of lung disease in the future. We do not expect any immediate benefits for you. If anything unusual or important were found on your scan as part of this research we would tell your Consultants team as soon as we found it.

What are the possible disadvantages and risks of taking part?

Taking extra time for the study may be inconvenient for you. CT scans involve exposure to radiation. Radiation is all around us in the natural environment. The additional radiation dose you would experience from 2 additional CT scans for taking part in this study is equivalent to about 5 years of natural background radiation. There is an increase in the risk of developing cancer many years after radiation exposure. The risk of a fatal cancer from 2 additional CT scans is about 2 in 40,000. If you only require 1 extra CT scan the risk is about 1 in 40,000. These risks are very small compared with the 1000 in 40,000 natural lifetime risk of fatal cancer.

What will happen with the results of the study?

The data will be published in medical journals and presented at academic meetings. No individual will be identified in any publication. Anonymised data may be shared with collaborating researchers within the EU in ethically approved studies.

Will my taking part in this study be kept confidential?

Yes. Your data will be stored both in paper and computerised form. It will be treated confidentially in accordance with the Data Protection Act. Regulatory authorities may wish to check that this research has been done properly, they may have access to your files and know your identity, but they are under a duty of confidentiality not to disclose details to others. With your permission we will notify your GP that you are participating in research.

Do I have to take part?

No, it is your choice. If you do decide to take part you will be asked to sign a consent form before going ahead. If you decide to take part you are still free to withdraw at any time and without giving a reason. Not taking part in this research, or deciding to withdraw from the study will not affect your medical care or legal rights in any way. If you decide not to take part, we would like to ask you to fill in a slip about how you made your decision, this is also voluntary. Your answers will be anonymous and confidential.

Can I withdraw from the study?

Yes, you may withdraw from the study at any time. If you withdraw before your data is used, we will remove your data from the study. If you withdraw after your data has been analysed we cannot change the overall results of the research.

What if there is a problem?

We do not foresee any significant risk of any harm as a result of participating in this study. If you are harmed due to someone's negligence, then you may have grounds for a legal action. If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms are available to you. Please contact the Patient Services Department.

Who is funding and organising this study?

The study is being funded by the British Lung Foundation and Sponsored by Heart of England NHS Foundation Trust. The Research Ethics Committee has reviewed and approved the study.

Patient Services Department

Telephone: 0121 424 0808

Email: patientservices@heartofengland.nhs.uk

For further information about the study please contact:

Chief Investigator: Mr Babu Naidu, MBBS MMedSci FRCS C-Th MD

Study manager: Ms Nicola Oswald, MBChB MRCS

Address:

MIDRU, Birmingham Heartlands Hospital, Bordesley Green East, Birmingham, B9 5SS

Telephone: 0121 424 1895

Appendix 3: CURVE study consent form

CURVE Consent formVersion 2.0 28.09.2016

Consent Form Study Title: CT assessment of Regional Ventilation of the lung (CURVE)

	Initials
1. I confirm that I have read and understood the patient information form Version 3 on the above project and have been given a copy to keep. I have had the opportunity to ask questions about the project and understand why the research is being done and any foreseeable risks involved.	
2. I agree to complete the tests in the above project which together with my existing data and scans may also be used in other ethically approved research by academic partners or industrial collaborators within the EU. In all instances my data will be anonymised.	
3. I understand participation is voluntary. I am free to withdraw from the study at any time without giving any reason and without my medical treatment or legal rights being affected.	
4. I understand that relevant sections of my medical notes and/or study data may be looked at by responsible individuals from the study team, the sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to access my records. I also give permission for my medical records to be looked at and information taken from them to be treated in strict confidence by responsible people from Heart of England NHS Foundation Trust.	
5. I understand that my GP will be informed if any of the results of the tests done as part of the research are important for my health.	
6. I understand that I will not benefit financially if this research leads to a new treatment or medical test.	
7. I know where to contact Mr Naidu, if I need further information.	
8. I agree to take part in this study.	

Signed:……..Date:……

Name (Block capitals) ……

I, (Name of investigator, block letters) ……have explained the nature and purpose of the study to ……..and believe that he/she understands what the study involves.

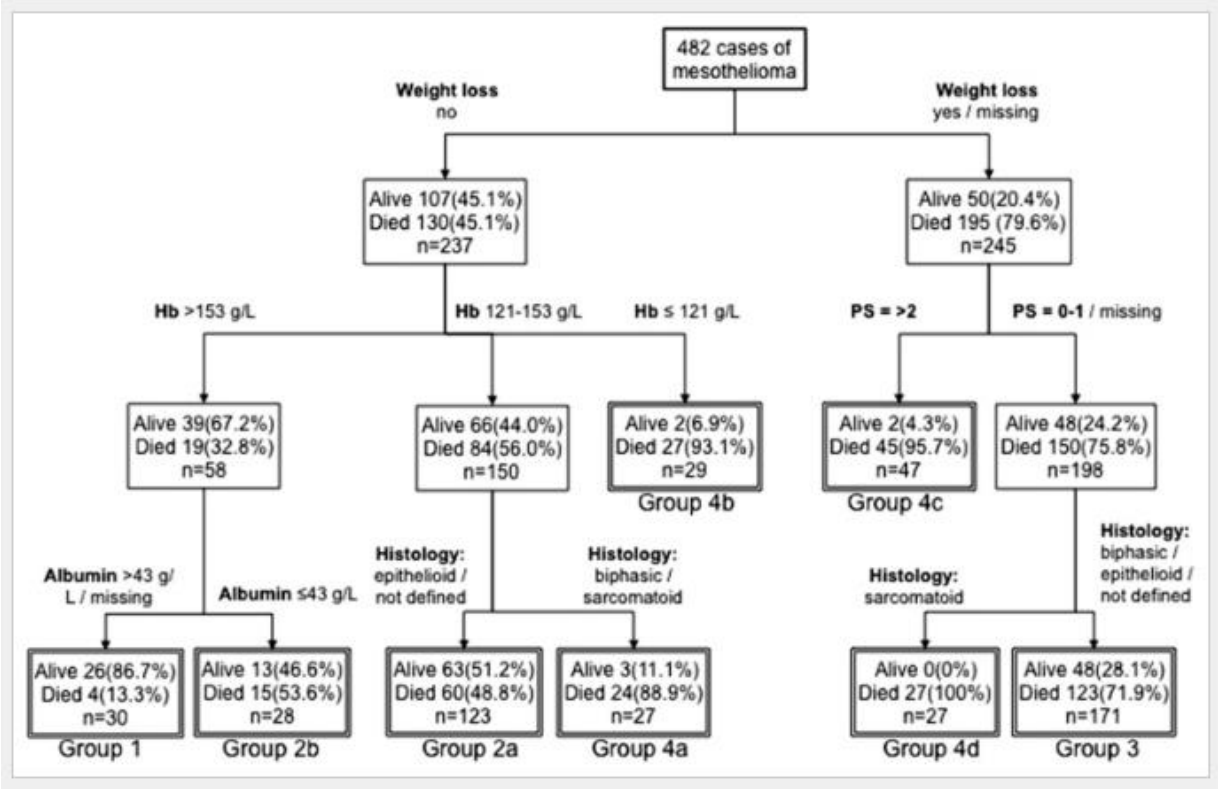
Signed: …….. Date:……..

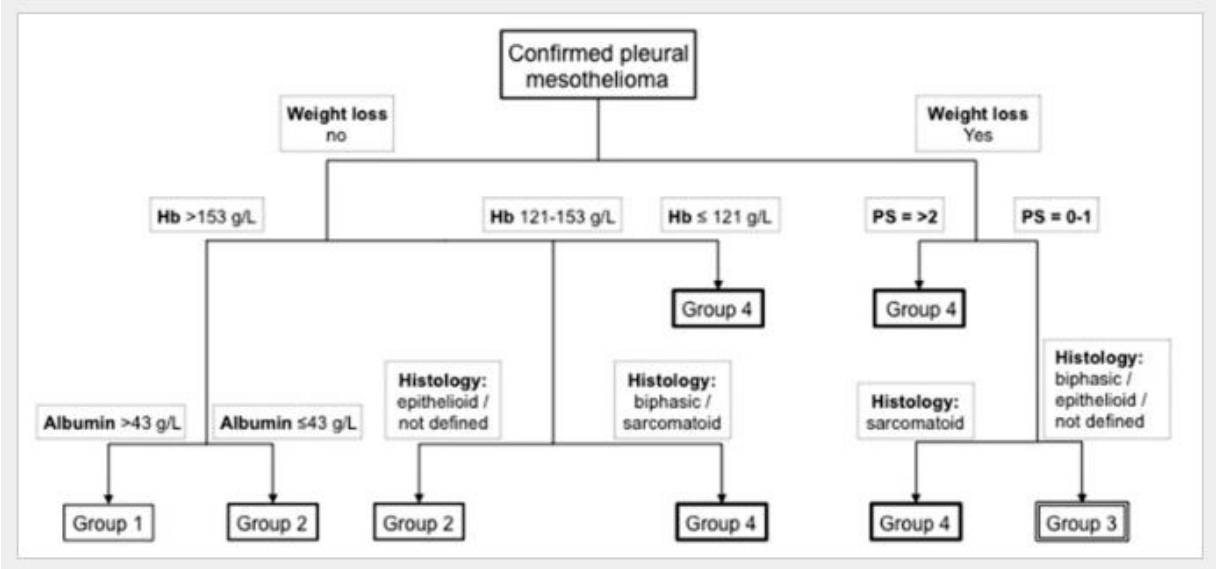
Appendix 4: ILD-GAP prognostic scoring system [305]

	Predictor	Points
ILD	ILD subtype	
	IPF	0
	Unclassifiable ILD	0
	CT-ILD/idiopathic NSIP	-2
	Chronic HP	-2
G	Gender	
	Female	0
	Male	1
A	Age, yr	
	≤ 60	0
	61-65	1
	> 65	2
P	Physiology	
	FVC, % predicted	
	> 75%	0
	50-75%	1
	<50%	2
	DLCO, % predicted	
	> 55%	0
	36-55%	1
	≤ 35%	2
	Cannot perform	3
	Total possible points	**8**

	Predicted mortality		
ILD-GAP Index	**1-year**	**2-year**	**3-year**
0-1	3.1	6.6	10.2
2-3	8.8	18.0	26.9
4-5	18.2	35.0	49.2
>5	33.5	58.4	74.8

Appendix 5: Brims decision trees [349]





Appendix 6: R markdown code for statistical analyses of diagnosis of pleural disease using SLP

```
# Univariable testing.
# Set up with variables in .csv file, age being used as example variable
library("ggpubr")
library("rcompanion")
library("ggplot2")
library("car")
library("psych")
SLP4R<-read.csv(file="SLP4R.csv")
#Formal testing, null=normally distributed, Shapiro Wilk test and density #plots visual inspection, repeat for each variable
ggdensity(SLP4R$age,
main="Density plot of patient age",
xlab="Age")
shapiro.test(SLP4R$age)
# Mann Whitney U test for non-parametric or t test for parametric
wilcox.test(SLP4R$age~SLP4R$meso)
t.test(SLP4R$age~SLP4R$meso)
#Calculate median and interquartile ranges or mean and standard #deviations by group (mesothelioma or non-mesothelioma)
tapply(SLP4R$age,SLP4R$meso,summary)
tapply(SLP4R$age,SLP4R$meso,mean)
tapply(SLP4R$age,SLP4R$meso,sd)
# Testing model assumptions
# Set up with desired variables in .csv file
SLPmodel<-read.csv(file="SLPmodelA.csv")
library("mlbench")
library("car")
library("tidyverse")
library("broom")
# Linearity with the logit
```

```
# Tested with inspection of scatter plots. First load data, then fit the model, #then predict probabilities to plot against the logit
model<-glm(meso~., data=SLPmodel,family=binomial)
probabilities<-predict(model,type="response")
predicted.classes<-ifelse(probabilities>0.5,"pos","neg")
head(predicted.classes)
numericSLP<-SLPmodel %>%
  dplyr::select_if(is.numeric)
predictors<-colnames(numericSLP)
mydata<-numericSLP%>%
  mutate(logit=log(probabilities/(1-probabilities))) %>%
  gather(key="predictors",value="predictor.value",-logit)
ggplot(mydata,aes(logit,predictor.value))+
  geom_point(size=0.5,alpha=0.5)+
  geom_smooth(method="loess")+
  theme_bw()+
  facet_wrap(~predictors, scales = "free_y")
#Identify outliers
boxplot(SLP4R$age,data=SLP4R,main="Age", xlab="", ylab="contribution")
#Testing assumption of no influential variables by plotting the #standardised residuals and then filter to only those greater than 3
model.data<-augment(model)%>%
mutate(index=1:n())
ggplot(model.data,aes(index,.std.resid))+
  geom_point(aes(colour=meso),alpha=.5)+
  theme_bw()
model.data %>%
  filter(abs(.std.resid) > 3)
#Testing for multicollinearity
car::vif(model)
# Binary logistic regression analysis
#Set up
library("InformationValue")
#Create and assess model
```

```
LogitMod<-glm(meso ~ SLP4R$IE50IQR + SLP4R$age +SLP4R$disease , data=SLP4R,
family=binomial(link="logit"))
predicted<- plogis(predict(LogitMod,SLP4R))
optCutOff <- optimalCutoff (SLP4R$meso,predicted)[1]
summary(LogitMod)
confint(LogitMod)
exp(cbind(OR=coef(LogitMod), confint(LogitMod)))
with(LogitMod,null.deviance-deviance)
with(LogitMod,df.null-df.residual)
with(LogitMod,pchisq(null.deviance-deviance,df.null-df.residual,lower.tail=FALSE))
#Produce ROC curve with analyses
plotROC(SLP4R$meso,predicted)
#Calculate sensitivity, specificity, PPV and NPV
sensitivity(SLP4R$meso,predicted)
specificity(SLP4R$meso,predicted)
sens<-sensitivity(SLP4R$meso,predicted)
spec<-specificity(SLP4R$meso,predicted)prev<-33/82
PPV<-sens*prev/((sens*prev)+(1-spec)*(1-prev))
NPV<-(spec*(1-prev))/((1-sens)*prev+spec*(1-prev))
```

Appendix 7: R markdown code for statistical analyses of survival in mesothelioma using SLP

```
# Set up
library(tidyverse)
library(survival)
library(survminer)
library(dplyr)
SLPsurvival<-read.csv(file="survivalnomissing.csv")
#Create binary variable from continuous variable by dividing data at the #median
Affected_Contribution_Binary<-
ifelse(Affected_Contribution<median(Transformed_Affected_Contribution),1,0)
#Kaplan Meier curve
surv_object<-Surv(time=SLPsurvival$futime, event=SLPsurvival$death)
KMfit<-survfit(surv_object~SLPsurvival$Brims_Binary, data=SLPsurvival)
ggsurvplot(KMfit,data=SLPsurvival,pval=TRUE)
#Cox proportional hazard ratio analysis
#Fit analysis and produce forest plots
fit.coxph<-
coxph(surv_object~SLPsurvival$Brims_Binary+SLPsurvival$Affected_Contribution,data
=SLPsurvival)
ggforest(fit.coxph, data=SLPsurvival)
cox<-
coxph(formula=Surv(futime,death)~SLPsurvival$Brims_Binary+SLPsurvival$Affected_C
ontribution, data=SLPsurvival)
#Test proportional hazards statistically and graphically
test.ph<-cox.zph(allcox)
ggcoxzph(test.ph)
#Test for influential variables
ggcoxdiagnostics(fit.coxph, type="deviance",linear.predictions=FALSE,
ggtheme=theme_bw())
#Test for linearity
ggcoxfunctional(fit.coxph, data=SLPsurvival)
#Transform data to meet linearity assumption
Transformed_Affected_Contribution<-(SLPsurvival$Affected_Contribution-0.425)^2
```