Robotic Techniques in Thoracic Surgery

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Master in Philosophy by Sabrina L Mason.

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Acknowledgements

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Abstract

Title: Robotic techniques in thoracic surgery

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Background: Minimally invasive techniques for thoracic surgery are safe and result in fewer complications compared with traditional open surgery. There may be advantages in adopting robotic thoracic surgery compared to video-assisted thoracoscopic surgery (VATS). Despite the surge in robotic thoracic surgery in the UK, good quality evidence is needed to substantiate the associated high capital costs and service fees.

Aims: To assess the impact of introducing a robotic thoracic surgery programme at Liverpool Heart and Chest Hospital (LHCH) and determine the clinical benefit and cost associated with robotic surgery for lung cancer resection; as well as mediastinal mass resection and lung volume reduction surgery (LVRS), compared to the more commonly used surgical approaches (open and VATS). This research reports on LHCH preparations for the COLT trial; a multicentre prospective cohort study comparing robotic, VATS and open techniques for lobectomy for early-stage lung cancer. The COLT pilot addresses potential issues concerning data collection and provides recommendations for the main COLT trial.

Methods: Three retrospective studies were undertaken to compare surgical approaches for lung cancer resection mediastinal mass resection and LVRS. The COLT pilot study was conducted prospectively for 2 months prior to being cut short by COVID-19.

Results: 90 lobectomy cases were included in COLT pilot (98.1% data completeness). Rates of minimally invasive surgery for lung cancer were high (75.6%). Post-operative outcomes were similar between robotic and VATS lobectomy with small differences between VATS and open lobectomy, regarding length of stay and pain. This was the first published series on robotic LVRS. Patients undergoing robotic LVRS required less IV morphine post-operatively (13.8mg vs

58.0mg, p=0.026) and were less likely to be admitted to critical care (8.3% vs 70.8%, p=0.001), compared with VATS LVRS. Robotic LVRS was marginally cheaper than VATS LVRS (£5421.63 vs £5695.46) due to reduced length of hospitalisation and critical care stay. Robotic LVRS had a short learning curve; operative time plateaued after 6 cases, similar to VATS LVRS. Introducing robotic mediastinal surgery resulted in significant increase in mediastinal masses being resected by a minimal invasive surgery (20% to 45%). Minimally invasive mediastinal surgery resulted in a shorter length of stay (4 vs 2 vs 2 days, open vs VATS vs robotic, p<0.0001) and less post-operative critical care admissions (88.64% v 27.59%, p <0.0001) than open surgery.

Conclusions: Retrospective analysis showed robotic lobectomies are less likely to require critical care admission. Robotic surgery may allow for an increase in rates of minimally invasive surgery, as demonstrated with robotic mediastinal surgery, which is beneficial in terms of length of stay and critical care admissions. Robotic LVRS patients had less pain and were less likely to be admitted to critical care compared to VATS LVRS. Robotic LVRS was at least as cost-effective as VATS LVRS.

List of Abbreviations

3D	Three-dimensional
a-VATS	"Assisted" video-assisted thoracoscopic surgery. Described as a 10cm mini-thoracotomy with rib spreading and the operation completed using both direct and monitor vision.
AChR	Acetylcholine receptor
AESOP	Automated Endoscopic System for Optimal Positioning
AFP	α-fetoprotein
AHRQ	Agency for Healthcare Research and Quality
AJCC	American Joint Committee on Cancer
ASA	American Society of Anaesthesiologists
β-hCG	β-human chorionic gonadotropin
BLVR	Bronchoscopic lung volume reduction
BMI	Body mass index
c-VATS	"Complete" video-assisted thoracoscopic surgery. Defined as the use of 4cm utility port, no rib spreading and 100% of the operation completed using the monitor view
CALBG	Cancer and Leukemia Group B
CI	Confidence interval
CO_2	Carbon dioxide
COLT	Cohort study comparing outcomes for different lobectomy techniques in units performing robotic thoracic surgery
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 19

CRF	Case report file
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular accident
EBUS	Endobronchial ultrasound scan
EBUS-TBNA	Endobronchial ultrasound guided transbronchial needle aspiration
EBVs	Endobronchial valves
EORTC	European Organisation for Research and Treatment of Cancer
ESTS	European Society of Thoracic Surgeons
EUS	Endoscopic ultrasound scan
FDA	United States Food and Drug Administration
FEV	Forced Expiratory Volume
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCT	Germ Cell Tumour
GP	General Practitioner
HCFA	Health Care Financing Administration
HD	High-definition
HDU	High dependency unit
HES	Hospital Episode Statistics
HRQoL	Health-related Quality of Life
IASLC	International Association of the Study of Lung Cancer
ICS	Intercostal Space

IQR	Interquartile range
ITMIG	International Thymic Malignancy Interest Group
ITU	Intensive Treatment Unit
LDH	Lactate dehydrogenase
LHCH	Liverpool Heart & Chest Hospital
LVR	Lung volume reduction
LVRS	Lung volume reduction surgery
MDT	Multi-disciplinary team
MGCT	Mediastinal germ cell tumours
MPNST	Malignant peripheral nerve sheath tumour
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
mVATS	Multiport Video-assisted Thoracoscopic Surgery
NASA	National Aeronautics and Space Administration
NETT	National Emphysema Treatment Trial
NICE	National Institute for Health and Care Excellence
NLCA	The National Lung Cancer Audit
NSAIDS	Nonsteroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
PA	Pulmonary Artery
PACS	Picture Archiving Communication System
PCA	Patient controlled analgesia
PET	Positron Emission Tomography

PET-CT	Positron Emission Tomography – Commuted Tomography
PRN	Pro Re Nata
QALY	Quality-adjusted life-year
QoL	Quality of life
RATS	Robotic Assisted Thoracic Surgery
RCT	Randomised Control Trial
ROMAN	Prospective, Randomised, Multicentric Study On Videothoracoscopic Vs Robotic Approach For Lobectomy Or Anatomical Segmentectomy in Patients Affected By Early Lung Cancer
RV	Residual Volume
SARP	Surgeon-Assistant Robot for Prostatectomy
SCLC	Small cell lung cancer
STS	The Society of Thoracic Surgeons
SVC	Superior vena cava
TIA	Transient Ischaemic Attack
TLC	Total Lung Capacity
TLCO	Transfer factor of the lung for carbon monoxide
TNM	The classification of malignant tumours – Primary tumour (T), Regional lymph nodes (N), Distant metastasis (M)
UK	United Kingdom
VATS	Video-assisted Thoracoscopic Surgery
VIOLET	VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy

VQ scan	Ventilation/perfusion scan
WCC	White cell count
WHO	World Health Organisation
WMD	Weighted Mean Difference

Chapter 1: Background

1.1 Lung cancer surgery and techniques

1.1.1 Introduction to lung cancer

Lung cancer is the most common cancer worldwide(1). Every year around 47,800 new cases of lung cancer are diagnosed in the UK(2). 1 in 13 men and 1 in 15 women born after 1960 in the UK will develop lung cancer(3). It is the second commonest cancer in women behind breast and the third commonest in men behind prostate and colorectal (4). Lung cancer is the leading cause of cancer deaths in the UK in both sexes (4). Compared with other high income European countries, age-standardised 5 year net survival rates were markedly lower in the UK from 1995-2014(5).

The incidence of lung cancer is strongly linked to increased age. It rises steeply from the age of 50 years and peaks in those aged between 70 – 79 years. Around 60% of cases are diagnosed in patients aged 70 years and over. The median age of diagnosis for NSCLC is 73 years and 70 years for SCLC patients. Patients with carcinoid tumours tend to be younger, with a median age of 65 years at diagnosis (6)(Figure 1). With an aging population, more elderly patients are going to require treatment for lung cancer. Elderly patients often have multiple co-morbidities, therefore minimally invasive surgery maybe especially beneficial in this age group.

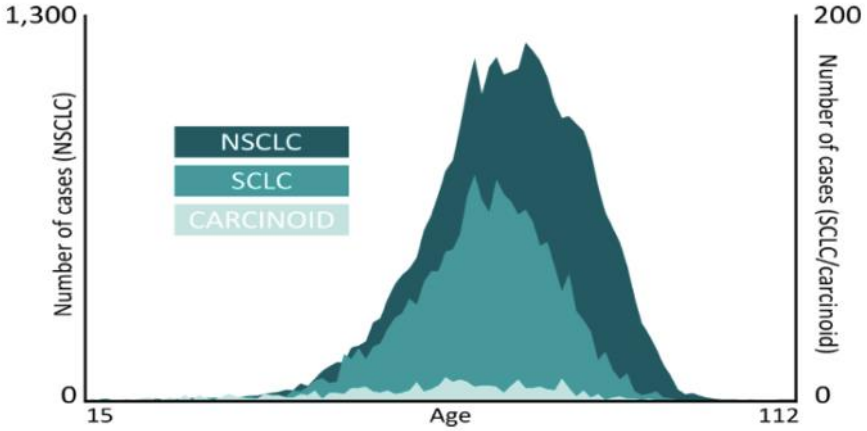

Figure 1: Age distribution of lung cancer cases by lung cancer subtype.

Source: Royal College of Physicians. National Lung Cancer Audit annual report 2016 (for audit period 2015). London: Healthcare Quality Improvement Partnership; 2017.

Lung cancer occurs more frequently in males, although the difference between males and females is closing. Over the last 10 years lung cancer rates have been decreasing in males but have increased in females(7). This change is almost certainly due to the prevalence of cigarette smoking in men peaking about two decades earlier than women(4). If diagnosed as early-stage disease, lung cancer has shown excellent clinical outcomes with high 5 year survival rates (8). Unfortunately around half of patients present with incurable stage IV disease (9) and lung cancer has one of the lowest 5-year net-survival estimates for any cancer, at less than 20% for both men and women(10)(Figure 2). Clinical trials have shown convincing evidence in the use of low dose CT screening to identify more lung cancers at an early stage and decrease mortality rates(11). Lung cancer screening has been implemented in the Unites States and recommendations have been put forward for its possible adoption in Europe (12).

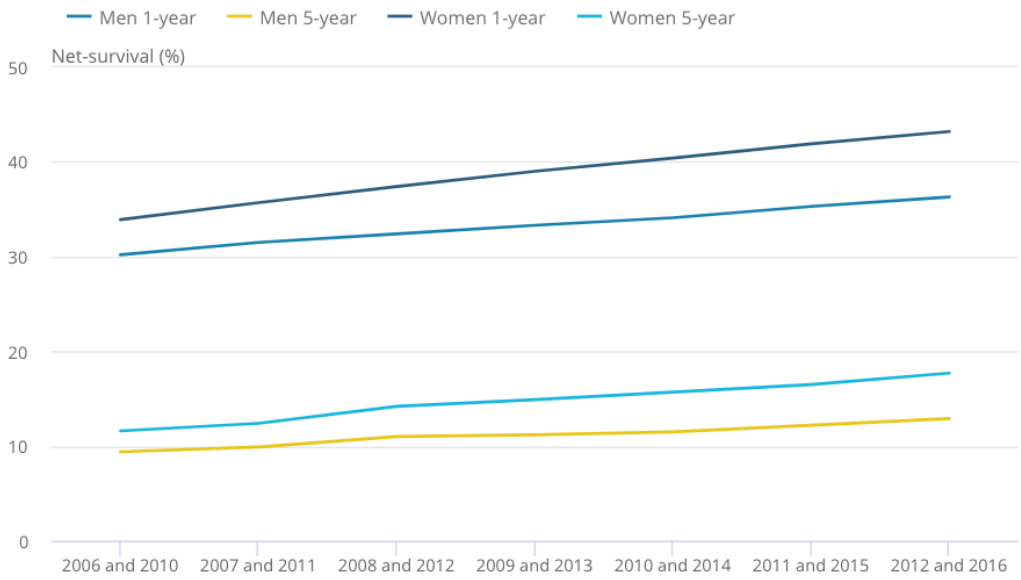

Figure 2: Age-standardised net-survival for men and women (aged 15 to 99 years) diagnosed with lung cancer (all stages combined). Rolling 5-year periods between 2006 to 2010 and 2012 to 2016, England.

Source: Office for National Statistics, Public Health England. Cancer survival in England: national estimates for patients followed up to 2017: Office for National Statistics; 2019 [cited 2020 8 March]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/nationalestimatesforpatientsfollowedupto2017#acknowledgements.

Lung cancer is also known to be associated with a greater disturbance to quality of life (QoL) than other cancers(13, 14). Lung cancer surgery can greatly affect patients' QoL. Removing a section of lung will lead to breathlessness, especially as a large proportion of patients will already have underlying lung disease. Patients may also get chronic pain from the incisions used to perform the operation. The use of minimally invasive surgery, especially robotic surgery, may reduce this.

There are two main types of lung cancer: small cell (SCLC) and non-small cell (NSCLC). NSCLC is divided into 2 main subtypes adenocarcinoma and squamous cell carcinomas(15). NSCLC makes up about 88% of all lung cancers, SCLC 11% and carcinoid tumours 1% (6). Adenocarcinoma is the most prevalent type, accounting for around 52% of NSCLC cases with confirmed subtypes (6). Squamous cell and SCLC are usually caused by smoking, with SCLC tending to be the far more

aggressive type. Whilst lung cancer is seen in never smokers, it is estimated that 72% of lung cancer cases in the UK are caused by either active smoking or environmental tobacco smoke (also called second-hand smoke)(15). Smoking cessation not only prevents a further decline in survival but an increase in life expectancy is seen in those who quit smoking at an earlier age(16).

Surgery is generally accepted as offering the best chance of cure in patients with NSCLC where a complete resection of the tumour can be achieved, there is no evidence of metastatic disease and the patient is fit enough to tolerate the operation. Prognosis without treatment is poor, carrying a mean survival time of less than a year(17). SCLC is generally treated with chemotherapy and radiotherapy for limited disease, and chemotherapy for advanced disease. NICE recommendations state that surgical resection for NSCLC, in the form of lobectomy, should be offered if curative intent is suitable, provided the patient is fit enough. Currently, no preference is indicated between open and minimally invasive techniques(18). With surgical resection offering the best chance of cure, it is vital that surgery is offered to as many patients as possible.

One of the problems is that lung cancer often remains asymptomatic until a late stage. In the UK in 2016, 74% of patients presented with Stage III or IV disease(6). Only 18.4% of patients with NSCLC in the UK underwent surgical resection in 2017 (19). Resection rates for early NSCLC (Stage I and II) are variable and range from as low as 37.5% up to 86.4%(20). Surgical rates have increased and were seen to rise by 5.4% between 2016 and 2017 (21). By increasing the early detection of lung cancer and surgical resection rates, the hope it that this will lead to higher cure rates. However, smoking also causes cardiovascular and other lung disease and therefore these patients often have multiple co-morbidities, which may affect their fitness for surgery.

1.1.2 From Open to Robotic Lobectomy

The evolution of pulmonary resection

Surgery is, at present, the treatment of choice for patients with early stage lung cancer(18). Surgical resection not only provides patients with the best chance for cure but also has the benefits of tissue diagnosis and molecular testing, lymph node evaluation and surgical upstaging, which can help guide adjuvant therapy. There is evidence of successful lung resections dating back as early as the 15th century (22), although largely in traumatic cases and later on in the treatment of tuberculosis. The first documented case of lung resection for a tumour was in 1861(22) but this was far from the modern thoracic surgery performed today and mortality rates were high(23). The ability to perform safe and effective lung resection is only possible due to the massive technological advancements made in the last century in anaesthetics, imaging technology and surgical technique. Previously, lung resection was a staged process where patients underwent multiple surgeries, each of a short duration. For example, in one operation the hilar structures would be ligated and then subsequently resected in a separate operation. This approach was necessary as the pneumothorax, which developed as a result of the chest wall incision, caused the lung to collapse down and patients quickly became hypoxic. With limited equipment and no antibiotics, surgeons also used this method to help control the build-up of respiratory secretions as well as reduce the risk of aspiration, haemorrhage and infection(24). The safety of thoracic surgery truly improved after the creation of a cuffed endotracheal tube and positive pressure ventilation in the early 1900s. Stemming from this, our modern day single lung ventilation system began to develop with the first endobronchial tube used by Gale and Waters in 1931 which allowed for isolation of one lung (Figure 3)(25). The tube was inserted into either the left or right main bronchus and when the carinal cuff was inflated it created an airtight seal for the intubated bronchus whilst occluding the other.

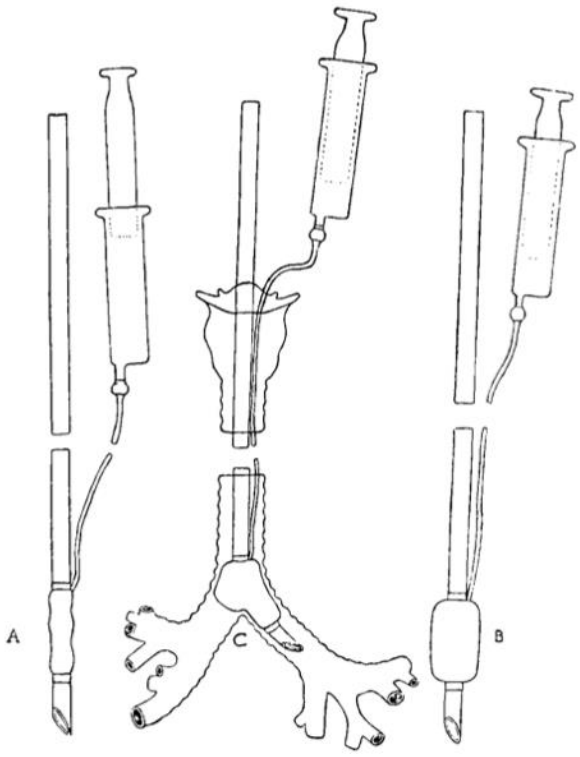

Figure 3: First endobronchial tube used by Gale and Waters in 1931. (A) Shows the catheter with surrounding rubber balloon callapsed. (B) Shows the rubber baloon inflated. (C) Shows catheter in place and balloon inflated, completely blocking bronchus on the side of operation and insuring nonleak contact of airway in the opposite bronchus.

Source: Gale JW, Waters RM. Closed Endobronchial Anesthesia in Thoracic Surgery. Anesthesia & Analgesia. 1932;11(6):283-8.

This model was developed over the years and today the Robertshaw double lumen tube is used in thoracic anaethesia (26). This double lumen tube comes in right and left sided types and one lumen is endobronchial and the other endotracheal, giving the advantage of being able to ventilate each side independently and allowing access to the non-ventilated lung. Now lung resections take place on a non-ventilated lung which provides better surgical access and the cuff protects any blood, purulent fluid or malignant cells from spilling into the contralateral lung.

These anaesthetic advancements created a less restrictive environment in which surgeons could practice. From the 1930s, thoracic surgery began to rapidly evolve, and the focus shifted towards improvements in surgical technique. For 30 years pneumonectomy was seen as the gold standard for treating lung cancer. The first successful one-stage pneumonectomy was carried out in April 1933, by Evarts

Graham(22). In 1932, following the introduction of the “hilar tourniquet” by Shenstone and Janes(24), hilar structures were ligated first before being divided. This was thought to have the advantage of preventing spillage of purulent sputum and blood into the contralateral lung. By 1940, there was an important step replacing simultaneous vessel ligation with individual hilar dissection, which prevented bleeding by establishing vascular control before dissecting the bronchus and removing the lung tissue.

Lung conservation techniques

Thoughts around the use of pneumonectomy for the treatment of lung cancer began to change in the mid 1900s, as surgeons observed high rates of mortality and morbidity. The major complications included respiratory failure, pneumonia, bronchopleural fistula, empyema and death(27).There was a move away from pneumonectomy towards lung conservation techniques. Today, lobectomy and sleeve resection are the gold standard for lung cancer resection and pneumonectomy is only indicated in large and central tumours, tumours that have invaded the lobar fissure or in the case of two distinct ipsilateral cancers(28). In 2017, lobectomy and bilobectomy accounted for 77% of lung cancer operations for NSCLC in England (Figure 4) (21).

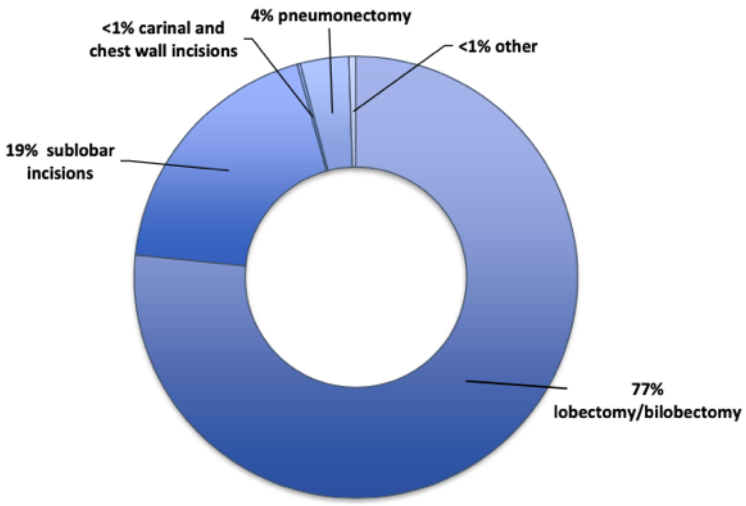

Figure 4: Lung cancer resections for NSCLC in 2017 by operation performed

Source: Royal College of Physicians, Society for Cardiothoracic Society in Great Britain and Ireland. National Lung Cancer Audit, Lung cancer clinical outcomes publication 2019 (for the 2017 audit period). London: Healthcare Quality Improvement Partnership; 2020.

Lobectomy was not a new concept. Blades and Kent described the use of individual hilar ligation for lower lobectomy in bronchiectasis patients in 1940(29). However, surgeons had previously dismissed lobectomy for the treatment of primary lung cancer, believing that this was not in line with their knowledge of pulmonary anatomy and could not possibly offer a chance for cure. Lobectomy was only performed for the treatment of lung cancer in patients whose pre-operative pulmonary function contraindicated pneumonectomy. In 1962, a case series of 518 patients treated for primary lung cancer by either pneumonectomy or lobectomy at the clinics of Dr Overholt and Dr Ochsner was released. It showed that lobectomy produced a comparable 5 year survival with pneumectomy but with fewer complications(30).

Lung conservation did not stop here, surgeons began to explore the bronchopulmonary segment as the primary unit for surgical resection for malignancy. Segmentectomy refers to the division of the lung along the anatomical borders which lie between its 19 segments. With wedge resection, however, no attempt is made to divide the individual vessels or bronchi which supply the segment, rather macroscopic clearance for tumour is performed ensuring a margin of normal lung tissue.

The role of sub lobar resection is still debated but, at present, is only indicated as an alternative to lobectomy for peripheral tumours where the patient has a limited pulmonary reserve(31). The reason being that the only randomised control trial which took place in 1995, reported a 3 times higher rate of local recurrence at 3 years in patients undergoing limited resection compared to lobectomy for T1N0 non-small cell lung cancer. No significant difference in postoperative complications or morbidity was found and there was a similar overall survival between the groups(32). Most of the sub lobar resections in this study were wedge resections not segmentectomies. These results may need to be re-evaluated in the context of the recent advancements in pre-operative imaging. High resolution CT scanners and screening projects are identifying smaller adenocarcinomas, adenocarcinomas in-situ and minimally invasive adenocarcinomas, through the findings of focal ground

glass opacities. Currently, these are managed depending on their radiological likelihood to be invasive adenocarcinoma, persistence despite antibiotic trial, core biopsy findings and the patient's fitness. Results from randomised trials, such as that led by the Japan Clinical Oncology Group (33) and the CALBG/Alliance 140503 phase III trial(34) that is still recruiting, are awaited to help determine the role of limited resection for small peripheral early stage lung non-small cell lung cancer.

Minimally invasive surgery

Although considered a modern technique, thoracoscopy was first described over 100 years ago. In 1913, a chest physician Jacobaeus described the use of thoracoscopy to remove adhesions and treat pneumothorax in tuberculosis patients. The technique ,which was known as the "Jacobaeus Operation", spread around the world but with the gradual decline of tuberculosis chest physicians in the 1950s began to explore the use of this technique to diagnose and treat wider range of pleuro-pulmonary diseases(22). Thoracoscopy was used to obtain lung and pleural biopsies, treat pleural effusions and in the 1960s the first reports of the technique being using to perform talc pleurodesis were seen. However it wasn't until the 1990s, when thoracic surgeons saw the advances made in minimally invasive abdominal surgery, that they considered whether the same principles could be applied to lung cancer resection(35). With the modern development of a light source, micro- camera and video systems, the technique became known as video-assisted thoracic surgery (VATS).

Any new surgical technique for lung cancer needed to be able to achieve the main aims of surgical treatment; complete resection with adequate hilar and mediastinal lymph node sampling or dissection to provide an accurate pathological stage for the disease in order to guide treatment options, such as postoperative chemotherapy. As methods to achieve safe dissection and control of the hilar vessels were developed, this minimally invasive technique for lobectomy was thought to provide the answer for reducing the significant postoperative pain known to be caused by thoracotomy. Post-thoracotomy pain is not to be taken lightly and shouldn't be

seen as transient but rather as an often chronic and potentially debilitating type of pain. Reports of as many as 30% of patients still experience pain at 5 years post thoracotomy(36). This pain is largely thought to be due to the forcible rib spreading and direct and indirect damage caused to the intercostal nerves.

At first, the feasibility and safety of VATS lobectomy had to be explored. The hilar vessels were to be isolated and divided individually but the traditional manual ligature technique was made problematic without rib-spreading and placing knots into the chest cavity through small incision was difficult. It was soon discovered that the use of stapling devices would play a large role in VATS lobectomy(37). The traditional posterior approach to lobectomy as seen with the use of posterolateral thoracotomy was transferred to this minimally invasive technique. In 1992 in Edinburgh, Mr William Walker developed his posterior VATS approach with the surgeon standing posterior to the patient, a 5cm utility port incision in the sixth or seventh intercostal space just anterior to the latissimus dorsi, a posterior 1.5cm incision in the auscultatory triangle nearest to the upper end of the oblique fissure to accommodate the camera and further small port in the midaxillary line level with the upper third of the anterior utility port (Figure 5) (38). The advantage of this posterior approach was that the intra-thoracic views were familiar to surgeons and the conventional approach of dissecting the pulmonary vessels via the interlobar fissure first, then completing the fissures, and then dividing the bronchus could be used.

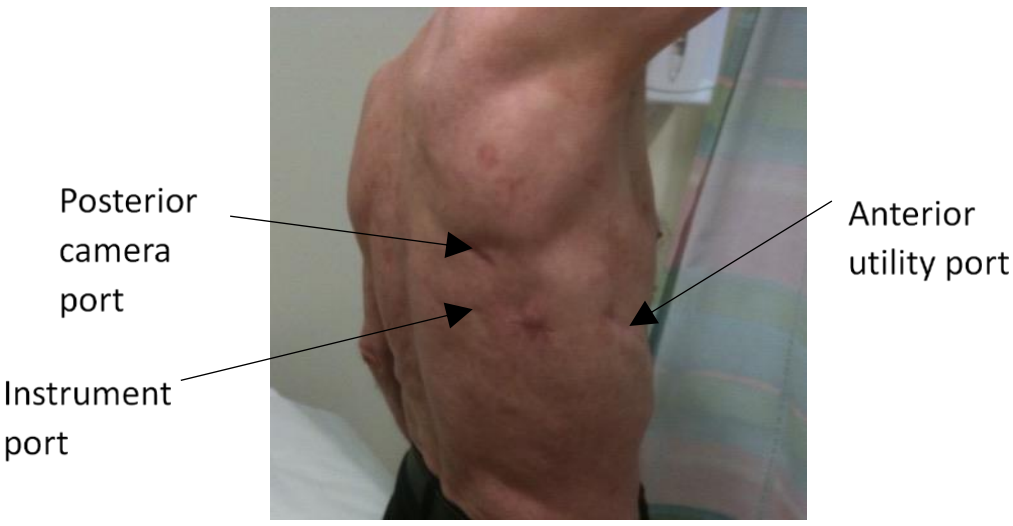

Figure 5: Incision scars for patient that underwent VATS via a posterior approach

In 1994, McKenna described his anterior approach to VATS lobectomy which evolved from his experience of 45 cases of thoracoscopic surgery for lung cancer. His method of working in the anterior to posterior direction, with a utility port in the fourth intercostal space in the anterior axillary line directly over the hilum, allowed for easier dissection and division of hilar vessels and for the procedure to be performed even if the fissures were poorly developed(39). Today the method of controlling the vein, artery and then the bronchus in an anterior to posterior approach is widely accepted (37).

Early experiences of the VATS Lobectomy

There was great enthusiasm for VATS lobectomy early on and although the number of surgeons using the technique was small, the rapid rise of VATS was evident in the large volumes of publications being produced by the late 1990s. Early case reports were encouraging, with overall mortality rates 0-2% and minor complication rates favourable to thoracotomy(40, 41). Major complications were also rarely seen(41). It seemed that VATS was gearing up to become the new preferred surgical technique. However its progress was to be delayed by the results of a randomised prospective trial of 55 patients which found no significant improvement in postoperative pain, operating time, intraoperative blood loss, duration of chest tube drainage, or length of hospital stay with VATS technique compared to thoracotomy(42). The resulting scepticism meant that many would become reluctant to use the technique until the safety and benefit of VATS could be proved, and thus the VATS lobectomy experienced a slow and cautious entrance into the modern thoracic surgical field.

On retrospective examination, some VATS studies may have produced unfavourable outcomes because operative techniques varied widely and reports showed that essentially the same operation was not being performed. This was explored in the work of Shigemura and his associates, which retrospectively compared outcomes for different video-assisted thoracoscopic approaches to

lobectomy in patients with NSCLC of stage T1bN0 for less (according to IASLC 8th edition)(43). “Complete” VATS (c-VATS) was defined as the use of 4cm utility port, no rib spreading and 100% of the operation completed using the monitor view; “assisted” VATS (a-VATS) was described as a 10cm mini-thoracotomy with rib spreading and the operation completed using both direct and monitor vision; open thoracotomy (open) was described as an operation under direct vision using a 20cm thoracotomy. Estimated blood loss was significantly less in the c-VATS group compared to the a-VATS and open groups. The c-VATS group also reported a statistically significant ($p<0.05$) shorter median length of hospital stay compared to a-VATS and open groups. Overall 5 year survival was similar between c-VATS, a-VATS and open (96.7%, 95.2%, 97.2% respectively). Following this work, one of the first studies which aimed produce a standardised description of VATS, as well as test the feasibility and safety of VATS lobectomy, was The Cancer and Leukemia Group B 2007 trial. This was a multicentre prospective trial which defined the following criteria for VATS lobectomy: no rib spreading, maximum length of incision for specimen removal of 8cm, individual dissection of the vein, artery, and bronchus, and standardized lymph node sampling. From the 111 patients recruited which had T1a-cN0 disease, 86.5% underwent a successful VATS lobectomy. Peri-operative mortality was reported as 2.7% and post-operative complications, such as arrythmia and prolonged air leak, were lower than seen in lobectomy via thoracotomy(44). With the VATS technique now clearly defined and shown to be safe, targeted research was now able to further explore the benefit of VATS over thoracotomy. This is described in Chapter 1.2.1.

Current guidelines and the adoption of VATS

The evidence in favour of VATS for lobectomy is growing. Yet at present, rates of VATS lobectomy in the UK vary greatly between practices, ranging from 10.3% to 84% (20). VATS uptake has so far followed the trend described in the Diffusion of Innovation Theory called the adoption curve. Between 1995 and 2005 the percentage of VATS lobectomies was low and remained at around 2.5%. Since 2008

the uptake for the technique has begun to more rapidly increase and reflects that clinician acceptance for the approach is growing (Figure 6)(45).

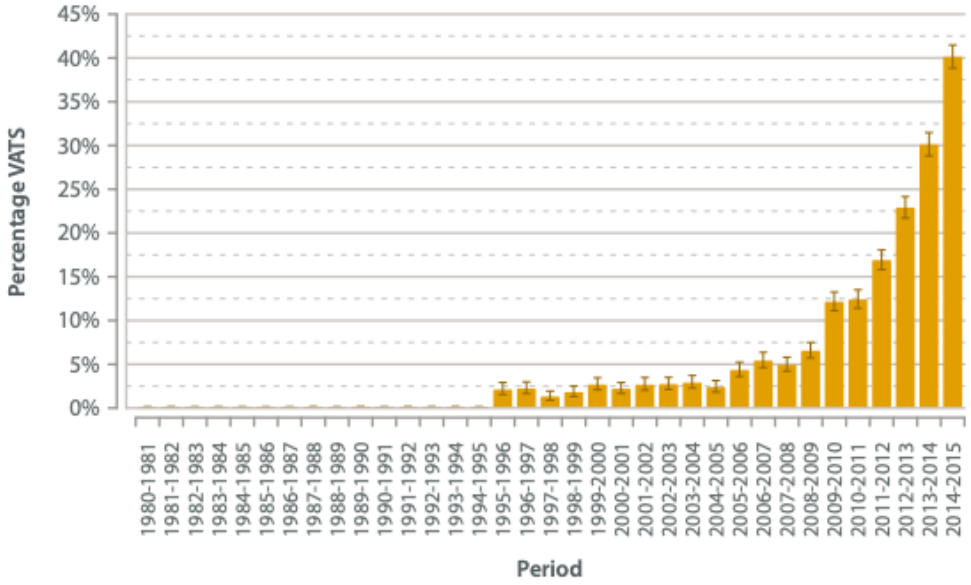

Figure 6: Surgery for primary lung cancer: VATS rate for all isolated lobectomies and bilobectomies; 1980-2015 (n=89,254)

Source: Society for Cardiothoracic Surgery in Great Britain & Ireland. Third National Thoracic Surgery Activity & Outcomes Report. Dendrite Clinical Systems Ltd; 2018.

In 2017, the VATS rate for lobectomy, bilobectomy and sleeve resection for NSCLC was reported as >50% of cases (21) (Figure 7) and the adoption of VATS appears to have entered the Early Adoption phase.

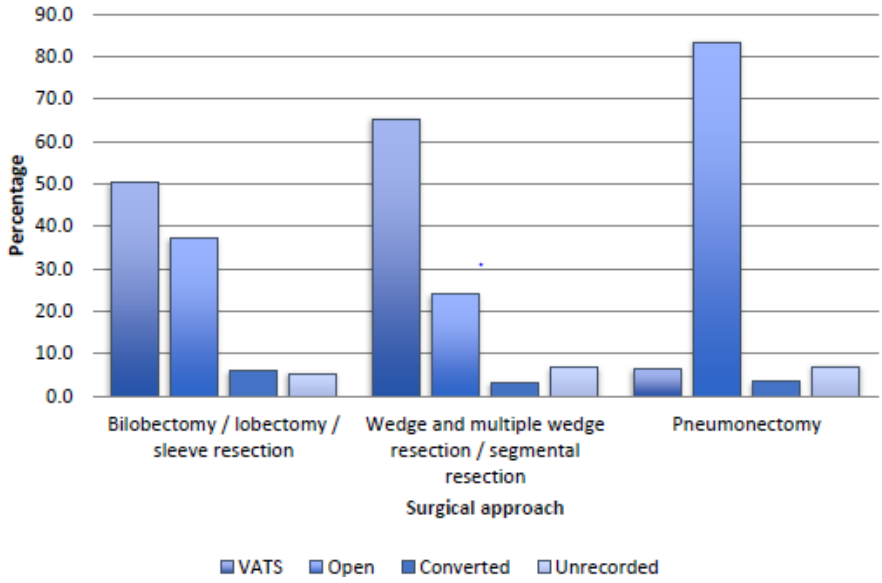

Figure 7: Surgical approach used by lung cancer resection performed in 2017

Source: Royal College of Physicians, Society for Cardiothoracic Society in Great Britain and Ireland. National Lung Cancer Audit, Lung cancer clinical outcomes publication 2019 (for the 2017 audit period). London: Healthcare Quality Improvement Partnership; 2020.

Yet without evidence from a well-designed and highly powered randomised control trial, clinical guidelines are reluctant to make a preference over the techniques. NICE guidelines from 2019 state that for those with NSCLC who are well enough and for whom treatment with curative intent is suitable, offer lobectomy (either open or thoracoscopic)(18). In addition, the British Thoracic Society and the Society for Cardiothoracic Surgery in Great Britain and Ireland Guidelines for the radical management of patients with lung cancer make no reference to a preferred surgical technique(31). The Getting it Right First Time Cardiothoracic 2018 report, details its concerns regarding the slow uptake of VATS when considering the benefits of reduced post-operative pain, complication rates, length of stay and facilitation to adjuvant chemotherapy that are seen. Hospital Episode Statistics from 2016 reports a hospital length of stay 1.9 days shorter with the use of VATS and therefore a potential for financial savings if uptake of the technique is increased. It recommends that patients being treated with surgery for Stage 1 lung cancer receive VATS or robotic-assisted lobectomy as the treatment of choice(20).

Robotic innovation in surgery

The robotic system enables surgeons to perform delicate and complex operations through a few very small incisions with magnification, high-definition visualisation, precision, dexterity and control. The first robotic-assisted surgeries were performed in the 1980-90s, with the ROBODOC (Integrated Surgical Systems, Davis, CA) used for orthopedic procedures and SARP (Surgeon-Assistant Robot for Prostatectomy) in urology. Early robots were all active systems, which held the purpose of carrying out repetitive pre-programmed tasks with a higher precision rate than the human hand(46). Later robotic surgery moved towards technology which was completely dependent on the surgeon's actions and could be remotely controlled to allow the surgeon to be in a separate location from the patient. This idea of telesurgery was developed under the National Aeronautics and Space Administration (NASA) with the objective to provide surgical assistance to astronaut's without the need for an

actual surgeon to be present(47). Progress came for robotic surgery when in 1993 the United States Food and Drug Administration (FDA) approved the first robotic system, AESOP (Automated Endoscopic System for Optimal Positioning), for abdominal surgery on civilians. At the same time as the successor to the AESOP was developed (ZEUS), the da Vinci system (Intuitive Surgical, Sunnyvale, CA, USA) was released on to the market. With the merger of the companies in 2003, the da Vinci became the only robot on the market. The da Vinci system is devised of three main parts: the surgical cart (from which the robotic arms extend), the master console (from where the surgeon controls the instruments) and the vision cart. The da Vinci system has evolved through various models, the current da Vinci X offers three-dimensional high vision with multiple degrees of magnification, mechanical hand controllers which offer 7 degrees of freedom of movement of the endo-wrist instruments and tremor filtration(48).

Robotic surgery truly began to gain traction in the treatment of prostate cancer and has since expanded its reach to other specialities including gynaecology, head and neck and colorectal surgery(49-51). With no robust evidence of its benefit over laparoscopic surgery, the rise in robotic surgery has largely been driven by marketing and patient pressures. Despite its rapid growth, thoracic surgery has been a late adopter of robotic technology. In particular, pulmonary resection for lung cancer has been hesitant in its implementation of robotic techniques compared with other areas such as mediastinal surgery. The evidence base for robotic surgery for lung cancer resection is therefore less mature than that of other surgical oncological specialities. Across a number of surgical fields, there have been phase 3 randomised control trials completed comparing robotic to minimally invasive and open surgery. In the treatment of colorectal and urological malignancy, these have provided high-quality evidence of the safety of robotic surgery and have shown no difference in complication rates or oncological outcomes in either the short or long term between robotic and existing surgical techniques (50, 52-54). Large comparative studies, including prospective multi-centre non-randomised trials and national database studies, also support the non-inferiority of robotic surgery over open and laparoscopic surgery when comparing

oncological outcomes (55-59). Data on cancer-specific mortality is generally lacking in these fields and endpoints are often surrogates measures of cancer control, such as positive surgical margins or recurrent disease. This is largely because trials reporting on long term survival require adequate funding to recruit sufficient numbers to be adequately powered and to complete years of follow up.

Cancer cure is the primary aim of surgery for localised disease but following this health-related quality of life and other patient outcomes are key. Robotic technology claims to offer greater precision, control and vision to the surgeon and a faster recovery time for patients. Despite the wealth of literature available and attempts at rigorous methodology, little measurable benefit has been demonstrated for robotic surgery over other minimally invasive techniques. The ROLLAR trial randomised 466 patients across 10 countries to robotic and laparoscopic surgery for the treatment of rectal cancer, exceeding their target sample size(50). The study found no difference in conversion rates, patient outcomes, pathological results or disease-free survival and concluded that robotic surgery was not cost-effective for the minimal improvement in quality of life seen. There is still a compelling need to validate the use of robotic surgery over standard techniques and only high-quality research can thoroughly assess its worth. However, whilst more robust evidence is awaited, few would wish to see innovation stunted and patients denied access to new health technologies. In the case of prostate cancer, the uptake was steep and between 2017 and 2019 89% of radical prostatectomies in the UK were performed robotically(60). Yet evidence that the technique yields superior functional outcomes remains inconsistent(52, 55). A key example of the value of surgical evaluation can be seen in cervical cancer. As in the treatment of various other cancers, it was thought minimally invasive surgery would offer better patient outcomes. In 2018, a randomised control trial reported significantly lower disease-free survival and overall survival with laparoscopic and robot-assisted radical hysterectomy compared with open surgery(49). Although results were likely affected by learning curve bias and lack of technique standardisation, the LACC trial is currently the best evidence available and has prompted the International Federation of Gynecology and Obstetrics

(FIGO) gynaecologic oncology committee to recommend open surgery as the gold standard for early-stage cervical cancer.

Historically the evaluation of innovative surgical procedures has been difficult. There are many reasons for this, but particularly when the intention of the new technique or technology is to better patient outcomes and endpoints cannot be measured as objectively as morbidity and mortality. Unlike pharmaceutical treatments, new surgical techniques evolve slowly and often the gold standard randomised control trial comparing treatment with placebo is not a suitable study design. In 2009, the Balliol Collaboration described the natural course of surgical development and put forward a set of recommendations, known as the IDEAL framework. This describes how surgical innovations should be assessed at each of the five stages(61). It recommends the use of feasibility randomised control trials and the evaluation of learning curves and potential equipoise problems. There is much controversy as to the right timing to conduct a randomised control trial in surgery. In the case of Yaxely et al., the study has been commended for its timing as clinical equipoise appeared to be well embedded(62). In the UK today, a similar clinical trial may find recruitment more challenging, and it may be too late for a randomised trial. Due the massive wave of enthusiasm for the innovation, robotic surgery is now the most commonly used technique for radical prostatectomy and patients and surgeons are less likely to be amenable to the process of randomisation. Looking at robotic lung cancer resection, equipoise would need to be carefully evaluated prior to the undertaking of a randomised control trial. Where a lack of equipoise exists, the IDEAL framework recommends the use of either expertise-based randomised trials, in which randomisation is performed by a third party, or the use of parallel non-randomised trials with the use of propensity matching to control for confounders(63). These study designs have the potential to increase study recruitment as well as mitigate the effect of surgeon preference and the selection bias this introduces. It is also important to consider whether, even with high quality data, a change in clinical practice would be feasible within the National Health Service (NHS). In the treatment of colorectal cancer, NICE has only

recommended robotic surgery within established programmes which is meant to discourage units from starting new programmes due to the increased costs(64).

In addition to the challenge of determining the correct timing for the evaluation of a new surgical technique, there are also significant methodological issues which require attention in the design of randomised control trials. In clinical practice there is variation in how procedures are performed, particularly during the development stage of a technique. For this reason, randomised control trials at this stage are of little value as a lack of standardisation introduces bias, which may compromise a trials internal validity. However, once the technical details of the operation have been established, the IDEAL framework encourages randomised control trials with the use of quality control measures. Randomised control trials have often been criticised for not reporting on the effect of surgeon expertise, although some would argue this reflects real clinical practice. The three common quality assurance measures reported include: entry criteria for surgeons, minimum procedural requirements and ongoing monitoring. Examples of entry criteria include a minimum number of cases and a peer review of operative technique(65, 66). Surgeon volume is known to significantly effect outcomes and the initial learning curve is generally associated with a higher risk of adverse events(67). Learning curves are an important source of variation to consider in clinical trials and can significantly impact patient-related endpoints as well as cost calculations. In fact, one of the scrutinises of the LACC trial is that surgeon experience was not adequately accounted for(49). In preparation for a randomised control trial, it is suggested that prospective databases studies with continued performance monitoring are first conducted, in order to define the learning curve(63). Adjusting for this variation can be difficult and there is a clear lack of guidance. Yaxely et al. tried to control for surgeon heterogenicity with the use of a single surgeon performing the open prostatectomies and another completing the robotic prostatectomies(62). However, the surgeons had differing levels of experience and trainees were also permitted to complete parts of the operations. Due to the trial design and limited information on trainee involvement, no assessment of the impact of learning curves or variation in surgeon experience could be made. Other

studies have tried to limit the learning effect by setting a minimum number of procedures surgeons must complete in order to be eligible for participation(50, 55, 65). Yet with the use of multi-level logistic regression, the ROLLAR trial has shown that despite setting this standard some of the surgeons were still on the learning curve of robotic surgery and results were influenced by surgeon experience(68). It would seem that, as in the CLASICC trial, continual ongoing quality control and random auditing of standards may be the preferential method(69).

Besides surgeon experience, there are other important considerations in surgical trials to ensure results are unbiased and credible. Randomisation is known to eliminate selection bias, with the aim that outcomes are the result of the intervention rather than differences in patient characteristics. However, the allocation sequence must be concealed from those assigning treatment groups otherwise results may be no more reliable than those from an observational study. To ensure this, studies have largely used computer-based programs masked from other members of the research team (54, 62, 65). Furthermore, blinding is recommended to mitigate the effect of preconceptions of the new technique on outcomes. In this field, blinding in randomised control trials is rarely reported. Whilst we acknowledge that it would be impossible to blind surgeons to participants treatment allocation, many trials have made little attempt at blinding patients or study investigators(49, 50, 54, 62, 70). Endpoints such as mortality and morbidity are unlikely to be affected by lack of blinding but more subjective measures such as functional outcomes or positive surgical margins may be. For this reason, studies have blinded study investigators and pathologists to treatment allocations(62). The most rigorous attempt at blinding has been reported in the VIOLET trial, where double blinding of both patients and research nurses was performed by using the same large dressings on all patients regardless of the incision type(65). The other source for potential confounders is the lack of standardisation in post-operative care across treatment groups. Trials often report that post-operative care was delivered as per local protocols(54). However, surgeon preference may be to send robotic cases back to the ward after surgery and open cases to critical care units, and thus outcomes such as frequency of critical care

admissions may not be a reflection of surgical technique. The VIOLET trial has established criteria to objectively measure when patients are medically fit for discharge, but further development and insight is needed into the effect of post-operative care and how disparities can be controlled for in future studies(65).

The introduction of robotic surgery for lung cancer resection

Over the last two years there has been a surge in robotic surgery in thoracic surgical units in the UK. The advantages of robotic-assisted thoracic surgery (RATS) for lung cancer resection include the idea of reduced surgical trauma to patients when compared to open surgery and VATS. The technique uses smaller incisions, ports placed along the same intercostal space (to avoid damage to multiple neurovascular bundles) and no rib spreading. The da Vinci ports are also placed with the remote centre at the level of the muscle layer, to decrease port site trauma and pressure on the intercostal nerve. RATS provides an aesthetic benefit (Figure 8) but also studies have suggested that patients have reduced postoperative pain, reduced length of hospital stay overall, spend less time on critical care, have reduced complications and a faster recovery time (71-75) .

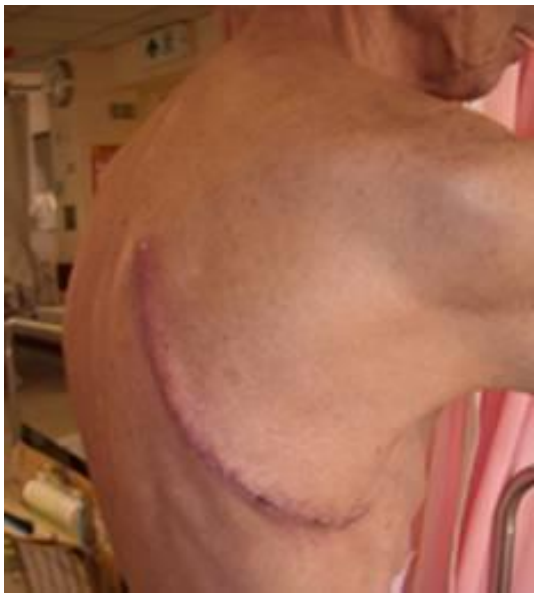

Figure 8: Incision scar posterolateral thoracotomy

From a surgeon's perspective the robot offers the benefit of CO2 insufflation which creates greater space within the thoracic cavity to work, as it collapses down the lung parenchyma and pushes the diaphragm inferiorly. Furthermore, the endo-wrist instruments provide a greater degree of movement than VATS instruments and mimic the movement of the human wrist, therefore providing improved surgical dexterity. This is particularly useful for lymph node dissection and taking down adhesions (Figure 9). As with any new surgical technique there is learning curve associated with it. However, different investigators have suggested that this may be as low as 20 cases (76-78), less than 50 cases described in the literature for VATS lobectomy (79). The da Vinci Surgical Skills simulator also uses the original surgical console, resulting in a more realistic training experience. The principal caveats of RATS are the lack of tactile feedback and the high costs associated with the purchase and maintenance of robotic equipment. Additionally, whilst the robot is good at performing movements in a confined space, manipulating the lung cane be more difficult. The lack of tactile feedback also can make it difficult to carry out a wedge resection and frozen section, if a pre-operative tissue diagnosis has not been obtained. An additional concern with robotic surgery is the potential difficulty that may be experienced if the patient needs to be converted to open surgery. With VATS the surgeon is at the table and can easily convert. With robotic surgery the robot must be de-docked to allow conversion.

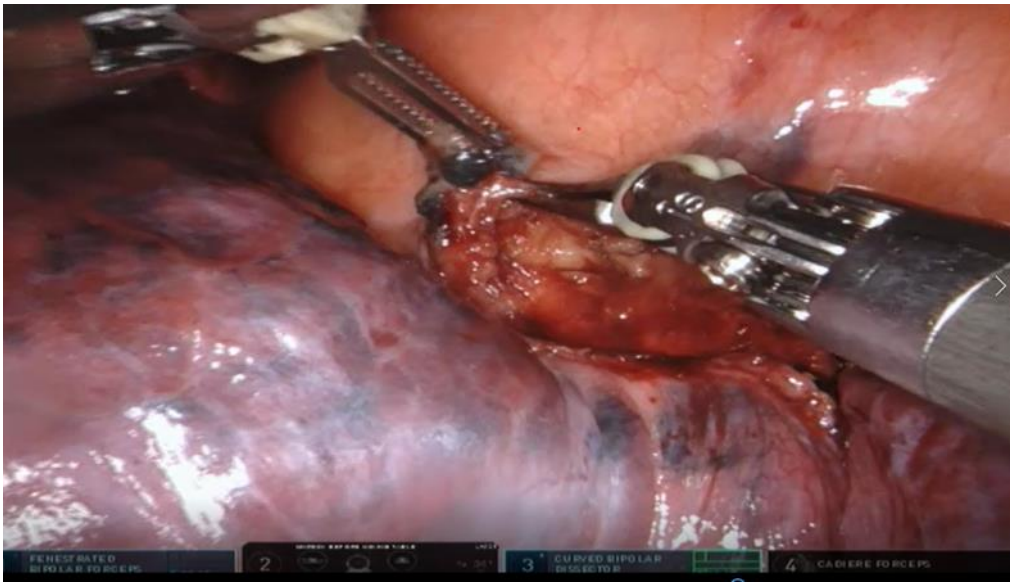

Figure 9: Lymph node dissection with robotic endo-wrist instruments as part of left upper lobectomy using the da Vinci X Surgical System.

The uptake of RATS for lung cancer resection has been gentler than in other areas of thoracic surgery, such as mediastinal masses and lung volume reduction surgery. The development of robotic surgery in these fields has been described in Chapters 4 and 5 respectively. Robotic lung cancer resection is currently between the stages of exploration and assessment according to the IDEAL pathway(63). Whilst rates of RATS for lung cancer have seen an increase, numbers remain small. In 2017, only 1% of all lobectomies and bilobectomies in England for NSCLC were completed robotically(21). It is likely that learning curves at this stage are mixed, with original innovators being comfortable with the technique and the rapidly growing number of new adopters still novice. There is mounting evidence to show that robotic lobectomy is safe and some reports have gone as far as to advise VATS or RATS lobectomy as the treatment of choice for patients with Stage 1 lung cancer(20). However, the technique remains novel. Evidence is mainly from large retrospective database studies and some propensity matched studies(72, 80-82). A small number of prospective propensity matched studies have been conducted, but on more depth review these were either single centre studies or only included a limited number of robotic surgeons(83, 84).

Large multi-centre prospective and randomised control trials are lacking. At this stage, the IDEAL framework recommends well designed prospective non-randomised studies or small feasibility randomised trials to prepare for future large randomised control trials(63). Despite being the gold standard in study design, currently a randomised control trial in robotic lung cancer resection would be difficult. Firstly, it is unclear whether the comparator to robotic surgery should be VATS or open surgery. At present, there is no definitive evidence as to which is the gold standard technique. Secondly, as previously stated many robotic surgeons will be on a learning curve and any study would need to account for this. Although a large prospective non-randomised study would not be able to control for selection bias, it may allow for a comparison of all three techniques without the influence of recall bias. Carefully designed a prospective multi-centre study could aid in the evaluation of learning curves, effect sizes, quality control measures and indications for robotic surgery. One randomised control trial already recruiting is the ROMAN

trial (NCT02804893). The trial is a prospective multi-centre randomised control trial comparing robotic and VATS approaches to early-stage lung cancer resection. Led by the Humanitas Research Hospital in Italy, its primary outcome is adverse events such as complication and conversion rates and the study plans to enrol 300 participants by 2022. Recruitment appears to be slower than other recent randomised control trials in the field but a formal report has yet to be released(85). Results of this trial are eagerly awaited and may provide a high-quality evidence base for the future of robotic lung cancer surgery.

1.1.3 Open Surgery

Open surgery for lung cancer resection is traditionally performed using a posterolateral thoracotomy in the UK. With single lung ventilation, the patient is positioned in the lateral decubitus position and the table is angled or a bean bag is placed under the patient's chest to spread the ribs and increase the intercostal space (Figure 10)

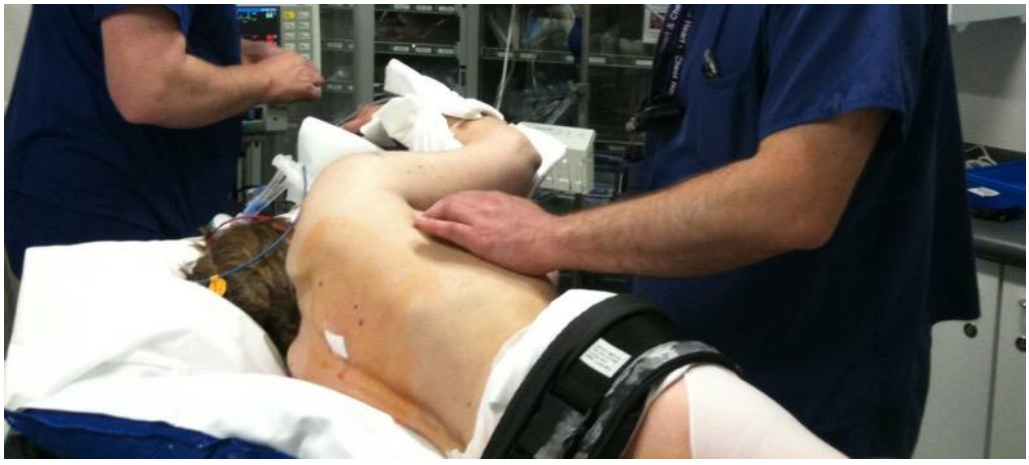

Figure 10: Patient positioned in the left lateral decubitus position following general anaesthesia and intubation with a double lumen tube.

The incision is made just anterior to the axillary line over the 4th to 6th ribs and curves posteriorly just below the tip of the scapula and then extends midway between the medial aspect of the scapula and the vertebral column. This incision is made in an oblique angle to mirror the direction of the ribs (Figure 11).

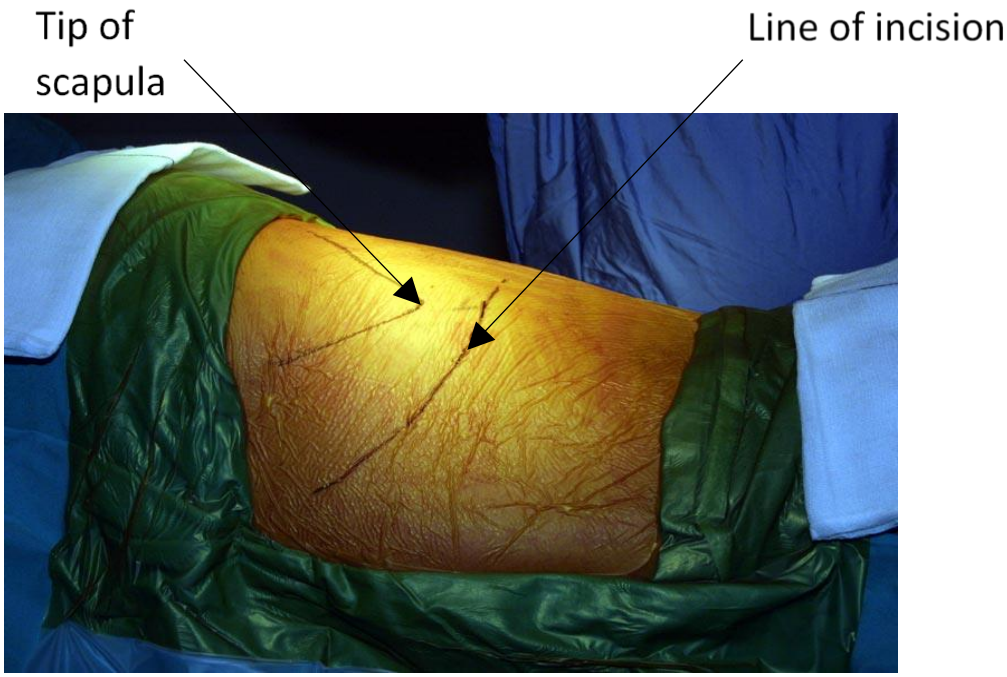

Figure 11: Right posterolateral thoracotomy. Patient is positioned in the lateral decubitus and markings show the borders of scapula and posterolateral thoracotomy incision extending in a lazy "s" shape from the anterior axillary line to midway between the scapula and vertebral column.

The subcutaneous fat and latissimus dorsi are then divided using electrocautery. In the serratus sparing technique, the serratus fascia is then dissected as close to the muscle as possible to allow the muscle to be retracted anteriorly. The scapula is then retracted and rib spaces are counted. Entry is usually gained through the 5th intercostal space but for peripheral tumours in the lower lobes the 6th intercostal space may be used. The tissue overlying the superior border of the rib inferior to the intercostal space chosen is divided and the patient should be placed on single lung ventilation if this has not already been done (Figure 12).

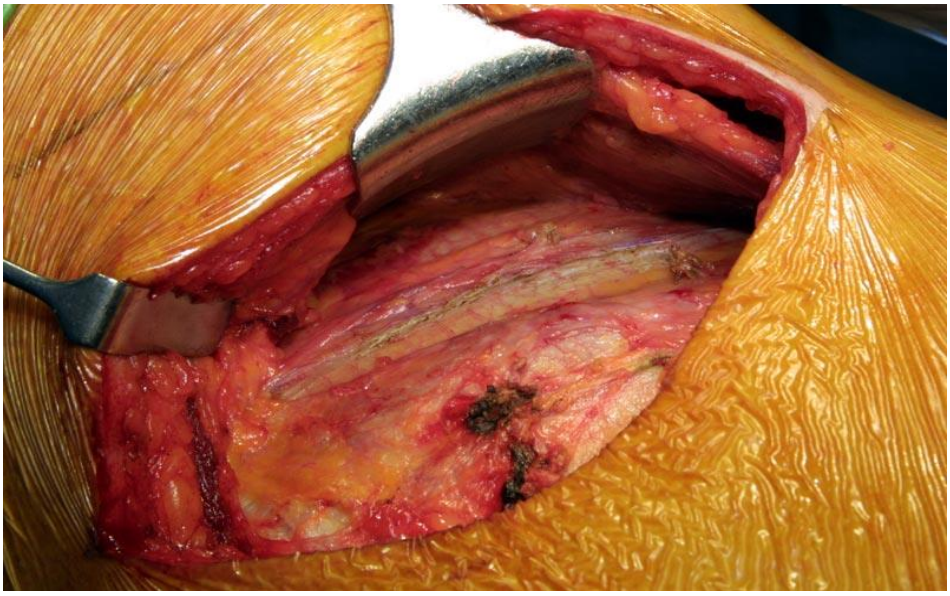

Figure 12: Latissimus dorsi and serratus anterior divided in a right posterolateral thoracotomy. Scapula retractor in position and tissue overlying superior aspect of the rib has been divided using electrocautery.

Then a small section of the intercostal muscle is divided off the superior aspect of the rib to create a pneumothorax and allow the lung to collapse down. A finger is placed into the chest to check for the presence of adhesions and then the intercostal muscle is divided anteriorly and posteriorly before a rib-spreader is introduced and slowly opened to separate the ribs.

There have been variations of the standard thoracotomy such as an anterolateral thoracotomy, muscle sparing thoracotomy or axillary thoracotomy used to try and decrease post-operative pain and the size of the incision.

Pneumonectomy

Following access via posterolateral thoracotomy, the extent of tumour invasion is assessed and the need for pneumonectomy evaluated. The pulmonary ligament is divided, and the mediastinal pleura is then incised to reveal the hilar structures. The hilar structures are then divided one by one. Traditionally, the order is vein, artery, and then bronchus but in practice this will depend upon anatomical findings(28) Dividing the vein first is thought to prevent the spread of malignant cells via the venous draining system. Intrapericardial dissection may be needed to gain proximal control of the pulmonary artery or veins in a very central tumour. Once the

pulmonary veins, artery and bronchus have been divided warm water is poured into the chest to test the bronchial stump for an air leak and, once this is excluded, the stump can be covered with a local flap. Mediastinal lymph node dissection is now performed and guidelines state that at least six lymph node stations should be sampled before N0 status can be confirmed(31).

Guidelines from the British Thoracic Society and Society for Cardiothoracic Surgery, acknowledge that pneumonectomy for primary lung cancer is still a high-risk procedure that holds a 30 day mortality rate in the UK of 5.8%[Error! Bookmark not defined.]. They advise that pneumonectomy should be avoided where possible due to its high post-operative mortality rate as well as its associated poor QoL (31).

Open Lobectomy

When performing an open lobectomy, a posterolateral thoracotomy is the traditional and widely utilised approach, due to the extent of visualisation achieved (Figure 13). First the lung is mobilised and adhesions are removed either with a sponge stick or cauterised if vascular.

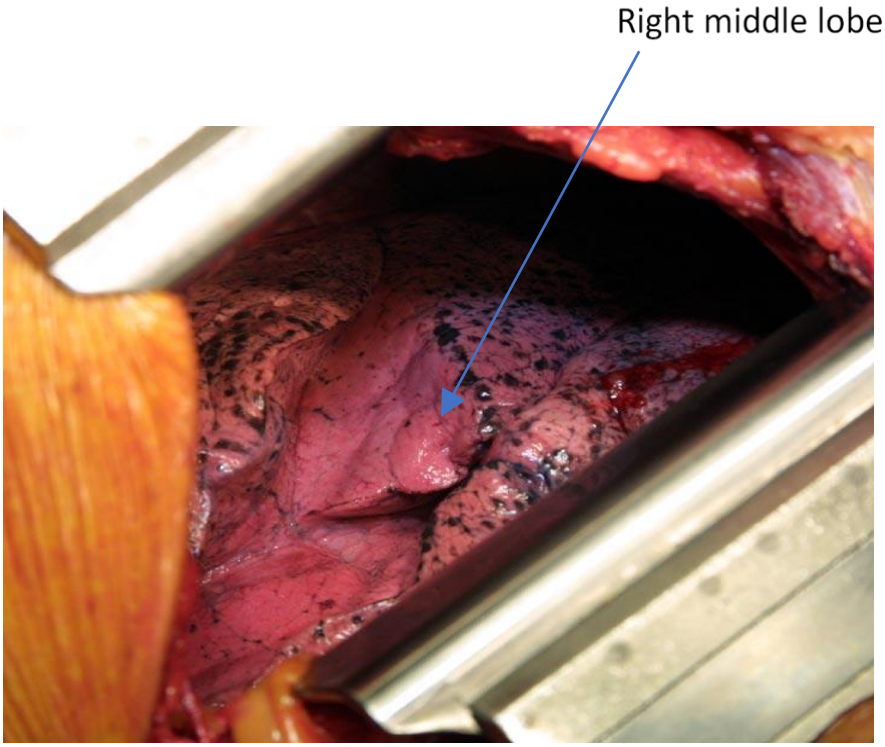

Figure 13: View of the thoracic cavity through posterolateral thoracotomy. Rib-spreaders in place.

Once this is complete, the inferior pulmonary ligament is divided with electrocautery and if visible the pulmonary ligament lymph nodes are sampled for staging. The intrathoracic structures are then examined and, if possible, the tumour is identified and the extent of the disease determined. The key principle of a lobectomy is to identify and divide the arterial, venous and bronchial supply to the lobe. In the presence of incomplete lobar fissures, the interlobar plane will need to be opened up. After identification of the branches of the pulmonary artery, the fissure can be completed using a stapling device and ensuring the interlobar arteries to the other lobes are not divided. An incomplete lobar fissure could be the result of congenital malformations, inflammatory processes or the spread of disease into the adjacent lobe. A detailed understanding of the branching of the pulmonary arteries and its variations is key. Pulmonary segmental arteries are fragile and for safe dissection scissors are used along the long axis of the vessel and when exposed a right-angled instrument is passed under it. The vessels are either ligated with a silk suture and then divided or an endovascular stapler is used. In the context of a right upper lobectomy, the mediastinal pleura is incised around the right hilum to expose the right pulmonary artery and its superior trunk and the superior pulmonary vein. The branches of the superior pulmonary vein to the upper lobe are divided between ligatures or with a vascular stapler. Superior arterial trunk and its apical and anterior segmental branches are dissected and divided. The final arterial supply to the right upper lobe is the posterior segmental artery, which is accessed via the oblique fissure. Before this can be divided, the oblique fissure must be completed otherwise there is risk of injury to the artery. The fissure between the upper and lower lobe is divided between the superior segment artery of the lower lobe and posterior ascending artery and the fissure between the upper and middle lobe is divided in the space above the middle lobe artery. Lastly, the upper lobe bronchus is divided either with a stapler or manually transected and sutured. Manual division is indicated in the presence of an endobronchial tumour to ensure the bronchus is resected proximal to the tumour. The pleural cavity is then irrigated and the bronchial stump and lung parenchyma tested for air leaks(28, 86). For cancer operations, mediastinal lymph node sampling is performed before a chest drain is placed and the chest closed (Figure 14).

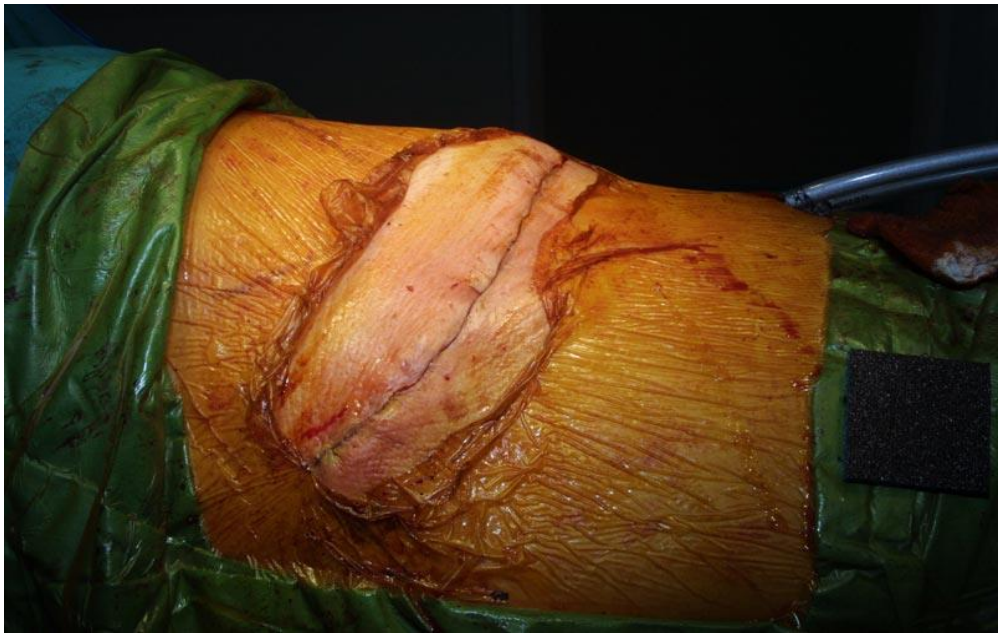

Figure 14: Posterolateral thoracotomy following closure of the ribs, muscle and fascia layers and skin.

1.1.4 VATS Lobectomy

In a modern VATS lobectomy using a standardised three-port anterior approach, the patient is positioned the same as in a posterolateral thoracotomy apart from the patient being positioned at the anterior edge of the operating table, so the surgeon doesn't have to reach over the patient. The surgeon stands anterior to the patient and a monitor is placed on each side of the operating table. A 10 mm, 30-degree angled HD video-thoracoscope is used. Initially, a utility port is made between the nipple and lower angle of the scapula in the fourth intercostal space just anterior to the latissimus dorsi. No rib spreading is used but a soft tissue retainer may be used. The camera is then inserted and the thoracic cavity is examined for any unexpected signs of advanced disease or extensive adhesions which may change the surgical plan. Following this a low anterior camera- port is made under direct vision at the level of the top of the diaphragm and anterior to the level of the hilum. Finally, an incision is made in the same rib space but posterior in the posterior axillary line (Figure 15).

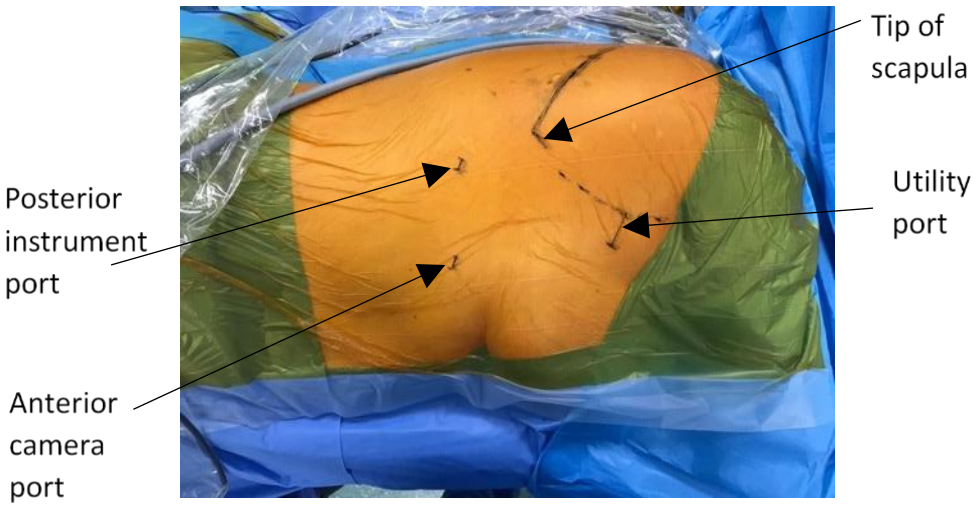

Figure 15: Placement of the three incisions made a right-sided VATS lobectomy via an anterior approach. Markings show the outline of the scapula, utility port in 4th ICS anterior to the latissimus dorsi, camera port in anterior axillary line at the level of the top of the diaphragm and posterior port in same rib space posterior axillary line.

Next the lung is manipulated with a peanut or sponge stick and the lung anatomy is examined to identify fissures and if possible the tumour. Vessels are divided with a vascular endoscopic stapler whilst incomplete fissures and the bronchus are divided with endoscopic staplers. In the context of a right upper lobectomy, the pleura over the anterior hilum is divided and thoracoscopic dissectors are passed behind the portion of the superior pulmonary vein to the upper lobe, to ensure there is sufficient space to introduce a stapler and divide the vessel.

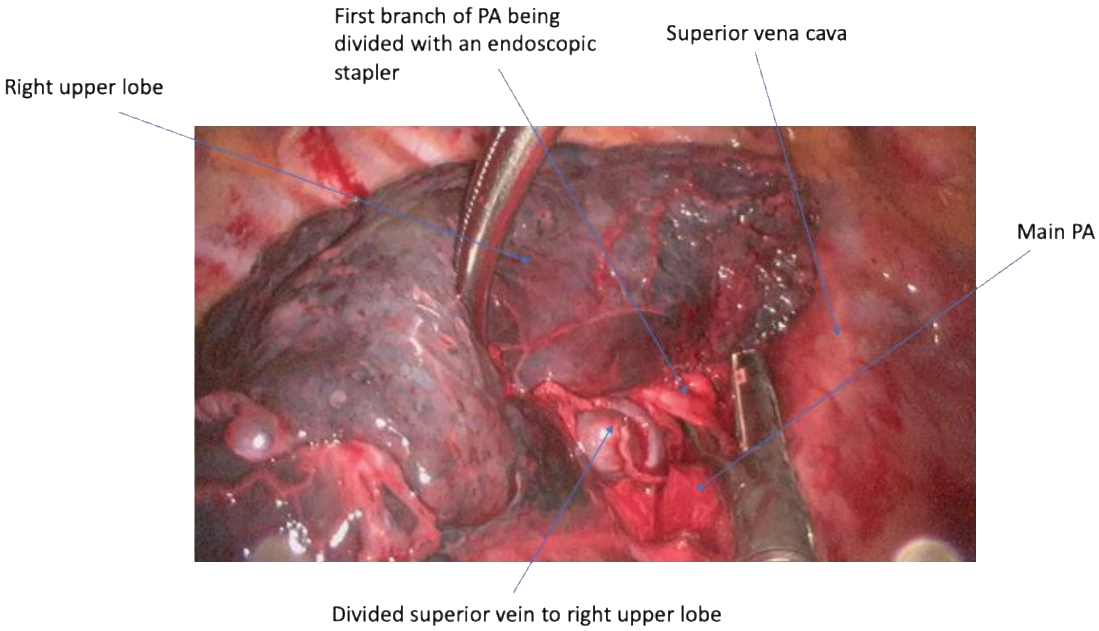

Figure 16: VATS right upper lobectomy. First branch of the right pulmonary artery (PA) is being divided with an endoscopic stapler.

With the vein divided, the pulmonary artery is more easily visualised, and the superior trunk is divided in the same way (Figure 16). The horizontal can then be divided and the presence of a posterior ascending pulmonary artery identified and divided. Following this the bronchus is clamped with an endostapler and the lung may be ventilated to check the middle and lower lobes fully inflate. The right upper lobe bronchus and the posterior part of the fissure are then divided one by one. The lobe is placed in an endobag before being removed from through the utility port to prevent the seeding of malignant cells.

1.1.5 Robotic Lobectomy

At Liverpool Heart and Chest Hospital robotic-assisted lobectomy is performed using the Da Vinci X surgical system, via a four-arm approach. The patient is placed in the same position as for VATS lobectomy. For a right upper lobectomy, the endoscope 12mm port is placed in the 7th or 8th intercostal space between the mid axillary line and the anterior axillary line. After inspection of the thoracic cavity with the endoscope, the CO2 insufflation is turned on to 6-8 KPa. Two 8mm ports are

placed posterior in the same intercostal space and a 12mm stapler port placed anteriorly. A 12mm utility port is placed between the camera and anterior stapler port (Figure 17). A space of 6-10cm should be left between the ports.

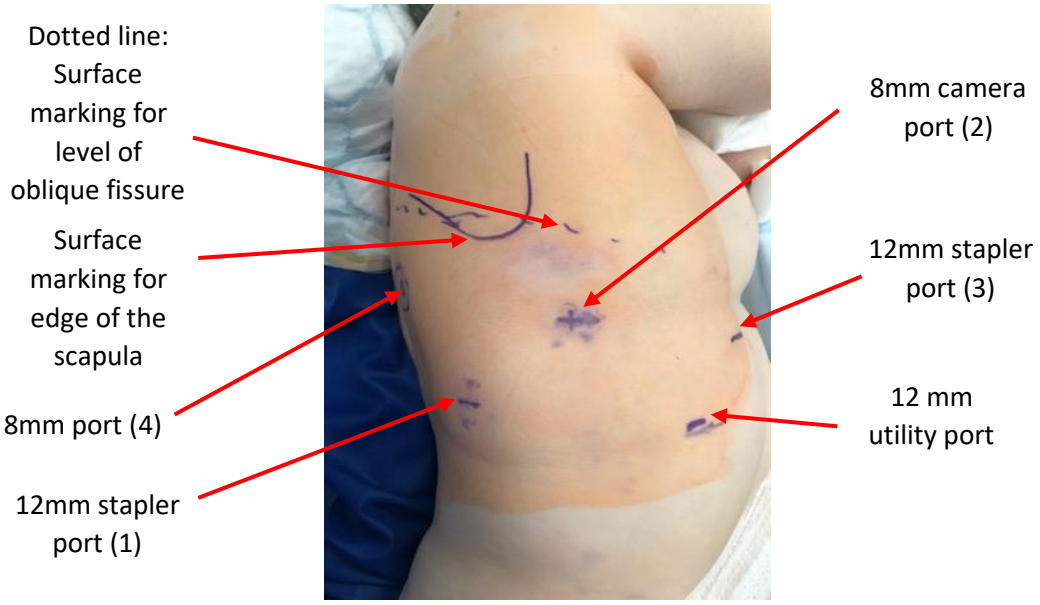

Figure 17: Port placements for robotic right upper lobectomy. Initial 8mm camera port (arm 2) placed in 7th/8th ICS between mid axillary line and anterior axillary line. 8mm port (arm 4) and 12mm stapler port (arm 1) placed posteriorly in same ICS. 12mm stapler port (arm 3) placed anteriorly in same ICS. 12mm utility port placed between camera and anterior stapler port.

The surgical cart is then driven to the head of the patient and positioned with the laser cross over camera port. The robot arms are docked to the ports. The surgeon then takes control of the robotic arms from the surgeon's console (Figure 18).

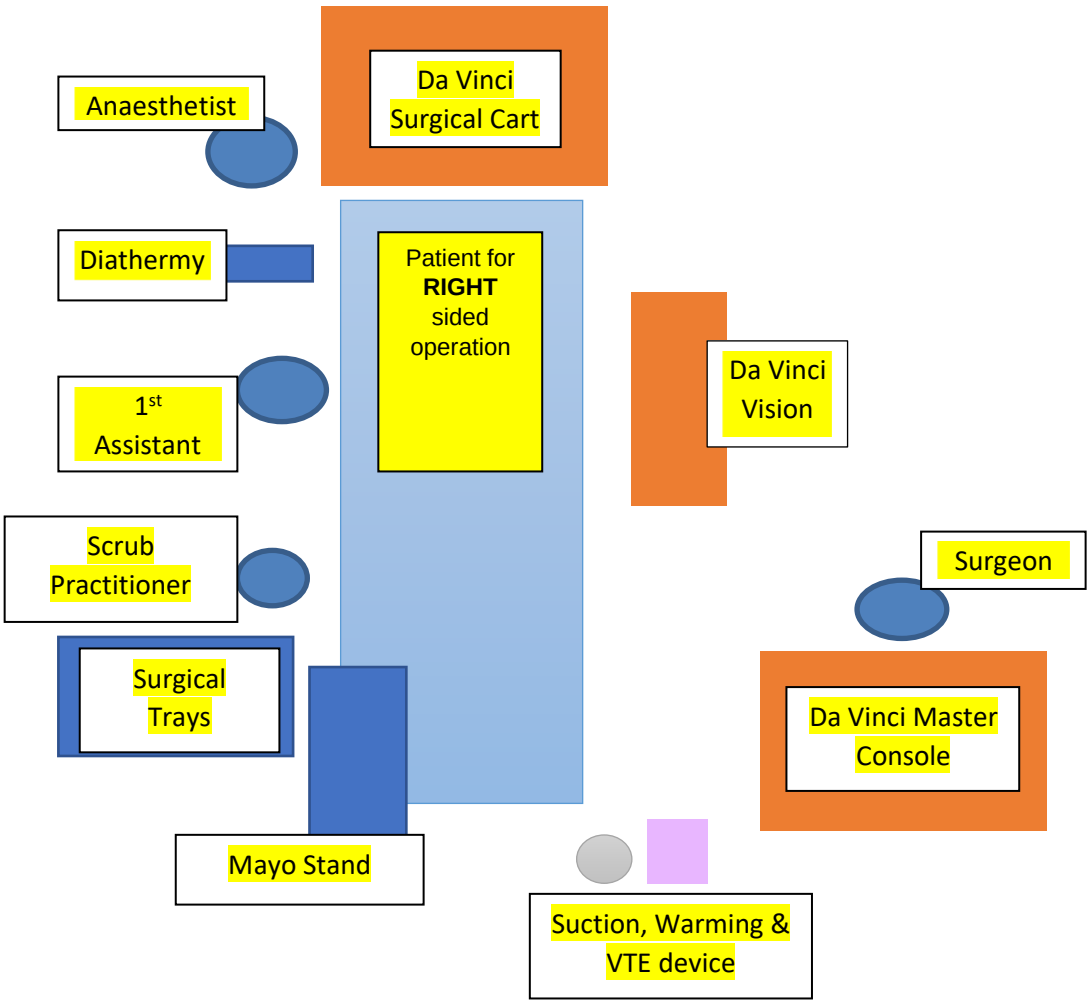

Figure 18: Da Vinci X set up for right robotic lobectomy

Following, the removal of adhesions using a diathermy spatula, the inferior pulmonary ligament is divided, and stations 8 and 9 lymph nodes are dissected. The posterior hilum is then opened, and station 7 lymph nodes harvested. The hilar dissection continues and the junction between the right upper lobe bronchus and bronchus intermedius is identified. Before moving anteriorly, the posterior exit point of the fissure is identified, and station 11 nodes dissected. The lung is retracted posteriorly, and the anterior mediastinal pleura incised to reveal the right superior pulmonary vein. The branches to the upper lobe are subsequently dissected and divided with a robotic stapler. Next, the truncus anterior branch of the pulmonary artery is dissected, and any level 10R nodes removed before the artery is divided with a stapler. The right upper lobe bronchus is then isolated and clamped to check for re-expansion of the middle and lower lobes before being

divided with a stapler (Figure 19). The posterior ascending pulmonary artery can be taken before or after the bronchus. The fissure is divided with robotic staplers. The lobe is then placed into an endobag before its removal. Dissection of lymph node stations 10R, 4R and 2R can then be carried out.

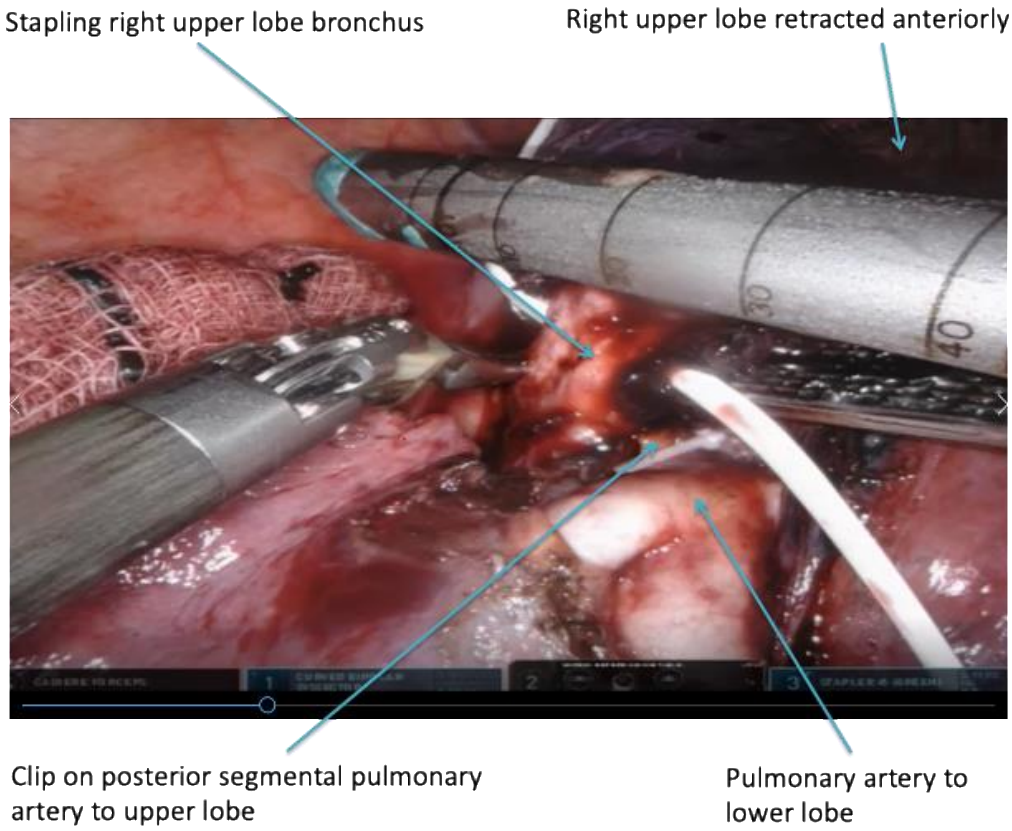

Figure 19: Robotic right upper lobectomy. A sloop has been passed around the right upper lobe bronchus before being divided with a robotic stapler.

1.1.6 Assessment for surgery

Diagnosis and staging lung cancer

Before the decision for surgical treatment can be made, adequate and up to date diagnostic and staging information must be available and an assessment regarding the risks of surgery should be carried out. NICE guidelines state that all patients with a chest x-ray suspicious of lung cancer or aged over 40 years with unexplained haemoptysis must be referred under the suspected cancer pathway for an

appointment within 2 weeks(87). To diagnose and stage the disease, an initial CT scan, with intravenous contrast medium, from the lower neck to at least the upper abdomen is recommended. The location and volume of the tumour should be reported on, as well as the site and size of any enlarged lymph nodes or presence any metastatic disease, to give a suggested TNM stage. Following this a PET-CT is required for all patients considering radical treatment. From here PET positive mediastinal lymph nodes should be further investigated with mediastinal sampling by endobronchial ultrasound (EBUS), mediastinoscopy, mediastinotomy or VATS, and the appearance of isolated distant metastases or synchronous tumours should be confirmed by biopsy or with further imaging(31). The indications for curative surgery in patients with lung cancer are shown in Table 1. British Thoracic Society guidelines state that all patients with stage T1a-3N0-1M0 lung cancer and acceptable risk should be offered surgical resection(31).

Table 1. Indications for lung cancer resection with curative intent

Universally recognised indications for surgery	Stage I and II lung cancer
Widely accepted indications for surgery	T3 N0-1 tumours requiring chest wall/diaphragm resection or tumours presenting with satellite nodules in the same lobe.
	T4 tumours requiring vertebral/carinal resection
	Pancoast tumours
Debatable indications for surgery	Single station N2 disease
	T4 with satellite nodules in another lobe
	Limited metastatic disease (T1-3 N0 M1b)

Assessing fitness for surgery

Whilst surgical treatment is widely accepted as offering the best chance for cure, it should only be carried out if the risk of post-operative mortality and morbidity are

not too high. There are three main areas to consider when accessing patients' fitness for surgery: risk of operative mortality, risk of cardiovascular morbidity and risk of poor post-operative QoL.

Lung cancer surgery is safe with a 30 day mortality of 2% reported (19). The cause of mortality following thoracic surgery is multifactorial and a large dataset is needed when attempting to identify predictive factors. The use of risk stratification models, such as Thoracoscore, are widely adopted and even form part of the British Thoracic Society and NICE guidelines (18, 31). The Thoracoscore risk model was developed from data on 15,183 patients and is a strongly discriminating model (c-index > 0.8). It predicts in-hospital mortality based on 9 variables (age, sex, dyspnoea score, American Society of Anesthesiologists score, performance status classification, priority of surgery, malignant disease, procedure type, and comorbidities)(88). Further models, such as Eurolung 1 and 2, were developed from the European Society of Thoracic Surgeons database comprising 47 960 patients and predict cardiovascular morbidity and 30 day mortality(89). Whilst important in informing MDTs and patients, it is important to recognise the limitations of risk prediction models in that they are developed from a specific patient population, although externally validated, and the potential impact of unrecorded variables on outcome.

Evaluation of risk of cardiovascular morbidity for the thoracic surgical patient is important as intrathoracic surgery is associated with an intermediate risk (1-5%) of cardiac death or nonfatal myocardial infarction(90). For this reason, regardless of operative risk, the American College of Cardiology guidelines should be used to assess peri-operative cardiovascular risk. Cardiology review is indicated in patients with active cardiac disease, poor cardiac function or with ≥ 3 cardiac risk factors and medical therapy optimised for those with coronary disease. Anti-ischaemic drugs such as aspirin, statins and beta-blockers should be continued peri-operatively and revascularisation treatment (such as percutaneous coronary intervention or coronary stenting) considered for those with stable angina(31).

Poor respiratory function creates concern due to the increased risk of in-hospital mortality and poor QoL due to dyspnoea and the possible need for long-term oxygen therapy. Pulmonary function tests including measures of carbon monoxide transfer factor are required for all patients. Post-operative dyspnoea is estimated by segment counting (Figure 20), which considers the patient's current lung function and predicts how this would decrease should functional segments be removed *(91).*

$$\text{Post-operative predicted value} = \text{Pre-operative value} \times \frac{\text{(Total number of segments-a) - b}}{\text{(Total number of segments-a)}}$$

Figure 20: Calculation for segment counting. The total number of segments is usually 19 (3 right upper lobe, 2 right middle lobe, 5 right lower lobe, 5 left upper lobe and 4 left lower lobe) unless the patients has had a previous lung resection. a is the number of obstructed segments and b is the number of unobstructed segments to be resected

Source: British Thoracic Society, Society of Cardiothoracic Surgeons of Great Britain, Party IW. Guidelines on the selection of patients with lung cancer for surgery. Thorax. 2001;56(2):89-108..

Traditionally, a predicted post-operative FEV_1 < 40% is the cut off for offering surgical resection due to the associated increased risk of postoperative complications and death, although the independent impact of FEV_1 has yet to be ascertained. Many different techniques can be used to assist in the estimation of post-operative lung function including ventilation and perfusion scintigraphy or quantitate CT scanning, as well as exercise testing such as shuttle walk tests, 6 or 12 min walk tests and formal cardiopulmonary exercise testing to predict VO_2 max. A VO_2 max < 15 mL/kg/min is associated with an increased risk of perioperative complications, whilst a VO_2 max < 10 mL/kg/min corresponds to a very high risk of postoperative complications. Crudely measured a patient that cannot climb a flight of stairs is considered to have a VO2 max of <10mL/kg/min(92). If surgical resection is to be offered to those with a moderate to high risk of postoperative dyspnoea, the patient needs to understand and accepts the risks. Alternatively, sub lobar

resection may be offered in place of lobectomy to those with a limited reserve function(31).

1.2 Evidence for minimally invasive thoracic surgery

1.2.1 Vats vs Open

1.2.1.1 In-hospital outcomes

In-hospital complications

Even from early experiences of VATS techniques for lung cancer resection, lower rates of in-hospital complications were seen in patients that had undergone lobectomy via VATS compared to open thoracotomy. Early VATS lobectomy literature is mostly comprised of small case-series or case-control studies, with the occasionally prospective study. In 2010, the American College of Surgeons Oncology Group Z0030 retrospectively reported on 752 patients (66 in the VATS group and 686 in the open lobectomy group) that had undergone lobectomy, bilobectomy, or anatomic segmentectomy. Results suggested a decrease in postoperative respiratory complications, with a statistically significant ($p < 0.05$) reduced rate of atelectasis requiring bronchoscopy and chest drainage lasting over 7 days in the VATS group (93). 30 day and in-hospital mortality were also reported, as they are the commonly used measures of operative mortality. On analysis of this national database favourable results were reported with the use of VATS, with a 30 day mortality rate significantly higher after thoracotomy than after VATS (2.9% vs 1.1%, $p = 0.02$)(94).

However, the large volume of retrospective studies are known to have potential bias due to the nature of their study design. Meta-analysis has been used to combine results from these studies, to improve the statistical power and create clearer conclusions as to the benefit of VATS lobectomy. Whitson *et al* 2008 meta-analysis of 39 studies showed that, of 3256 thoracotomy and 3114 VATS lobectomy patients, there was a significantly reduced overall complication rate (16.4% v 31.2%; p= 0.018) and a significant reduction in the chest tube duration by an average of 1.5 days in the VATS group (95). The main disadvantage of this data is that it was largely obtained from observational sources as only one randomised

study was included. A more recent systematic review and meta-analysis compared open with minimally invasive techniques for lobectomy and included results from 7 randomised control trials with a total of 1,276 randomised patients. In this review The International Society for Minimally Invasive Cardiothoracic Surgery consensus members scrutinized the articles in line American College of Cardiology/American Heart Association clinical practice guideline recommendations and 15 evidence-based statements achieved consensus. It concluded that conventional multiport VATS (mVATS) lobectomy is associated with a decreased risk of adverse events compared to open lobectomy (36% versus 42%; 88,460 patients) (Class IIA, Level C-LD)(73).

However, the main evidence comes from two recent randomised control trials. The VIOLET (VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy**)** study is the largest double blinded randomised control trial to date comparing clinical efficacy, safety and oncologic outcomes for VATS vs open surgery for lobectomy. Run across 9 UK thoracic surgical centres, it has reported early outcomes on 503 randomised patients between July 2015 to February 2019. VATS lobectomy was found to be associated with a reduction in overall in-hospital complications compared to open (32.8% v 44.3%, p=0.008) and no difference in serious adverse events in the early post-operative period(85). Similarly, the randomised trial that ran across 5 thoracic centres in China between 2008-2014 reported positively on VATS. It showed a statistically significant reduction in intraoperative blood loss and similar postoperative complications in the first 28 days compared with axillary thoracotomy (96). Most would agree that VATS lobectomy is at least as safe as open thoracotomy when considering serious adverse events and may in fact reduce peri-operative morbidity and mortality.

Length of stay

Length of in hospital stay is also compared as, not only is it a reflection of post-operative complications and the speediness of early post-operative recovery, but it is also a parameter for cost-effectiveness. However, it must be noted that length of stay is subject to a variety of confounding variables, such as differing hospital

discharge protocols, patient's willingness or reluctance to leave hospital and social considerations. Early discharge practices are often encouraged and have been shown not to lead to an increase in readmissions(97) . Retrospective institutional studies have observed modest reductions in length of hospital stay with the use of VATS techniques (93, 98). Large national database analysis, using propensity score matching, has revealed statistically significant reductions in length of hospital stay by around 1 to 2 days following VATS lobectomy compared to thoracotomy (99, 100). Analysis of the ESTS database showed that mean post-operative hospital stay was 2 days shorter for VATS patients (7.8 days v 9.8 days, p=0.0003)(100). Hospital Episode Statistics (HES) data for England reported a similar benefit on in-hospital stay and, in 2016, average length of stay was 1.9 days shorter for lobectomy procedures undertaken with VATS (6.8 days) than those without (8.7 days) (20). Meta-analysis has conferred with this but suggest that the benefit may be even greater. Whitson et al. reported that the VATS approach was associated with a significantly shorter (p = 0.016) overall hospital length of stay (8.3 days) than thoracotomy lobectomy (13.3 days)(95). More recently, preliminary results of the VIOLET Trial have confirmed that a reduction in hospital stay is seen with the VATS approach and showed that patients randomised to the VATS group had a shorter median (IQR) length of stay of 4 days (3 to 7) versus 5 days (3 to 8) in the open group (85). As further results become available, we may be better able to assess how great a reduction in hospital stay VATS techniques can offer.

Pain and Quality of life (QoL)

One of the key rationales for the application of minimally invasive techniques is the notion that they reduce tissue trauma and therefore reduce post-operative and allow for a faster return to baseline QoL. Post-operative pain and QoL may be the hardest outcomes to accurately measure and various approaches have been seen in the literature. However, QoL and post-operative pain are two of the most important outcomes for patients. They are much more concerned with how much pain they are going to have and what their QoL is going to be compared to staying a day longer in hospital. The use of a Visual Analogue scale is commonly used to measure pain, although this is massively influenced by various patient factors and if

adequate analgesia is given there may be only a small or no observed difference in scores between those that have had open vs minimally invasive surgery. A surrogate measure, which seems reasonable considering the known deterioration in QoL in cancer patients, is to compare pre and post-operative QoL using validated questionnaires. EuroQol 5 Dimensions (EQ5D) questionnaire assesses generic aspects of health and the European Organisation for Research and Treatment of Cancer (EORTC) 30 item Quality of Life Questionnaire (QLQ-C30) is one of the most widely used instruments to assess health-related QoL in cancer patient.

A meta-analysis has concluded that from studies comparing either Visual Analogue Scores, QoL questionnaires, 6-minute walking test or post-operative FEV1, conventional multiport VATS can improve postoperative pain (Class IIA, Level B-R), and may be associated with improved QoL (Class IIB, Level B-R), and overall function (Class IIB*,* Level C-EO) when compared to open lobectomy (73). The greatest evidence in favour of this comes from a double blinded randomised control trial in Denmark, which investigated outcomes for VATS versus anterolateral lobectomy. The proportion of patients with clinically relevant pain (numeric rating scale ≥3) was significantly lower during the first 24 h after VATS than after open surgery (VATS 38%, 95% CI 0·28–0·48 *vs* thoracotomy 63%, 95% CI 0·52–0·72, p=0·0012). The VATS patients also reported significantly less frequent episodes of moderate-severe pain (p<0.001) in the 52 follow up weeks. QoL according to the EQ5D was significantly better after VATS but no significant different was seen on to results of the QLQ-30. The study concluded that postoperative pain and QoL was better after VATS than thoracotomy. Yet the benefit may be even greater than has been reported, as the comparison was made against axillary thoracotomy rather than a posterolateral approach. The posterolateral approach is considered to be more painful and thus it seems that an even greater reduction of pain may be seen when comparing VATS to posterolateral thoracotomy(101). The VIOLET trial, has also shown promising results when comparing visual analogue scores, with a lower median score In the VATS group of 3 (IQR 1-5) on day 2 post-op compared to the open group of 4 (2-5) (85).

1.2.1.2 Oncological outcomes

Long-term survival

Early critics if the VATS technique argued that the in-hospital benefits seen were insignificant if the main objective to provide a chance of cure and prolong survival were not met. Many surgeons in the early 2000s reported on either the overall 3 year or 5 year survival of their patients but most studies were retrospective and only one small prospective randomised trial of 100 patients was published by Surgi and colleague. Consistently the data showed that similar mortality rates between VATS and open techniques but data on long-term survival was scarce (102). Data on long-term survival is gathering. Institutional propensity matched studies, have revealed no significant difference in overall 5 year or disease free survival for VATS and open lobectomy (103). A large propensity matched analysis of 1195 patients in each treatment category, confirmed that there was no statistically significant difference between VATS and open techniques in terms of three year overall survival, disease-free survival, or cancer specific survival (104). VATS was seen to be of oncological equivalence to thoracotomy. Meta-analysis has concluded the same, seeing an with the absolute survival advantage ranging from 5% at 1 year to 17% at 4 years postoperatively for patients undergoing VATS compared to open lobectomy (95) and concluding that multiport VATS may be associated with improved overall survival and a similar disease-free survival compared to open (Class IIB, Level c-LD)(73).The VIOLET trial has yet to report on long-term survival, however, a randomised trial China has recently presented results for 5 year follow up on 432 randomised patients. VATS showed no inferiority to thoracotomy lobectomy in terms of oncological efficacy. Disease free survival rates were similar for VATS and open surgery (58% vs 62%, p=0.686) and there was no significant difference in overall survival at 5 years post-op (74% vs 71%, p=0.497)(105).

Lymph node sampling and nodal upstaging

For studies which were unable to obtain data on or have yet to report long-term survival for VATS and thoracotomy patients, other parameters of oncological efficacy have been seen. Sufficient lymph node sampling or dissection is considered

important as it not only allows for the detection of clinically occult metastases but accurate disease staging, which is needed to guide adjuvant treatment. Various studies have reported a higher or a similar total number of lymph nodes/stations sampled and higher nodal upstaging in open compared to VATS procedures, yet this has not been seen to translate into a difference in survival (94, 103, 106). Pooled analysis of 6714 patients, also showed no difference in the total number of lymph node stations dissected and, whilst nodal upstaging was shown to be significantly reduced in multi-port VATS compared to open lobectomy, there was again no significant difference seen in recurrence free or overall survival (73). It is possible that the difference in nodal upstaging is seen due to surgeons choosing thoracotomy for patients with larger and more central tumours, but the study was not able to confirm this. A small prospective randomised trial, showed favourable results that mediastinal lymph node dissection can be performed as effectively in VATS as open surgery (107). For those that doubted the ability of minimally invasive techniques to provide adequate lymphadenectomy, larger randomised trials have now reported no compromise in early oncological outcomes with the use of VATS technique, seeing no difference in lymph node upstaging or complete resection rates (85, 96). VATS resection appears to provide an adequate oncological operation for patients with early-stage NSCLC.

Studies that have shown that VATS lobectomy is associated with a better survival than open lobectomy have hypothesised that this may be due to patients in the VATS group being more likely to receive adjuvant chemotherapy if indicated. Peterson *et al*. have shown that patients are more likely to receive adjuvant chemotherapy than after open lobectomy(108). However, the numbers of patients who require adjuvant chemotherapy is small, and the benefits of adjuvant chemotherapy are also small. It is therefore unlikely that this alone is the cause of survival benefits seen in some studies.

1.2.1.3 Cost effectiveness

VATS lobectomy has been shown to be superior to thoracotomy when examining early postoperative outcomes, such as adverse events, length of stay, post-

operative pain and morbidity, and is at least as adept in terms of oncological efficacy. With financially restrained health care systems, cost- benefit analyses of the VATS approach have been reported. Yet, with no standardised approach to estimating costs, the literature gives the impression that VATS is at least as, if not more, cost effective than thoracotomy, but no solid consensus has been made. Most studies divide expenses into direct and indirect costs, and few include postoperative costs after discharge, such as for outpatient appointments, readmissions, emergency department visits and radiology costs. Reports from single institutions are mixed, some indicating that costs vary depending on patient characteristics (109) and others that VATS offers lower costs as a result of a lower rate of prolonged length of stay (110). The first comparative analysis was made by Park *et al* who retrospectively reported on 269 patients that underwent lobectomy by thoracotomy and 87 by VATS, concluding that the use of VATS technique resulted in decreased cost. The majority of this saving was attributable to the decrease in length of stay with VATS patients (average of 2 days less than thoracotomy) and a smaller surgeon's fee (111). One of the caveats with this data is that it did not include costs occurred post discharge, which was shown to be of importance as it may account for up to 40% of total 90 days costs (112). When accounting for this, risk-adjusted total 90 day costs were found to be lower for VATS lobectomies than open (112). Again, this was largely due to shorter hospital stay and reduced pot-operative complications with VATS.

Multi-institutional analysis of 3,961 patients undergoing lobectomy by thoracotomy or VATS, even after adjusting for confounding variables with multivariable regression, reported significantly higher costs for open lobectomy than VATS lobectomy. Interestingly, a significant association in the VATS lobectomies was noted between surgeon experience and cost, with average costs ranging from $22,050 for low volume surgeons to $18,133 for high volume surgeons. This association was not seen with open lobectomies (113). It is well known that there is steep learning curve associated with VATS technique and this analysis showed that with surgeon experience comes greater hospital savings. Surgeon experience most likely also accounts for differences in operative time seen in the literature, with

some reporting longer surgery time with VATS (113) but a recent randomised trial finding VATS advantageous with reduced median operative time compared to open lobectomy (96). Additionally, Park et al did not account for costs after discharge and there being a significantly reduced risk of adverse events in the VATS patients, the economic impact may be even greater in terms of cost and morbidity. Further multi-institutional studies and meta-analysis have seen similar trends, with initially high VATS procedural costs being offset by shorter hospital stay and reduced complications(73, 114) . Whilst it would appear that VATS can be a cost-effective technique for lobectomy, particularly as surgical experience with the technique increases, we await the cost analysis from the VIOLET Trial to shed further light on the situation.

1.2.2 Robotic vs Open

1.2.2.1 In hospital outcomes

In-hospital complications

Although robotic-assisted thoracoscopic surgery (RATS) is increasing in popularity. It is a relatively new approach and less centres use this approach when compared to video-assisted thoracoscopic surgery (VATS), therefore fewer publications are available comparing RATS to open lobectomy. Additionally, we must be aware that the technique for robotic lobectomy varies by centre and by country. Some report completely portal four or three-arm RATS, with various port placements, and others add an additional utility port (75, 115, 116). The first studies comparing RATS and open lobectomy showed very favourable outcomes for robotic surgery (115, 116). Reporting on a single surgeon's experience, Cerfolio *et al* showed that peri-operative outcomes following 106 RATS lobectomy cases were superior to lobectomy via rib and nerve sparing thoracotomy (75). There was a trend towards lower operative mortality (0% vs 3.1%, p= 0.11) and significantly lower morbidity in the RATS group compared with 318 propensity-matched open cases (27% v 38%, p=0.05)(75).

As larger cohort studies and multi-institutional national database analyses were released, a true difference in peri-operative mortality was seen with robotic lobectomy compared to open thoracotomy (82). In fact, a propensity matched cohort including 3,689 RATS lobectomy cases reported a statistically significant reduction in 30-day mortality compared to open lobectomy (1.7% v 2.4%, p=0.006)(71). Furthermore, RATS lobectomy was shown to result in significantly less intra-operative blood loss and statistically lower rates of post-operative complications(82), including fewer post-operative blood transfusions, prolonged air leaks and shorter chest drain duration compared to open lobectomy(74, 116, 117). However, caution must be taken when interpreting these results. Two of the studies, although matching their robotic cases with open cases from the STS National Database, only included early-stage tumours and excluded patients with T3/4 disease from the analysis (74, 117). One study also included segmentectomies and resection for benign pathology, and a significant difference in the pre-operative clinical staging was seen between the robotic and open groups, with a higher proportion of cases with larger and node positive tumours being resected by thoracotomy (74).

Further evidence from a large nationwide database has conferred with the idea that RATS lobectomy offers fewer post-operative complications (72). Oh D.S. *et al* reported on 2775 propensity matched RATS lobectomy cases and established that RATS was associated lower overall postoperative (34.6% v 43.2%, $p < 0.0001$) and 30-day complication rates (37.8% v 45.8%, $p < 0.0001$). Interestingly, one single-institution study looked at 81 high-risk patients in a sub analysis. They concluded that even in high-risk patients, those undergoing RATS lobectomy were less likely to have any pulmonary complications compared to if they had undergone an open procedure (28% vs. 45%, $p = 0.02$). Moreover, the difference in pulmonary complications was more pronounced in high-risk patients and less so for intermediate or low risk(118) .

Despite the rapid growth of robotic resection and the evident benefits in some centres, the number of cases is still low. With the lack of prospective randomised trials comparing RATS to open lobectomy, meta-analysis provides the strongest

evidence. Most meta-analyses have concluded that RATS is favourable over open thoracotomy in terms of peri-operative mortality and morbidity. However, the strength of these conclusions is poor. Cao *et al.* and O'Sullivan *et al.* identified that RATS lobectomy was associated with a lower overall morbidity compared to open lobectomy and Agzarian *et al.* reported reduced rates of prolonged air leaks, blood loss and shorter chest drain duration (119-121). However, these results were pooled from 3 small retrospective studies. The most comprehensive meta-analysis reported that there was no significant difference in perioperative morbidity between RATS and open lobectomy (122). The authors acknowledged that this was not consistent with database studies(72, 82, 118) and considered that RATS was at least comparable to thoracotomy and may even be superior in high-risk patient groups.

The only randomised trial to date comparing RATS lobectomy to open lobectomy took place in 3 thoracic centres in China (123). This multicentre randomised trial aimed to assess the safety and efficacy of RATS for cN2 NSCLC resection compared to axillary thoracotomy. Early outcomes on 58 RATS and 55 thoracotomy cases reported significantly less intraoperative blood loss (86.3 mL v 165.7 mL, $p < 0.001$) and shorter chest drain duration (4 v 5 days, $p=0.01$). Although there were less complications in the RATS group, no significant difference was observed (27.6% v 38.2%, $p = 0.23$). It should be noted that results may vary as this trial only included patients with cN2 disease and compared RATS to axillary thoracotomy. Additionally, it included bilobectomy, sleeve resection and pneumonectomy, although these numbers were small.

Existing literature suggests that RATS lobectomy may in fact be superior to open lobectomy, but the level of evidence is poor. Due to the small number of RATS lobectomy cases being performed, a large multicentre prospective trial is needed to confirm whether RATS holds an advantage over open surgery for lobectomy in terms of peri-operative outcomes.

Length of stay

As previously stated, length of stay is used as a measure of time of recovery following surgery. Although length of stay is influenced by many variables and is perhaps not the most important outcome for patients, is it an easy outcome to collect and is reported in many studies. Most small case series and larger databases studies concluded that length of hospitalisation was significantly shorter following RATS lobectomy compared to open lobectomy. However, there is variation in the extent that post-operative stay is reduced and the average length of stay following RATS lobectomy seems to vary by centre.

Both single and multicentre studies, as well as database analyses, have suggested that length of stay following RATS lobectomy may be as short as 2 to 4 days (75, 115, 117, 118). Others have described a longer average length of stay of around 5 – 7 days (71, 72, 82, 83). The only randomised trial reported 10 days as the mean length of stay for their RATS group(123). It should be noted that the studies that reported longer lengths of stay, in general, also reported longer lengths of stay for their open cases. This may suggest a difference in the hospital discharge protocols between centres.

Most studies have reported that RATS lobectomy appears to the reduce length of stay by around 2 days (72, 75, 83, 118), although a large database study has suggested that the difference may be less pronounced (71). Meta-analysis studies agree with the idea that RATS lobectomy reduces post-operative stay by around 1-2 days compared to open lobectomy (73, 119). One meta-analysis reported that RATS lobectomy results in a greater than 2 day reduction in post-operative stay (WMD: −2.20, 95% CI: −3.05 to −1.37)(122) whilst another reported a more modest reduction by 1.40 days (WMD −1.40, 95% CI −1.96 to −0.85, $P < 0.00001$)(120). The only randomised trial comparing RATS and open lobectomy has also reported a reduction in length of stay by 1 day in the RATS group but no statistically significant difference was detected between the groups (10 v 11 days, p=0.07)(123).

It is difficult to determine whether the shorter hospital stay seen with RATS lobectomy is due to a true difference in the rate of recovery or whether surgeon

preference and hospital protocols tend to result in patients staying longer following open thoracotomy. A prospective study with defined discharge criteria, which records the date patients are medically fit for discharge, may shed light on the true benefit of RATS lobectomy over open. Nonetheless, the benefit of a reduced hospital stay is probably more of a triumph when considering hospital costs than patient outcomes. One or two extra nights in hospital is probably of little importance to patients, who generally take a few weeks to fully recover from this type of surgery.

Pain and Quality of life (QoL)

One of the key advantages of minimally invasive thoracic surgery is that it claims to result in less post-operative pain compared to open surgery. With the benefits of VATS over open thoracotomy described in terms of pain and quality of life (QoL)(73), it has been hypothesised that RATS would result in a similar outcome. However, despite RATS often being described as offering lower pain and improved QoL, there is extremely little evidence to substantiate that RATS lobectomy is superior to open lobectomy in this respect. Cerfolio *et al.* reported significantly lower postoperative numeric pain scores out of 10 in the RATS group than the open group at 3 weeks (2.5 v 4.4, p =0.04)(75). No other pain scores were reported, so it could not be determined whether this difference was seen in the immediate post-operative period. Furthermore, the study reported that patients in the RATS group had significantly higher average mental health scores in the 12-item Short Form Health Survey at 3 months (53.5 vs 40.3, $p<0.001$), but that a similar trend in the physical health section did not reach statistical significance. This may suggest the possibility that QoL is better in the short term after RATS lobectomy than open lobectomy, but the argument is weak.

In a similar small retrospective study, the RATS group showed lower average pain scores from post-operative day 3 to 9 compared to the open group, however the authors reported RATS and VATS collectively as a minimally invasive group (124). There was a significant decrease in acute pain from day 4 in the minimally invasive

group compared to the thoracotomy group, but numbers were small with less than 40 patients undergoing RATS. Overall, no significant difference in chronic pain was found between the minimally invasive and open groups, although chronic numbness was more frequently seen after open lobectomy (11.6% v 25.5%, p=0.02).

Another small study reported significantly reduced mean pain scores at rest for the RATS group compared to the open group on day 3 and 5. There was no difference in pain on coughing or in post-operative opioid consumption (125). This study is again another example of a small retrospective study which reports on pain measures. No large multicentre study or meta-analysis has reported on pain or QoL. As stated in O'Sullivan *et al*. "despite almost every paper on the topic citing perceived lower pain scores for robotic surgery, there is no evidence to support this, and as such, an analysis of postoperative pain was not possible and is required in future studies".(p533,120)

1.2.2.2 Oncological outcomes

Long-term survival

As a new technique, reports on long-term survival following RATS lobectomy are perhaps even scarcer than other outcomes. Small case series have reported 5 year survival following RATS lobectomy for stage I primary lung cancer as 63.6% (119, 126) and 80% at a median follow up of 42 months (127). It should be noted that one of these studies included a small number of pneumonectomy and bilobectomy cases (127). In one of the largest multicentre case series to date, Park *et al*. reported an excellent overall 5 year survival rate of 80% in group of 325 patients, with higher stage specific survival rates for stage I and II NSCLC (128). In another multicentre study, 5 year stage-specific survival following RATS lobectomy for NSCLC was: 83% for stage IA, 77% for stage IB, 68% for stage IIA and 70% for stage IIB (129).This seems to concur with other reports (130) and is similar to Wilson *et al.,* who reported an overall 2 year survival of 87.6%(131).

Unfortunately, none of these studies included a comparative arm of thoracotomy patients. The results of overall 5 year survival following open lobectomy for early stage NSCLC has been described in meta-analysis studies as 67%(73) and 65.6%(95), and in a recent randomised trial as 71% (105). It therefore seems that RATS lobectomy may be equivalent to open lobectomy in terms of overall survival.

The few large propensity matched database studies available have shown no significant difference in 5 year overall survival between RATS and open lobectomy(83, 84). In fact, there was no significant difference in stage specific survival or recurrence free survival for early-stage NSCLC between RATS and open lobectomy(83). Most systematic reviews would agree that the evidence is sparse, but current findings support that idea that RATS is similar to open lobectomy in terms of long-term oncological outcomes (119, 120, 122). We await the long-term outcomes from the only randomised trial that has yet to compare RATS and open lobectomy, but appreciate that only patients with cN2 disease were included in this study (123). There is certainly a need for further evidence regarding long-term survival but there is no evidence that RATS lobectomy should be discouraged on the basis on oncological outcomes.

Lymph node sampling and nodal upstaging

A commonly perceived benefit of RATS lobectomy is that the superior optics and wristed instruments allow for a safer and more thorough lymph node dissection(75, 115, 132). Although the idea is plausible, the evidence to support this is modest at best. Some small retrospective studies have reported very positive results with superior numbers of lymph nodes and lymph node stations harvested (133). They have shown significantly higher numbers of N1-level lymph nodes (6.8 v 3.8 and 4.0, $p<0.0001$) and overall of lymph nodes (14.9 v 11.7 and 12, $p = 0.0007$) dissected in the RATS lobectomy/segmentectomy group compared to the VATS and open groups respectively(132). Others showed no difference in lymph node dissection (75, 115, 134).

Larger propensity matched studies have shown that RATS provides at least as good a lymphadenectomy as open thoracotomy but whether robotic surgery offers any

advantage to lymph node dissection is questionable. Rajaram *et al.* reported on 3689 RATS lobectomy cases and found that RATS had a slightly higher mean number of examined lymph nodes compared with open thoracotomy (9.9 v 9.6 nodes, p = 0.003), but no difference was seen in the propensity matched analysis(71). Other database studies and meta-analysis have reported similar lymph node harvests between robotic surgery and open thoracotomy (83, 122). However, data from a large single centre study has supported the idea that RATS is associated with a greater thoroughness of lymphadenectomy. The study found that the median number of lymph node stations sampled was higher in the RATS group than the VATS or open ($p<0.001$) and argued that with a greater number of cases a significant difference would be seen in nodal upstaging(84).

Yet when deliberating on the adequacy of lymph node dissection, perhaps we should consider whether the variation in results is in fact due to surgical technique or is influenced significantly more by the surgeon's approach and the importance placed on extensive lymph node dissection (131). If robotic surgery does result in a more extensive lymph node dissection, from the limited literature available this does not appear to have translated into an increase in overall or disease-free survival (83, 84, 122).

The only randomised trial has shown comparable results between RATS and axillary thoracotomy lobectomy, in terms of the number of lymph nodes, lymph node stations and N2 lymph nodes sampled(123). It would seem that whilst in theory RATS could offer more extensive and easier lymphadenectomy, the data does not yet fully support this.

1.2.2.3 Cost effectiveness

The main factor which appears to have limited the uptake of robotic surgery in thoracic centres is the initial capital investment and associated cost commitments, as well as the longer operating times reported by some centres(122). Furthermore, as some centres share the robot with other specialities, they may be unable to gain adequate access to the robot. When considering the cost of RATS lobectomy, as well as the direct and indirect hospital costs there are also robot specific costs.

These include the cost of purchasing and servicing the robot and the cost of robotic drapes and other robotic disposables(135).

Critics quote the high cost as a major hindrance to the growth of robotic lung resection. Small retrospective studies that reported on in-hospital costs found that RATS lobectomy cases cost more than open cases(115, 136), although there was no statistically significant difference in overall cost between the surgical techniques (136). The results of the first randomised trial have also shown that the overall cost for RATS lobectomy is significantly higher than for open lobectomy (¥100,367 v ¥82,002 , P<0.001)(123). However, details of how this cost analysis was undertaken was not reported.

The evidence is varied and systematic review has highlighted the difficulty in reaching conclusions regarding cost effectiveness as there are no prospective cost comparisons (121). The most comprehensive review of the observational studies available, concluded that the cost of RATS lobectomy is similar or even lower than that of open lobectomy(135). Other studies have reported that RATS may be cheaper than open lobectomy(111, 137). However, one of these studies had no comparative arm and the number of cases was small. The lowest reported cost for RATS lobectomy actually included the amortization of capital equipment and maintenance costs however, the cost appears to have been greatly influenced by the short length of post-operative stay, the low complication rates and the fact it was a high-volume centre(114, 137).

No consensus has yet been reached but the environment and factors which could lead to a more cost-effective robotics programme for lung cancer have been identified. For example, shorter length of hospitalisation and high case load are considered important variables to reduce the cost (111, 138). Similarly, RATS lobectomy has been associated with a longer operative time compared to open (122) and as operative time reduces with the rapid learning curve (77, 139, 140) it is believed costs will be driven down(135). Others have also cautioned against the comparison of cost-effectiveness between surgical techniques which have not been confirmed to be of equal clinical efficacy(141). The clinical benefits of RATS need to be better established before the financial impact can be justified.

1.2.3 Robotic vs VATS

1.2.3.1 In-hospital outcomes

In-hospital complications

As a minimally invasive technique, robotic-assisted thoracic surgery (RATS) is thought to offer similar benefits to video-assisted thoracic surgery (VATS) and thus a greater extent of the literature compares RATS to VATS lobectomy. Critics worry about the safety of RATS lobectomy with the lack of tactile feedback and the potential difficulties associated with the management of intraoperative bleeding. In a small case series of 26 RATS cases, a slightly greater drop in post-operative haemoglobin was seen in the RATS group compared to the VATS group and there were 2 more conversions due to bleeding (142). As more studies have been released the evidence doesn't suggest that there is any increased risk in the use of robotic surgery compared to VATS. Large database studies concluded that post-operative complication rates and 30-day mortality were similar between RATS and VATS lobectomy(80, 81). As a new technique it is also worth considering whether reports are of early experiences of robotic surgery, as it is likely that outcomes have improved with the learning curve and developments in robotic techniques and equipment (130). On analysis of lobectomy cases by high-volume surgeons, an improvement in in-hospital mortality was even reported in the robotic group compared to the VATS group (0% vs 1.6%, $p = 0.02$)(82).

We await the results of the ROMAN trial (NCT02804893), a prospective multicentre randomised trial aiming to compare VATS and robotic approaches for lobectomy and segmentectomy for early-stage lung cancer. However, without evidence from a randomised trial or large prospective multicentre study, various systematic reviews and meta-analyses have tried to reach conclusions as to whether post-operative outcomes are equivalent between the approaches. Some meta-analysis studies have reported on a few specific complications and found that there was no difference between the techniques in terms of blood loss or blood transfusion rates, rates of prolonged air leak or chest drain duration (120, 121). Others have reported similar overall complication rates between RATS and VATS (73, 122, 143,

144) and on occasion an improvement was actually seen with RATS (72). 30 day mortality rates following RATS lobectomy are low and at least comparable with that of VATS lobectomy (0.93% v 1.17%, p = 0.85)(73). Some meta-analyses have even concluded that RATS lobectomy is superior in peri-operative mortality(120, 122, 143, 145).

RATS lobectomy appears to be safe and seems to be at least as good as VATS in terms of post-operative outcomes. Conversion rates to open surgery are also compared between the techniques as they reflect the suitability and safety of the approach. Most large database studies have found similar or lower conversion rates with robotic surgery(72, 83). Meta-analysis studies have concurred with this, reporting equivalent (121, 122, 145) or lower rates (143) of conversion. Conversion rates appear to decrease with experience (121). With improvements in robotic technology, it has been suggested the RATS may be better suited in more complex cases. Resection of more advanced disease or following induction treatment, which are usually contraindications for VATS, may be feasible by a robotic approach(146, 147).

Length of stay

It would be assumed that length of stay following RATS lobectomy would be the same as seen with VATS. Most retrospective database analyses found length of stay to be similar between the techniques (80-82), although a few retrospective studies have suggested that this may be shorter with RATS lobectomy (72, 74). A large propensity matched database study comparing 2951 RATS lobectomy cases, found that the median length of hospitalisation was slightly shorter for the RATS cohort than that for the VATS cohort (6.9 days versus 7.3 days, $p < 0.0060$)(72). The authors suggested this was due to the reduced complication rate in the RATS group (34.1% v 37.6%, p= 0.0061) and that fewer patients were discharged to a transitional health facility compared to the VATS group, which can delay hospital discharge. This highlights the caution that should be taken when drawing conclusions from length of stay as it cannot be assumed that any observed differences are the result of a difference in post-operative recovery.

Most meta-analysis studies would agree that length of hospitalisation is similar between RATS and VATS lobectomy (73, 121, 122, 145, 148). Liang *et al*. reported shorter durations of in-hospital stay, with a mean hospital stay of 4.90 days in the RATS group and 5.23 days in the VATS group (SMD −0.08, 95% CI −0.23 to 0.07, p = 0.292)(143). However, O'Sullivan *et al.* reported a statistically significant reduction in hospital stay compared to the VATS (WMD −1.40, 95% CI −1.96 to −0.85, p < 0.00001)(120). It would seem that RATS lobectomy most likely results in a similar duration of hospital stay compared to VATS lobectomy. However, as these results were drawn from only retrospective observational studies, we await the outcomes of the ongoing multicentre randomised ROMAN trial (NCT02804893) comparing robotic and VATS resection for early-stage lung cancer.

Pain and Quality of life (QoL)

The number of studies describing post-operative pain following thoracic surgery are limited. Evidence is adding up in favour of reduced post-operative pain following lobectomy via VATS compared to thoracotomy (73, 85, 101). It would therefore be reasonable to consider that robotic surgery would hold a similar benefit over open surgery. However, there are even fewer studies comparing post-operative pain between VATS to RATS lobectomy.

A small retrospective study comparing 46 robotic lung cancer resections with VATS, concluded that patients undergoing completely portal robotic lung resection had a shorter duration of narcotic use (p=0.039) and returned to work or usual activities sooner(p=0.003)(134). The authors rightly highlighted that this was a rudimentary pain assessment and that a blinded trial, reporting accurate narcotic measurements and visual analogue scores, was needed.

There has been little consensus over the best way to measure post-operative pain in clinical studies. Kwon *et al* undertook a retrospective review comparing acute and chronic pain following RATS, VATS and open anatomic lung resection, using visual analogue scores and the PainDETECT questionnaires (124). Although it seemed that the robotic group had lower mean pain scores, particularly in the later

post-operative days, there was no statistically significant difference in pain scores between the RATS and VATS group (p= 0.6469). This is similar to results seen in other small cohort studies (149).There was also no observed difference in chronic pain reported, although more patients in the RATS group than the VATS group (69.2% v 44.2%, p=0.033) felt that the surgical approach had affected their pain, 88.2% said this was in a positive way(124). This perhaps reflects patients' positive perceptions of robotic surgery.

The only study to report on quality of life following RATS and VATS lobectomy used the European Organization for Research and Treatment of Cancer QLQ-30 quality of life questionnaire (EORTC). Only 9 patients in the RATS group and 20 patients in the VATS group completed the questionnaire. There was no statistical difference in the global health status or symptoms scale median scores between the groups. The results were positive in that they suggested that long-term quality of life was similar to that of the general population(150). There is a need for high quality evidence looking at post-operative pain and quality of life following RATS lung resection. All reports are from small retrospective studies, from which few conclusions can be drawn.

1.2.3.2 Oncological outcomes

Long-term survival

The comparative oncological effectiveness of RATS and VATS lobectomy is not well established. A few small retrospective studies have reported that RATS as equal to VATS in terms of overall long-term and disease-free survival (83, 84, 151-153). Larger database analyses reported similar outcomes (154, 155), with no difference in overall survival (71.4% v 73.1%, p = 0.366) or cancer specific mortality (16.6% v 14.9%, p = 0.639) between RATS and VATS lobectomy at 3 years(155).

Unfortunately, many of the case series describing long-term survival following RATS lobectomy have no comparative arm. Cerfolio *et al.* reported one of the largest multicentre retrospective reviews, with 1339 RATS lobectomy cases for NSCLC included. With a mean follow up of 30 months, they reported a 5 year stage-specific

survival of: 83% for stage IA, 77% for stage IB, 68% for stage IIA, 70% for stage IIB, 62% for stage IIIA , and 31% for stage IIIB (129). Results from further studies have also shown positive outcomes for survival (128, 156). These seem comparable to VATS and are similar to the results of meta-analysis studies, reporting overall 5 year survival of 72% (73), and a randomised trial, reporting a 5 year survival of 74% (105). However, we must be cautious when making this comparison as follow up was incomplete in these studies and numbers at 5 years are small.

Most meta-analyses comparing RATS and VATS lobectomy have failed to report on long-term oncological outcomes, and state that the body of evidence needed is not yet available (120). Those that attempted to compare long-term survival reported favourably on robotic surgery, with no difference noted in 2 year (86% RATS v 86% VATS, p=0.38) or 5 year survival (77% RATS v 73% VATS, p=0.38)(73). However, these conclusions were drawn from only one or two studies.

A small prospective study including 12 RATS lobectomy cases, found RATS to be similar to VATS in terms of overall 5 year survival (100% vs. 87.5%, p=0.386) and disease-free survival (82.5% vs. 75.6%, p=0.589)(157). However, this sample size is too small to draw any firm conclusions. A randomised trial (NCT03134534), aiming to report on short and long-term oncological outcomes following robotic and VATS lobectomy for NSCLC, is currently recruiting. If results are favourable to robotic surgery, this data will greatly add to the argument that the robotic approach is safe for lung cancer resection.

Lymph node sampling and nodal upstaging

Those who advocate for the uptake of robotic surgery as a minimally invasive approach for lung resection, often emphasise that RATS is better suited for lymph node dissection compared to VATS. In particular, surgeons have reported greater confidence in the dissection of N1 nodes, which may increase rates of nodal upstaging and subsequently oncological outcomes(130, 146). With the narrow set of evidence available, RATS seems to be comparable to VATS in terms of lymph node sampling but the superiority of RATS has yet to be seen in the data.

There have been few large studies to report on oncological outcomes but data from small retrospective studies have shown no significant difference in the total number of lymph nodes dissected or nodal upstaging (134, 157). Although, a few studies have suggested that RATS maybe superior to VATS (84, 131, 158). One study showed that the robotic group had a higher mean number of stations sampled (open 4.0 v robotic 3.8 v VATS 3.6; p= 0.001) and higher rates of overall nodal upstaging for clinical stage N0/N1 NSCLC (open 21.8% v robotic 16.2% v VATS 12.3% (p = 0.03) compared to the VATS group (158).

Larger database studies revealed similar outcomes between RATS and VATS lobectomy in terms of the total number of lymph nodes resected (83) and nodal upstaging (80, 83, 154). Meta-analysis has agreed with this and has detected no difference in the mean number of lymph nodes/lymph node stations sampled or the rates of nodal upstaging(73, 122).

Furthermore, if a true difference exists between robotic and VATS lymph node dissection, we would expect to see a difference in rates of uptake to chemotherapy. Very few studies report on rates of adjuvant chemotherapy following lung cancer resection by robotic surgery and VATS, and so far, no difference has been seen (154). This could change as increasing evidence becomes available.

1.2.3.3 Cost effectiveness

Perhaps the main caveat preventing the widespread implementation of RATS for lung cancer resection is the high costs associated. During the early experience of robotic surgery, most institutions reported the higher hospital costs compared to VATS lobectomy (81, 111, 133, 150). Large database studies reported a similar result (159, 160). Paul *et al.* examined 2498 RATS lobectomy cases between 2008 and 2011 from the National Inpatient Sample and determined that the median estimated total costs were significantly more than for VATS lobectomy ($22,582 vs $17,874, p< 0.05)(159). The few meta-analysis and systematic reviews commenting

on cost agree that robotic surgery is more expensive, although these conclusions were draw from a limited number of studies (73, 119).

Studies have suggested that the factors leading to higher costs with robotic surgery are increased operative times and the greater expense of robot specific disposables and instruments(81, 133, 142). It should also be considered that centres may have been early in the learning curve when analysis was undertaken and, as seen in many reports, robotic case numbers per year were small (111, 136, 161). Those that reported on the amortization of capital costs and maintenance fees showed the effect of variation in case number. Novellis *et al*. divided the capital cost of the robot (€2 million) and annual service cost (€20,000) by 400 procedures annually over 8 years(161), whereas Deen *et al.* calculated the cost of 4 robots ($8 million) plus annual service costs divided by an average of 2403 cases per 22 months on a 10 year straight line depreciation(136). Further complicating the issue is that some thoracic centres may share their robotic technology with other specialities. As proficiency increases, larger case numbers are seen and operative and theatre set-up time falls, RATS lobectomy could prove to be cost-effective.

Those that have seen no increased cost with robotic surgery compared to VATS, also reported shorter lengths of hospital stay in their robotic group and similar post-operative outcomes(114). Kneuertz *et al*. found no difference in direct, indirect (including costs of amortization of capital equipment and servicing), operating room or total charges between the techniques(114). There are opportunities for reducing the cost of robotic surgery and as the technique becomes were widespread the current monopoly on equipment may be broken, further decreasing the cost.

Whilst important, the justification of robotic surgery perhaps extends beyond cost-effectiveness. The rate of VATS lobectomy is just over 50% for lobectomy, bilobectomy and wedge resection(21). It is apparent that not all cases are suitable for VATS resection or perhaps the learning curve associated with VATS is unfavourable to some surgeons(79). Robotic surgery has a shorter learning curve and may be more feasible in cases of multiple adhesions and sleeve resection for central tumours (162). With the benefits of minimally invasive surgery over open

thoracotomy as previously described, the advantage of increasing rates of minimally invasive procedures should be considered. The perceived patient, surgeon and hospital benefit should also be taken into account and further evidence is needed regarding functional outcomes, quality of life, complication rates, re-admission rates and long-term survival.

Chapter 2: Robotic assisted surgery for early-stage lung cancer: a retrospective study

2.1 Introduction

Minimally invasive techniques for lung cancer resection have not only been shown to be safe but the benefits include better aesthetic results, less post-operative pain and a faster surgical recovery time with a better quality of life in the post-operative period compared to traditional thoracotomy(73, 85, 101). It is thought that robotic assisted thoracic surgery (RATS) for lung cancer resection may offer similar advantages to those seen with VATS. However, robotic assisted techniques are thought to overcome the limitations seen in VATS, with improved three-dimensional optics and wristed instruments which provides greater degrees of freedom of movement and rotation to mimic the natural movements of the human wrist (163). The uptake of the VATS technique for lung cancer resection has been slow and cautious and is associated with significant learning curve, thought to be around 50 cases (79). The transition to robotic assisted surgery from thoracotomy maybe a more attractive option to surgeons than developing VATS skills. Robotic technology may allow for easier lymph node dissection and pulmonary artery dissection and its uptake may result in an increase in the percentage of lung cancer surgeries completed by minimally invasive techniques.

At present, the number of lobectomies performed robotically is low, with the technique being used for less than 1% of all lobectomies and bilobectomies for NSCLC in England (21). Due to the high initial procurement and maintenance costs, robotic technology is not broadly available and consequently the data on robotic lobectomy for lung cancer resection is limited. Large series on robotic lobectomy for lung cancer and the long-term outcomes are missing. Early studies have described the safety and feasibility of robotic lobectomy (116, 117, 128), although not all of these studies had a comparative arm. Retrospective database studies have been conducted to gather data on a larger number of robotic lobectomy cases for lung cancer and have reported favourably on RATS when compared to open and

VATS lobectomy(72, 80, 81). RATS for lung cancer resection may, in fact, prove to be cost-effective due the associated reduction in length of hospital stay and good peri-operative outcomes(114). Authors have stated that comparative studies on RATS within single institutions are needed as post-operative protocols vary greatly between regions and thus results are not always comparable(164). The place of robotic surgery for lobectomy has yet to be determined and from the literature available it has not been established whether robotic surgery holds any true benefit over VATS in the case of lobectomy for lung cancer resection.

In 2017, Liverpool Heart and Chest Hospital launched the UK's first robotic cardiothoracic surgery programme and the first robotic lobectomy was performed using the Da Vinci X in December 2017. Liverpool Heart and Chest Hospital is one of the leading centres for VATS in the UK. We report on early experiences of RATS lobectomy for lung cancer resection at Liverpool Heart and Chest Hospital.

2.2 Aims and objectives

The aim of this study is to evaluate the experience of robotic surgery for lung cancer resection over past 2 years at Liverpool Heart and Chest Hospital and report on the efficacy of RATS lobectomy in comparison to VATS lobectomy. We expect RATS lobectomy will result in similar outcomes to those seen with the VATS technique.

The primary objective is to compare in-hospital outcomes following robotic and VATS lobectomy. The outcome measures of this study are:

1. Peri-operative outcomes (length of hospital stay, adverse events, admissions to critical care).
2. Technical outcomes (conversion rates)

2.3 Methods

Study design

We conducted a retrospective study comparing all robotic lobectomy cases for suspected or confirmed lung cancer to VATS lobectomy at Liverpool Heart and Chest Hospital. From July 2013 to July 2018, the lung cancer surgery database at Liverpool Heart and Chest Hospital was prospectively filled. We have reviewed and cleaned the dataset and identified a total of 2005 lobectomies (or bilobectomies) for known or suspected lung cancer in this period. In this group, 895 lobectomies were undertaken by VATS. Patients who underwent pneumonectomy, wedge resection or sleeve resection were excluded. Robotic thoracic surgery was introduced to Liverpool Heart and Chest Hospital in 2017, with the first robotic lobectomy completed in December 2017. From theatre records, we identified all patients who underwent robotic lobectomy for suspected or confirmed lung cancer at Liverpool Heart and Chest Hospital up to January 2020. A dataset was designed, with data fields similar to the hospital's lung cancer database. This was retrospectively completed for 58 robotic lobectomy cases using the hospital's electronic patient records.

Approvals

All data was collected as part of routine clinical practice and therefore ethical committee approval was not deemed necessary. Approval for data analysis and comparison of groups was granted from the Clinical Audit and Effectiveness group (ref CAEG/ 17th October 2017).

Pre-operative work up and operative technique

All lung cancer patients being considered for surgery resection underwent a full work up pre-operatively. This includes a recent CT scan of the chest, PET- CT, lung function tests and full blood count. Some patients may have undergone additional investigations such as biopsies or a CT/MRI brain scan.

Robotic and VATS lobectomy were performed as described in Chapter 1. All lymph node management is undertaken in accordance with the International Association

of the Study of Lung Cancer (IASLC) recommendations where a minimal of 6 nodes/stations are removed, of which 3 are from the mediastinum that includes the subcarinal station (165).

Patients were extubated in theatre and sent to the recovery unit before being discharged back to the ward or critical care unit. Post-operative care was the same as is routinely practiced at Liverpool Heart and Chest Hospital.

Outcome measures

1. Staging

All staging was as per the IASLC TNM 8th edition stage classification(8).

2. Length of stay

Length of stay describes the length of hospital stay post-operatively, from the date of surgery until discharge.

3. Complications

Complications were prospectively coded on the hospital's electronic patient record system. Prolonged air leak was described as lasting for more than 5 days postoperatively.

Statistical analysis

Data is presented on an intention to treat basis. The data was grouped by robotic and VATS approach, with continuous variables reported as a mean and standard deviation for normally distrusted variables, and median and interquartile range for non-normal distributions. For normally distributed variables unpaired Students t-test was used, and for categorical variables chi-squared tests were used. Continuous variables of non-normal distribution were analysed using Mann-Whitney tests. *p* values less than or equal to 0.05 was considered statistically significant.

2.4 Results

Between July 2013 and July 2018, 2005 lobectomies (or bilobectomies) were performed at Liverpool Heart and Chest Hospital. Of these 895 were attempted VATS. These are compared with 58 robotic lobectomies performed between December 2017 and January 2020. There were 85 patients in the VATS group that were converted to open operations (9.5%) and 4 in the robotic group (6.9%). Two patients in the robotic group were completed VATS: one due to arm failure on the robot and the other due to incomplete resection following lingulectomy, so a VATS left upper lobectomy was performed (3.4%). Reasons for conversion are not recorded on the database.

Pre-operative characteristics are shown in Table 1. The groups were very evenly matched apart from there being significantly more patients with COPD in the VATS group and they had a lower mean TLCO. The mean age of all patients was 68.9 years. 44.6% of patients were male.

Table 1. Pre-operative characteristics

Characteristic	**VATS**	**RATS**	**p value**
Number	895	58	-
Age (mean ±SD)	69.5±9.1	68.0±9.7	p=0.2334
Sex = Male (n (%))	405 (45.8%)	20 (34.5%)	p=0.0944
BMI (mean ±SD)	26.9±9.4	26.6±5.2	p=0.2334
Smoking status	Non 113 Ex 531 Current 239 Unknown 12	Non 11 Ex 35 Current 11 Unknown 1	p=0.1137

FEV1(% predicted) (mean ±SD)	68.9%±13.5%	102.4±26.4%	p=0.2334
FVC (%predicted) (mean ±SD)	102%±20.6%	99.1%±20.4%	p=0.3997
TLCO (%predicted) (mean ±SD)	55.7%±15.8%	77.4%±17.4%	p=<0.0001
COPD (n (%))	460 (51.4%)	19 (32%)	p=0.0043
Cardiovascular co-morbidity (n (%))	480 (53.6%)	23 (39.6%)	p=0.1666
Previous CVA/ TIA (n (%))	1 (7.7%)	4 (5.4%)	p=0.9803
Diabetes (n (%))	2 (15.4%)	11 (14.9%)	p=0.7686

With regards patients who had previous ipsilateral thoracic surgery there were 7 patients in the VATS group and no patients in the robotic group.

Operative characteristics are shown in Table2. Patients in the VATS group were more likely to require an upper lobectomy and in the robotic group a lower lobectomy.

Table 2. Operation characteristics

Characteristic	**VATS**	**RATS**	**p value**
Number	895	58	-
Left-sided (n (%))	352 (39.3%)	21 (36.2%)	p=0.4568
Bilobectomy	4 (0.4%)	0	Not performed
Upper Middle Lower	596 (66.6%) 37 (4.1%) 258 (28.8%)	13 (22.4%) 3 (5.1%) 42 (72.4%)	p<0.0001

Table 3. Post-operative outcomes

	VATS	**Robotic**	**P value**
Post-operative destination Ward Critical care Unknown	 77 (8.6%) 765 (85.5%) 43 (4.8%)	 47 (81%) 11 (19.0%) 0	 p<0.0001
Length of stay (median [IQR])	4 [3-7]	3 [3-7]	p=0.0063

Post-operative robotic patients were significantly more likely to go back to the ward than VATS resections (Figure 1). There was a significantly shorter post-operative length of stay in the robotic group (Figure 2).

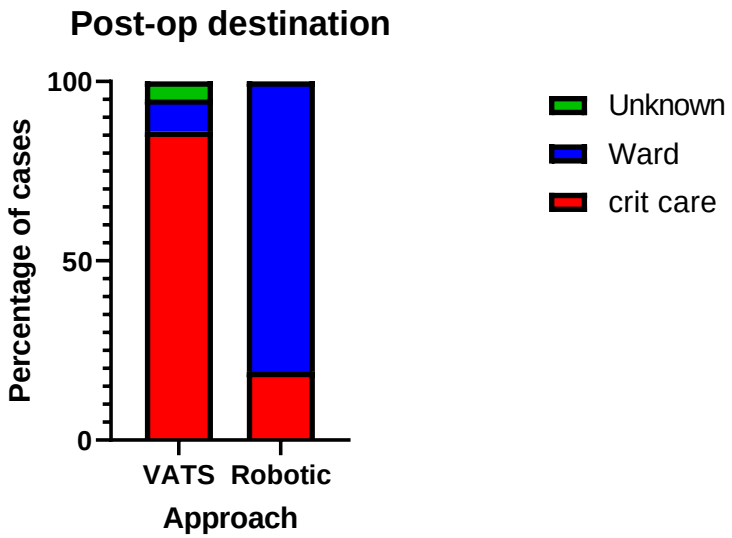

Figure 1. Bar graph showing post-operative destination by surgical approach. Post-operatively RATS patients were significantly more likely to go back to the ward than VATS resections (p<0.0001)

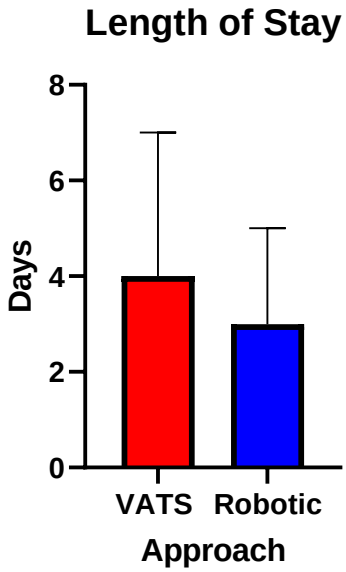

Figure 2. Bar graph showing post-operative length of stay by surgical approach. The box represents the median and error bar the 75th centile. Post-operatively RATS patients had a significantly shorter length of stay than VATS resections p=0.0063

Details of post-operative outcomes are shown in Table 4. There was a decrease in overall complication rates in the robotic group, however there were similar incidence of respiratory complications between the two groups. There was also no difference in the readmission rates to critical care.

Table 4. Post-operative Complications

	VATS	RATS	P value
Any complications (n (%))	224 (25.0%)	11 (17.2%)	p=0.0093
Respiratory complications (n (%))	141 (15.8%)	8 (13.7%)	p=0.1909
Critical care re-admission (n (%))	63 (7.0%)	3 (5.2%)	p=0.3485
Death (n (%))	5 (0.56%)	0	p=0.5682

2.5 Discussion

This data shows that a robotic lobectomy programme can be introduced safely with similar results to VATS lobectomy. The robotic lobectomy group had a significantly shorter length of stay (4 v 3 days, p=0.0063) and required significantly less critical care admissions post-operatively (85.5% v 19.0%, p<0.0001). There was a lower overall complication rate in the RATS group (25.0% v 17.2%, p=0.0093). These differences suggest there may be a potential benefit of robotic lobectomy.

The mean age of the whole cohort is 68.9 years. This is lower than the national average (9). This probably reflects the lower than average life expectancy in the Liverpool region (166). Somewhat surprisingly is the female predominance. National data shows that 52.2% of lung cancer cases occur in males(9) and the VIOLET trial reported that 49.5% of participants were male (85). There has been a

decrease in lung cancer rates for males and increase for females over the past decade (7).

The decrease in median length of stay in the robotic group by one day suggests there may be a faster recovery in RATS lobectomy patients. Shorter length of hospital stay by around 2 days have been shown when RATS lobectomy has been compared to open (72, 75, 83, 118). When compared to VATS lobectomy the length of stay for robotic lobectomy in the literature has been shown to be similar and, in some cases, shorter in duration (72, 73, 120, 143, 148). The shorter length of stay seen in the robotic group was probably due to the overall lower complication rate in this group. It was somewhat surprising that it was mainly a difference in non-respiratory complications that led to this difference. One would hypothesise that robotic surgery causes less pain and therefore less respiratory complications. Also, both groups were evenly matched for non-respiratory co-morbidities and the robotic group had a high mean TLCO. Again, one would therefore expect possibly less respiratory complications. This requires evaluating further in prospective studies.

In this study RATS lobectomy patients were significantly more likely to go to the ward rather than critical care post-operatively when compared to VATS lobectomy. The exact reasons for this are unclear. It may be due to less tissue trauma and blood loss during a robotic lobectomy, although we do not have data to support this theory. Another possible explanation is that this is a type I error and there may have been a change in unit practice over time to send more anatomical lung resections back to the ward. The COLT pilot study should answer this.

The conversion rates in this study are in line with national data(21) and the mortality rate lower (21). Comparing morbidity rates to published datasets is difficult. Results appear similar to other retrospectively published series(75). They are however lower than those seen our prospectively collected database(Chapter 3) and other randomised trials, thus highlighting one of the disadvantages of this type of study(123).

The main limitation of this study is its retrospective and non-randomised nature. Therefore, results may have been subject to information and selection bias. In addition, robotic and VATS cases were sampled from different time periods. The groups appeared to be evenly matched and, upon discussion with the statistician, we decided against propensity matching as the only difference in pre-operative characteristics found were rates of COPD and percentage predicted TLCO. Furthermore, there were a number of potential confounding factors that could not be accounted for as they were not included on the retrospective database, such as trainee involvement, use of frozen section, presence of incomplete fissures and tumour position. Lastly, by propensity matching we would assume that all lobectomies, whether performed robotically or by VATS, held the same technical difficulty.

One of the differences that we did see between the groups was there were more lower lobectomies in the robotic group (72.4% v 28.8%). This suggests that this may be one of the surgeon's selection criteria for performing a robotic rather than a VATS lobectomy.

This study was conducted as a single centre retrospective study. Both overall and respiratory complication rates were significantly lower in this retrospective analysis than in the COLT pilot (Chapter 3). This can be a problem of retrospective databases where the data is entered later. Another problem is that the severity of the complications is not graded. In addition, the retrospective database provides no details on post-operative pain, quality of life, or details that would enable us to do a cost analysis. The follow-up period in the robotic group is relatively short and therefore long-term outcomes cannot be assessed.

2.6 Conclusions

It has been shown that robotic lobectomy is at least as safe as VATS lobectomy. The robotic lobectomy group had a significantly less complications, significantly shorter length of stay and required significantly less critical care admissions post-operatively, suggesting the potential benefit of robotic surgery. A further well-

designed prospective cohort or randomised studies are required to fully assess complications, pain, quality of life, and the economic impact of robotic lobectomy.

Chapter 3: COLT pilot study: **C**ohort study comparing **O**utcomes for different **L**obectomy **T**echniques in units performing robotic thoracic surgery

3.1 Introduction

Lung cancer is the leading cause of cancer death worldwide and the survival rate for patients diagnosed with lung cancer in the UK is amongst the lowest in Europe (167). In 2018, 39,205 patients were diagnosed with lung cancer in the UK (19). The National Lung Cancer Audit (NLCA) reported that 18.4% of patients with non-small cell lung cancer underwent surgical resection as part of their treatment in England and Wales (19). There has been a steady increase in the proportion of lobectomies performed by VATS (45). The proportion performed by robotic assisted thoracic surgery (RATS) in the UK remains very low (21).

There is variation in surgical resection rates across the UK. It is noted in the NLCA report that adjusted surgical resection rates varying from 10% to 37% and 52 organisations failed to meet the audit standard of 17% (19). Despite the Getting It Right First-Time report (20) recommending that patients with early stage lung cancer be operated on by minimally invasive surgery, geographical disparity is wide between the type of techniques used. Some units achieve minimally invasive surgery rates of 84%, whilst the lowest unit rate was 10.3% (20). Surgical approach for lung cancer is driven by surgeon preference rather than informed by evidence leading to patient benefit. The VIOLET trial will determine the role of VATS compared to open surgery (65), but the place of robotic thoracic surgery will remain unknown. The currently recruiting ROMAN trial (NCT02804893) is a multicentre randomised trial which aims to enrol 300 participants by 2023 and compare VATS and robotic approaches for lobectomy. To date there are no randomised trials or large prospective multicentre studies which compare robotic lobectomy to other surgical techniques. With a possible easier adoption, robotic surgery may allow for an increase in minimally invasive lung cancer surgery.

Mortality after lobectomy is 2.3% (31) and common complications include bleeding, chest and wound infections, prolonged air leak and arrhythmia. The mortality rate for resections performed by minimally invasive surgery compares favourably with the open approach(45) and a recent literature review by Cao and colleagues, also reported lower perioperative morbidity, pneumonia, atrial arrhythmia and a shorter hospital stay in patients who underwent VATS lobectomy compared to open surgery(168).

Over the last two years there has been a surge in robotic-assisted thoracic surgery (RATS) in thoracic surgical units in the UK. The robotic system enables surgeons to perform delicate and complex operations through a few very small incisions with magnification, high-definition visualisation, precision, dexterity and control. This may lead to reduced surgical trauma to a patient's body compared to open and VATS techniques. The evidence so far is limited but from the studies available it has been suggested that patients undergoing robotic lung resection have a reduced length of stay overall, spend less time on critical care, have reduced complications and a faster recovery time; all of these culminating in a better patient experience (72, 83). Robotic lung resection has been shown to be cost effective when compared to thoracotomy (111, 137). This is largely due to a shorter hospital stay and lower complication rate (114, 137). A study by Kent *et al.* (82) uses a large national database in America (State Inpatient Database) to compare open, VATS and robotic lobectomy. In both the unmatched and matched analysis robotic lobectomy compares favourably with both VATS and open lobectomy (82).

Good quality data comparing robotic lung cancer resection to open surgery and VATS is not currently available. At present, there are no large prospective studies or randomised trials comparing robotic surgery for lung resection to other techniques. There is, therefore, a need for a well-designed and conducted trial to provide the evidence base for the uptake and delivery of this surgical approach.

The COLT trial (**C**ohort study comparing **O**utcomes for different **L**obectomy **T**echniques in units performing robotic thoracic surgery), is a multi-centre prospective cohort study comparing outcomes and cost effectiveness of different techniques of lung cancer resections in units performing robotic thoracic surgery. In preparation for the COLT trial, a dataset was developed. From this a minimal dataset was formed, the COLT pilot study case report file (CRF) (Appendix A).

3.2 Aims and objectives

The aim of the COLT pilot study was to finalise the dataset, in order to move forward with the full COLT trial.

The primary objective of the COLT pilot study was to assess whether adequate data could be collected in preparation for the full prospective COLT trial and to determine issues around data collection and assess data completeness.

Our secondary objective was to evaluate the CRF and to determine how to improve data collection prior to the commencement of the full COLT trial. Secondary outcomes were:

1. Short term patient outcomes (intra-operative complications, length of hospital stay, ITU admissions, adverse events, in hospital morbidity, patient reported pain scores and post-operative analgesia requirements).
2. Technical outcomes (operative time, conversion rates and equipment use).
3. Early measures of oncological efficacy (intra-operative lymph node sampling, complete resection rates and the proportion of patients upstaged to pN2 disease).

3.3 Methods

Study design

The study included all patients $\geq$16 years of age that underwent lung resection for known or suspected lung cancer between 20th January 2020 and 24th March 2020 at

Liverpool Heart and Chest Hospital. Patients were identified using the operative list on the hospital's intranet system. The CRF was used to capture patient data (Appendix A). These were prospectively completed using Liverpool Heart and Chest's electronic patient record system and Picture Archiving Communication System (PACS), with surgeons completing operative details (Section C) in theatre. Data was collated in an encrypted Microsoft Excel spreadsheet and approvals given from Liverpool Heart and Chest Hospital for remote access.

Approvals

Data collection and analysis was granted approval by the Clinical Audit and Effectiveness group (ref CAEG/ 17th October 2017).

Operative technique

All patients who were deemed suitable for a minimally invasive approach had a minimally invasive approach attempted. The choice of minimally invasive approach was at the surgeon's discretion and this study had no influence over patients' treatment plans.

Surgery was performed as described in Chapter 1. All lymph node management is undertaken in accordance with the International Association of the Study of Lung Cancer (IASLC) recommendations where a minimal of 6 nodes/stations are removed, of which 3 are from the mediastinum that includes the subcarinal station (165).

As this is a pragmatic study, post-operative care was the same as is routinely practiced at Liverpool Heart and Chest Hospital.

Outcome measures

1. Staging

Staging was as per the IASLC TNM 8th edition stage classification (8).

2. Length of stay

Length of stay was calculated from the date of surgery until discharge. The time at which patients are considered medically fit-for-discharge and when they are

physically discharged from hospital were both be recorded. Some patients who are considered medically fit-for-discharge may not necessarily be discharged immediately as in some instances social and other factors may necessitate extended hospitalisation.

3. Adverse events

Adverse events were recorded from the time of surgery to discharge as defined in the CRF (Appendix A). Severity of adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (169) and the worst grade experienced by the patient during their in-hospital stay was recorded. Frequencies of adverse events will be described, and treatment differences will be reported with 95% confidence intervals.

4. Pain measures

The degree of post-operative pain experienced by patients undergoing robotic, VATS or open surgery was an important consideration when comparing different surgical techniques. Patients were asked to verbally report on their pain from day 1 post-operatively on a scale of 0-3:"0" = no pain, "1" = mild pain, "2" = moderate pain and "3" = severe pain. If the patient reported a range, then the highest score was recorded. Due to the pragmatic nature of this study standardising the use of analgesia is impractical and, if implementable, would produce data unrepresentative of real clinical practice. Patients' analgesic requirements were recorded at baseline, intra-operatively, in the post- operative phase and at discharge. The type of analgesia was categorised according to its class, as described by the World Health Organisation's (WHO) pain relief ladder, into paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDS), mild opioids, strong opioids and adjuvants. It was documented whether this was taken regularly by the patient or only when necessary (PRN).

Statistical analysis

Data is grouped according to robotic, VATS or open approach. Continuous variables were presented as median (interquartile range) and categorical data as the relative

percentage. Due to only three cases in the robotic group, data is displayed in the tables for information only and did not form part of the statistical analysis. Open and VATS group were analysed on an intention to treat basis. T-tests were used for normally distributed continuous variables and chi-squared tests for normally distribution categorical variables. For continuous variables of non-normal distribution Mann-Whitney tests were used. A *p* value less than or equal to 0.05 was considered statistically significant.

3.4 Results

Between 20th January 2020 and 24th March 2020 data was captured prospectively on all 99 patients who underwent a lung resection at Liverpool Heart and chest Hospital. The COLT pilot ceased on this date due to COVID-19 pandemic. Despite this, data completeness was 98.1% with 9,906/10,098 data fields complete (see Appendix A).

The cohort of patients in each group are shown in Figure 1. 12 patients underwent a planned open lung resection, 83 a VATS lung resection and 3 patients a robotic lung resection. 2 patients in the VATS group had a frozen section that revealed benign disease and therefore are excluded from the analysis. 7 patients in the VATS group underwent a wedge resection for suspected metastatic disease and therefore are excluded from the analysis. 1 patient who was listed as a VATS/open lung resection, on bronchoscopy it was seen he needed a sleeve resection and an open operation performed. As no attempt was made to perform a VATS operation this patient is included in the open group.

Data is presented on an intention to treat analysis. There were 8 patients in the VATS group were converted to open operations (10.8%). The reasons for not receiving the intended surgery are shown in Table 1. 1 patient in the robotic group was converted to open due to injury to the pulmonary artery.

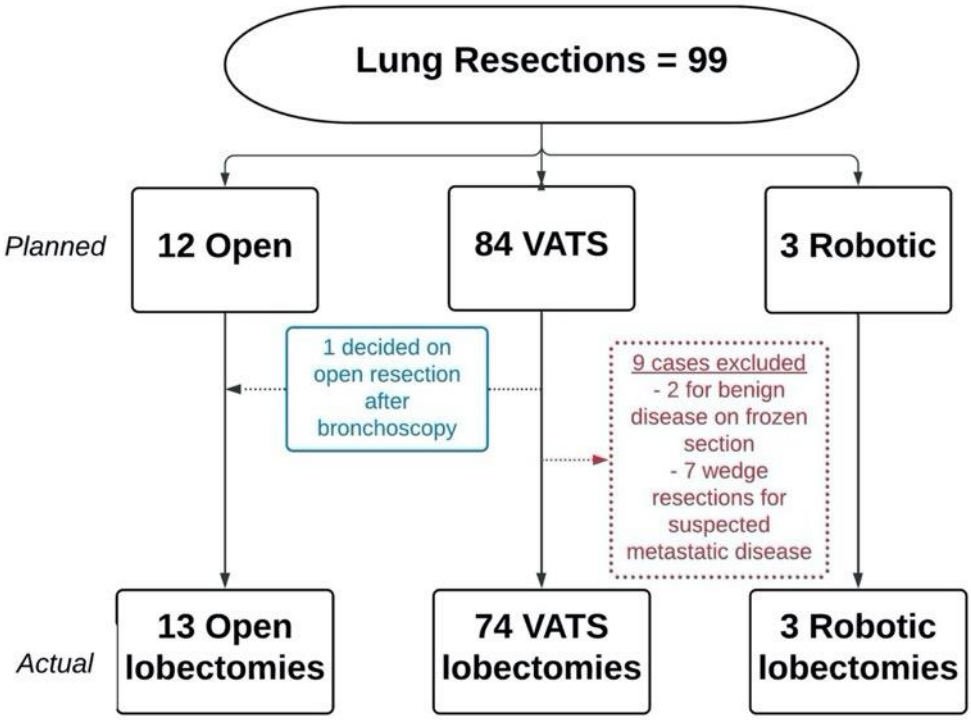

Figure 1: Patient cohort for COLT pilot study. 1 patient was moved from the VATS to the open group as it was decided on bronchoscopy that the patient required a sleeve resection via open surgery, and no attempt was made to perform a VATS operation. 9 patients were excluded from the analysis; 2 patients were found to have benign disease on frozen section and 7 were wedge resections for suspected metastatic disease.

Table 1. Factors for conversion from VATS to open surgery

Factor	**Number of cases**
Tumour crossing the fissure and unable to properly define extent	1
Unable to dissect out pulmonary artery safely	2
Unable to identify lesion	1
Incorrect bronchus divided and needed re-anastomosing	1
Adhesions	1
Bleeding from pulmonary artery	2

Pre-operative characteristics are shown in Table 2. There was no difference between groups. The mean age of all patients was 67.8 years. 30% of patients were male.

Table 2. Pre-operative characteristics

Characteristic	**Open**	**VATS**	**Robotic** *	**p value**
Number	13	74	3	-
Age (median [IQR])	65 [57-71]	71 [63-73]	71 [60-75]	p =0.1680
Sex = Male (n (%))	5 (38%)	21 (28%)	1 (33%)	p=0.7589
BMI (median [IQR])	26.1 [20.6-28.9]	26.3 [23.0-29.1]	25.7 [19.4-38.5]	p=0.1552
Smoking status	Non 3 Ex 8 Current 2	Non 9 Ex 41 Current 24	Non 1 Ex 2 Current 0	p=0.4315
Performance status	O 9 1 2 2 1 >2 1	O 35 1 34 2 2 >2 0	O 2 1 1 2 0 >2 0	p=0.1294
Pre-op Haemoglobin, g/L (median [IQR])	133.5 [127.3-141.3]	135 [129-145]	149 (137-152)	p=0.1552

Pre-op WCC (median [IQR])	9.0 [7.2-10.6]	7.75 [5.9-9.0]	6.5 [6.1-8.1]	p=0.1053
FEV1(% predicted) (median [IQR])	84.70 [63.25-99.48]	90 [78.50-66.00]	95 [66-120]	p=0.4964
FVC (%predicted) (median [IQR])	97 [88.10-120.4]	105.2 [93-117.0]	102 [66-129]	p=0.7663
TLCO (%predicted) (median [IQR])	75.50 [55.02-87.50]	69.53 [59.85-83.12]	91 [74-101]	p=0.2111
Respiratory co-morbidity (n (%))	4 (30.8%)	26 (35.1%)	0	p=0.4390
Cardiovascular co-morbidity (n (%))	6 (46.6%)	45 (60.8%)	3 (100%)	p=0.2167
Previous CVA/ TIA (n (%))	1 (7.7%)	4 (5.4%)	1 (33.3%)	p=0.1620
Chronic pain (n (%))	2 (15.4%)	2 (2.7%)	0	p=0.1146
Diabetes (n (%))	2 (15.4%)	11 (14.9%)	0	p=0.7686
Alcohol >14 units per week (n (%))	1 (7.7%)	20 (27%)	2 (66.7%)	p=0.0850

*Due to small numbers the statistical analysis not performed on robotic group. Column for information only.

With regards previous thoracic surgery, 1 patient in the open group had previously had a right middle lobectomy and had an upper lobectomy for local recurrence. 1 patient in the VATS group had a left lower lobectomy followed by a right upper lobectomy for leiomyosarcoma metastasis.

Prescence of pre-operative histology and staging is shown in Table 3. Pre-operative biopsy was attempted in 68.9% patients and conclusive in 53% of the patients who underwent anatomical lung resection. There were 7 benign anatomical lung resections: 1 in the open group and 6 in the VATS group. Of the benign resections 3 patients (including the 1 patient in the open group) had no attempt at obtaining pre-operative histology, 1 had a failed CT biopsy, 1 had an inconclusive biopsy, 1 had a highly suspicious biopsy, and one had a negative EBUS. Success rate of CT guided biopsy was 35 (34 malignant, 1 true negative) out of 44 patients (79.5%).

Table 3. Pre-operative histology and staging

	Open	**VATS**	**Robotic***	**p value**
Pre-operative Histology (n (%))	9 (69%)	37 (50%)	2 (66%)	p=0.3936
Resection for suspected metastatic disease (n (%))	0	4	1 (33%)	Not performed
T	1 2 >1 11	1 51 >1 11	1 1 >1 1	p<0.0001
N	0 10 1 or 2 3	0 69 1 or 2 5	0 2 1 or 2 0	p=0.0604

*Due to small numbers the statistical analysis not performed on robotic group. Column for information only.

Table 4. Operation details

Characteristic	**Open**	**VATS**	**Robotic***	**p value**
Number	13	74	3	-
Pneumonectomy Bilobectomy Lobectomy Segmentectomy	1 1 10** 1	0 1 72 1	0 0 3 0	Not performed
Sleeve lobectomy	2	0	0	Not performed
Frozen section performed	0	6	0	Not performed
Operative time, minutes (median [IQR])	162 [110-229.5]	149.5 [123.8-178.3]	253 [242-293]	p=0.6147
Number of lymph node stations sampled (median [IQR])	5 [2.5-5.5]	4 [3-5]	2 [2-4]	p=0.3183

*Due to small numbers the statistical analysis not performed on robotic group. Column for information only.

**Including 2 sleeve lobectomies

Out of the initial cohort of 99 patients, 8 patients received frozen section. 6 of these revealed NSCLC and we therefore proceeded to perform a VATS lobectomy. Patients with a higher T stage were more likely to get an open operation although the N stage did not affect approach.

Table 5. Post-operative characteristics

	Open	**VATS**	**Robotic** *	**P value**
Number of drains	1 8 2 5	1 68 2 6	1 3 2 0	p=0.0024
Post-operative destination	Ward 4 Critical care 9	Ward 60 Critical care 14	Ward 3 Critical care 0	p=0.0001
Length of stay (median [IQR])	4 (4-5)	3 (2-6)	7 (2-15)	p=0.1548
Pain score day 1 (median [IQR])	2 (1-2)	2(1-2)	1 (0-2)	p=0.8528
Pain score day 2 (median [IQR])	1 (1-2)	1(1-2)	1(0-1)	p=0.7355
In-hospital strong opioids (n (%))	4 (30.8%)	40 (54.0%)	3 (100%)	p=0.3089
Any complications (n (%))	5 (38.5%)	31 (41.9%)	2 (66.7%)	p=0.8168
CTAEv5 1-2 (n (%))** CTAEv5 ≥3 (n (%))	3 (23.1%) 2 (15.4%)	15 (20.3%) 16 (21.6%)	1 (33.3%) 1 (33.3%)	p=0.3112

Respiratory complications (n (%))	4 (30.8%)	27 (36.5%)	2 (66.7%)	P=0.6914
Critical care re-admission (n (%))	0	3 (4.1%)	1 (33.3%)	P<0.0001

*Due to small numbers the statistical analysis not performed on robotic group. Column for information only.

**patient grouped according to the complication with the highest CTAE grade.

Post-operative characteristics are shown in Table 5. There was no significant difference in operation time between open and VATS approach. It is, however, noted that the 3 robotic operations all took longer than the 75th centile for the open and VATS cases. Patient in the open group were more likely to have 2 chest drains compared to the VATS group (p=0.0024). All the robotic patients only had 1 drain.

Post-operative VATS patients were significantly more likely to go back to the ward than open resections (Figure 2). All three robotic resections went back to the ward rather than critical care. The median length of stay in the VATS group was 3 days and 4 days in the open group. This did not however reach statistical significance.

The overall complication rate was 42.2% with no significant difference between the VATS and the open group. 21.1% of patients had a complication of grade 3 or above. Again, there was no statistical difference between the VATS and the open group. There were more patients re-admitted to the critical care unit in the VATS group than the open group.

Five patients in the cohort were re-admitted to ICU: 4 in the VATS group, and 1 in the robotic group. There was 1 in-hospital mortality in the VATS group. This patient had undergone a left lower lobectomy for metastasis then underwent a right upper lobectomy for further metastasis. Following this the patient developed an acute lung injury in the non-operated lung and required ventilation. While on ICU the

patient developed COVID-19 infection and died. A further patient in the VATS group died of an unknown cause, two months following discharge.

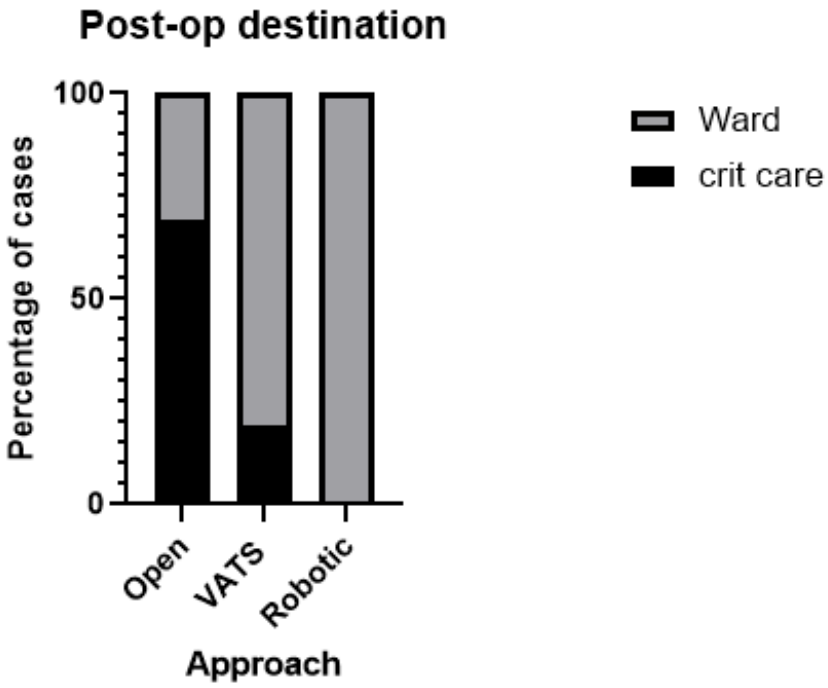

Figure 2: Bar graph showing post-operative destination by surgical approach. Post-operative VATS patients were significantly more likely to go back to the ward than open resections (p=0.0001)

Pain scores were similar for all groups on day 1 and 2 post-operatively and there was no significant difference in the percentage of patients requiring strong opioids post-operatively.

In regard to early oncological outcomes, one patient in the VATS group had an R1 resection while in the open group one had an R1 and one an R2. All robotic resections were R0. The number of lymph node stations harvested was not statistically different between the groups (Figure 3).

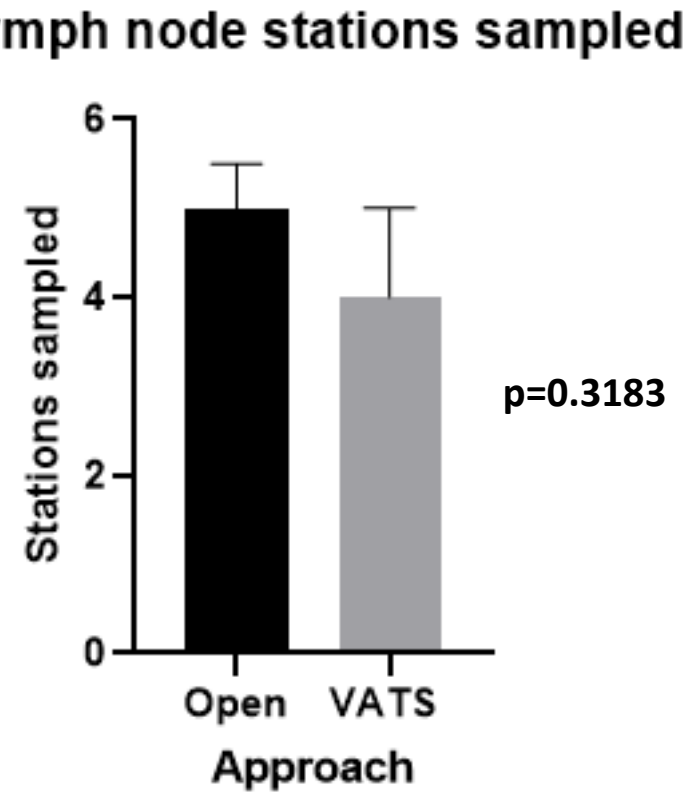

Figure 3: Bar graph showing number of lymph node stations sampled by surgical approach. Error bars show the 75th centile. There was no statistically significant difference in the number of lymph node stations sampled between the open and VATS approach (p=0.3183)

3.5 Discussion

The COLT pilot study shows that a high-quality, detailed dataset can be successfully collected. In spite of the fact that this study was cut short due to COVID-19, data was collected on 90 lobectomy cases and 98.1% data completeness was achieved, which bodes well for the successful implementation of the full COLT trial.

VATS lobectomy

The overall proportion of patients receiving minimally invasive surgery was 75.6%, higher than the national average (21). The majority of planned procedures were

VATS (82.2%), demonstrating that Liverpool Heart and Chest Hospital is one of the leading centres in the UK for VATS. The conversion rate is this study is in line with national data (21).

Robotic lobectomy

This study included 3 robotic lobectomy cases. The reason for this being that robotic surgery at Liverpool Heart and Chest was stopped in early March due to COVID-19.

Open lobectomy

The number of planned open cases was lower than expected at 13 out of 90 cases (14.4%). National data suggests approximately 44.2% of lung resections are performed by open surgery (21). This figure includes pneumonectomies, the majority of which are performed open, and cases which are converted from VATS to open.

Patient characteristics

The groups were evenly matched in terms of age, sex, BMI and co-morbidities suggesting these do not influence choice of approach. The mean age of the whole cohort is 67.8 years. This is lower than the national average (9), but similar to our retrospective data (Chapter 2). This probably reflects the lower than average life expectancy in the Liverpool region (166). Somewhat surprisingly is that only 30% of patients were male. National data shows that 52.2% of lung cancer cases were in males(9) and the VIOLET trial reported that 49.5% of participants were male (85). There has been a decrease in lung cancer rates for males and increase for females over the past decade (7) but the difference seen is most likely a result of our small case numbers.

Pre-operative histology

Pre-operative biopsy was attempted in 68.9% patients and conclusive in 53% of the patients who underwent anatomical lung resection. This is similar to that reported in the VIOLET trial (170). The percentage with pre-operative histology was higher in

the open group than the VATS group, as would be expected due to the larger and more centrally located tumours. Of the 7 patients who were found to have benign disease following anatomical lung resection, 1 in the open group had a segmentectomy and 6 in the VATS group had lobectomies. In the robotic group, 2 out of 3 patients had pre-operative histology and there were no resections for benign disease.

Intra-operative histology via frozen section

The surgeons at Liverpool Heart and Chest indicated the difficulty in performing frozen section robotically, due to the inability to palpate the mass. This is seen as one of the disadvantages of robotic surgery. As it is more difficult to do get intra-operative histology via RATS, one may expect pre-operative histology to be required in more cases. In our cohort, 10.5% of patients in the planned VATS group required a frozen section. This could explain why a small percentage of patients would have had a VATS rather than robotic lobectomy. However, there are various ways one can get around the lack of tactile feedback required in order to perform a frozen section robotically. These include injection of methylene blue around the lesion or marking the tumour with a wire or radioactive tracer (171). Data was not collected on whether a frozen section was planned but not carried out. The plan for frozen section may influence the choice of VATS or robotic surgery and should be recorded in the full COLT study.

Surgical approach

The T stage appeared to influence the approach of surgeons, whilst the N stage had no effect. Larger tumours, and tumours invading the chest wall, diaphragm or mediastinum are more difficult to resect via VATS and therefore, not surprisingly, were more likely to be resected by an open approach. With regards the N stage having no influence over approach, this probably reflects the experience of the surgeons in VATS lobectomy. It is generally appreciated that resecting a lymph node containing cancer can make an operation more difficult. In future studies one may have to be aware of a potential difference in N status between the robotic and VATS group. Yang *et al.* shows that robotic surgery may result in an easier and more

comprehensive lymph node dissection(84). However, surgeons newer to robotic surgery may choose to resect the more difficult, lymph node positive cases by VATS, leading to a bias in results.

In-hospital outcomes

Minimally invasive lung resections (VATS and robotic) were less likely to require a critical care bed after the operation, suggesting that less intensive hospital care is needed post-operatively than with open surgery. However, post-operative destination is often decided on prior to surgery and this finding be a type I error and the result of performance bias. Although the median length of stay was lower in the VATS group (3 days) than the open group (4 days), it did not reach statistical significance. A significant proportion of in-hospital costs are critical care stay and overall length of hospitalisation, thus minimally invasive surgery should be cost-effective. Cost effectiveness will be included in the full COLT trial.

Length of post-operative stay was favourable in both our open and VATS group, with a median of 4 and 3 days respectively. National audit data has reported a median length of stay of 6 days for all lung cancer resections (21), and an average of 8.7 days for open lobectomy and 6.8 days following VATS lobectomy(20). Liverpool Heart and Chest Hospital's median length of hospitalisation for open lobectomy (4 days) and VATS lobectomy (3 days) is comparable to the VIOLET trial (85), a reflection of the units' experience and high rates of VATS lung cancer resection.

The overall complication rates for open (38.5%) and VATS (41.9%) lobectomy were similar to that described in the VIOLET trial, although the VATS group didn't show any benefit in lower complications(85). As this was a pilot study, we did not expect to observe a statistical difference. More patients in the VATS group were re-admitted to critical care. This was not observed in our retrospective study (Chapter 2) and may be due to the small sample size.

Early oncological outcomes were satisfactory for VATS and open operations with no significant difference in the number of incomplete resections or number of lymph node stations harvested.

Post- operative pain

Patients in the open group were significantly more likely to have a 2 chest drains compared to the VATS group and no robotic patients had more than 1 chest drain. Chest drains are a significant cause of post-operative pain.

There was no difference between open and VATS groups in terms of pain scores or number of patients requiring strong opioids. The use of adequate post-operative analgesia following lung resection, provides excellent pain control and we wouldn't expect a large variation in pain scores between the groups. Thus, this may be a type II error as a result of either a small effect or sample size. The VIOLET trial reported a small difference between VATS and open surgery on day 3 (median pain score 3 v 4, respectively) (85). In the pilot COLT study, we measured pain on a 4-point scale, which may not have been sufficient. Pain is an important outcome for patients and we would recommend using the visual analogue score, which rates pain on a scale of 0-10, in the full COLT trial.

Advantages and limitations of the COLT pilot study

This prospective pilot trial has a number of advantages over a retrospective design. Prospective studies are tailored to collect the desired data fields and the dataset is designed to look at specific outcomes. Retrospective studies are limited by the data that has already been captured and are influenced by information bias. Prospective collection is thought to result in a more accurate dataset as patients are actively followed. We analysed data on an intention to treat bias, which is beneficial as it reflects actual clinical practice. However, as some procedures were converted from VATS to open, the VATS group includes patients which underwent open surgery. Therefore, the true benefit of minimally invasive surgery in terms of reduced pain, fewer complications and reduced length of hospital stay may not be seen.

The pilot COLT study was limited to a single centre at Liverpool Heart and Chest Hospital. However, the plan is that the full trial will be multicentre. Unfortunately, the pilot study was cut short due to COVID-19. Non-essential surgeries at Liverpool Heart and Chest Hospital were cancelled from 24th March 2020, limiting the number of lobectomy cases performed. Robotic surgery ceased a few weeks prior to this. Furthermore, all non-coronavirus research activity ceased and non-essential personnel, including medical students, were excluded from clinical areas from 11th March 2020 making data collection very difficult. Due to low numbers of robotic cases, we would recommend that future studies are multicentre.

Design and recommendations for the future COLT trial

The aim of the COLT trial is to generate high-quality evidence to compare a range of clinical and patient-reported outcomes between all types of lung cancer surgery (VATS, robotic and open) in order to inform current NHS practice, health policy and individual surgeon and patient decision-making. A randomised control trial, the ROMAN trial (NCT02804893), is currently recruiting and aims to compare RATS and VATS for the treatment of early-stage lung cancer. The primary endpoint is adverse events and secondary outcomes include operative time, pain and quality of life. However, it has been noted that there is no intention to conduct a cost analysis in this trial. Cost effectiveness is a one of the key arguments against robotic surgery and the COLT trial aims to report on health care costs at 90 days with the use of national hospital episode statistics. Additionally, the current gold standard for lung cancer resection is not yet known, and thus even following the results of the ROMAN trial the place for robotic surgery may not be clear. A prospective cohort study will allow for accurate and comprehensive data collection and the comparison of open, VATS and robotic techniques.

Although randomised control trials are at the highest level of the study hierarchy, their main advantage is being able to detect differences between the new intervention and control group. Suggested benefits of a robotics programme include a shorter learning curve and a reduction in the total rate of pulmonary

resections by open thoracotomy(172). A randomised control trial with strict quality control measures may not be able to detect these differences or perhaps demonstrate the full potential of robotic surgery. Furthermore, the ROMAN trial has set strict exclusion criteria to create a more homogenous study group, but this may compromise the external validity of its results. The benefit of a non-randomised and pragmatic cohort study is that exclusion criteria are scarce, and the trial is designed to reflect current clinical practice. As previously discussed, a randomised control trial would be difficult at present due to the range in surgical expertise. In addition, recruiting significant numbers may be challenging as rates of robotic surgery are still low and some units have limited access to robotic technology. McColloch et al. have emphasised the value of prospective studies to deal with potential methodological shortcomings such as endpoints, sample sizes and surgical variation prior to a randomised control trial(63). Prospective multicentre studies also have the advantage over retrospective series of being able to design many of the features of the study such as outcomes, technique standardisation and eligibility criteria, as described in the COLT protocol (Appendix E), and are not influenced by information bias.

The primary endpoint for the COLT trial is self-reported physical function at 5 weeks post-surgery, as early recovery is expected to be one of the main advantages of robotic surgery. At around one month post-surgery most patients will return to their normal activities, and it was thought that at this point the benefit of robotic surgery would be most apparent. Extensively validated questionnaires (EQ-5D and QLQ-50) will be used to analyse QALYs and HRQoL, as they are considered to be consistent and reliable tools. Resource utilisation and adverse health events will be reported up to 90 days. Although other studies have reported on these outcomes up to 1 year (65), it was thought that the signal to noise ratio would be higher at 3 months. Long term overall and cancer-free survival are perhaps the most significant outcomes to consider in terms of safety. However, studies require adequate funding, resources and participants to be able to complete extended follow up and this is outside the scope of this study. The COLT trial aims to report on overall survival up to 1 year.

3.6 Conclusions

The pilot COLT trial undertaken at Liverpool Heart and Chest Hospital has demonstrated that adequate data collection may be undertaken for the full trial, with the inclusion of visual analogue pain scores and details of planned frozen section. The full COLT trial will require dedicated research nurses and a data manager to ensure data completeness and not be dependent on busy surgeons to complete CRFs. Ninety lobectomy cases were included in this pilot study and the percentage of VATS cases was higher than expected. This needs to be taken into account when designing a full trial, to ensure there is sufficient power.

Chapter 4: Robotic approach to mediastinal mass resection: initial results at Liverpool Heart and Chest Hospital

4.1 Background

Mediastinal masses

The mediastinum is defined as the area between the thoracic inlet and diaphragm, bounded laterally by the medial pleura, anteriorly by the sternum and posteriorly by the thoracic vertebra. Surgical subdivisions split the mediastinal space in an anterior to posterior direction into the anterior, middle and posterior compartments(173)(Figure 1).

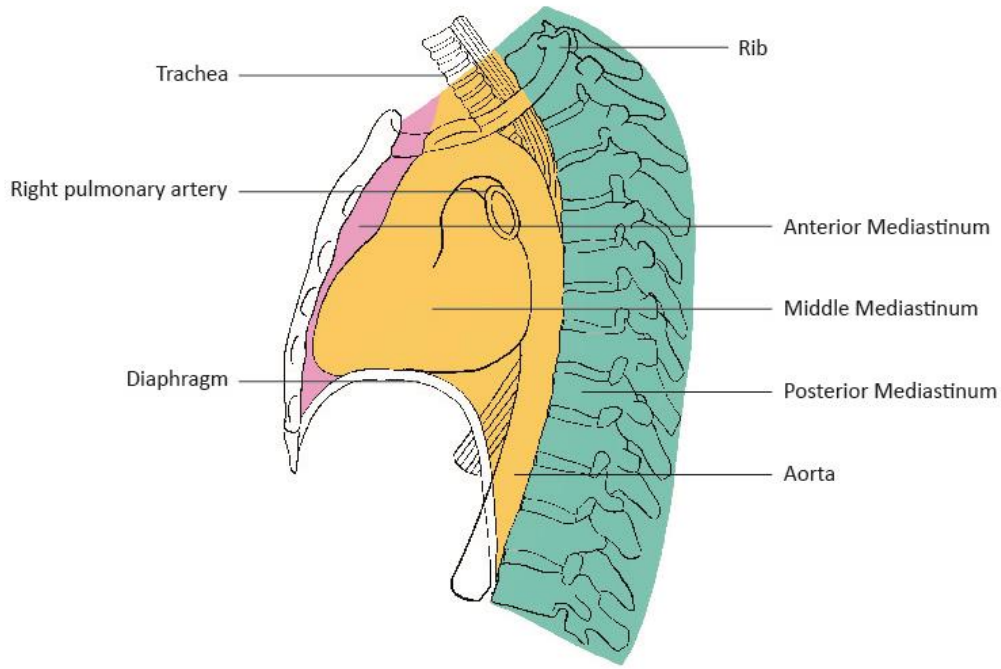

Figure 1: Mediastinal mass compartments. Image provided by Katherine G. Buller.

Mediastinal masses are grouped according to the compartment from which they originate (Table 1).

Table 1: Table showing the possible causes of masses in each mediastinal compartment

Compartment	Anterior mediastinum	Middle mediastinum	Posterior mediastinum
Anatomy	Thymus, fat, lymph nodes	Trachea and main stem bronchi, lymph nodes, heart, pericardium, great vessels, oesophagus and thoracic duct	Sympathetic chain, thoracic spinal ganglia, azygous and hemi-azygos venous system
Mediastinal masses	- Thymoma or thymic hyperplasia - Thyroid (retrosternal goitre) - Germ cell tumours - Lymphadenopathy	- Tracheal and bronchial tumours - Lymphadenopathy - Foregut cysts (bronchogenic, oesophageal) - Pericardial cysts - Heart: enlarged chambers (e.g. enlarged left atrium in mitral valve disease), cardiac tumours - Aortic aneurysm - Oesophageal tumours - Hiatus hernia	- Neurogenic tumours (e.g. neurofibroma, schwannoma, ganglioneuroma, phaeochromocytoma) - Lymphadenopathy

The most common mediastinal masses found in adults are thymomas, thyroid masses, lymphomas and lymphadenopathy. The most common mediastinal tumours that present in adults are thymic epithelial tumours, germinal cell tumours, lymphoma and neurogenic tumours. Around half of all mediastinal masses

are located to the anterior compartment, with the majority originating from the thymus, whereas one fourth are found in the middle and posterior compartments (174). Most mediastinal masses are detected incidentally on chest x-ray. However, some patients may present with symptoms caused directly by the mass i.e. dyspnoea, cough, dysphagia or chest discomfort whilst others may experience systemic features relating to the underlying pathology. The clinical symptoms, or the lack of, may give clues as to the diagnosis, such as the presence of B symptoms which are commonly described in lymphoma.

Masses of thymic origin

The thymus is a primary lymphoid organ located in the anterior mediastinum. The anterior thymus is in relation to the sternum, the posterior to the upper pericardium and laterally to the mediastinal pleura, lungs, pericardium and great vessels. It's two horns extend upwards towards the inferior thyroid and it extends down to the 4th or 5th costal cartilage. There are various causes of thymic masses. An overall enlargement of the thymus can result from thymic hyperplasia, which is noted to occur in children and young adults or following chemotherapy treatment. Other benign masses include thymolipomas and thymic cysts (Figure 2). Thymic cysts are identified as fluid-filled structures on CT and can be differentiated from cystic thymomas with the use of MRI (174).

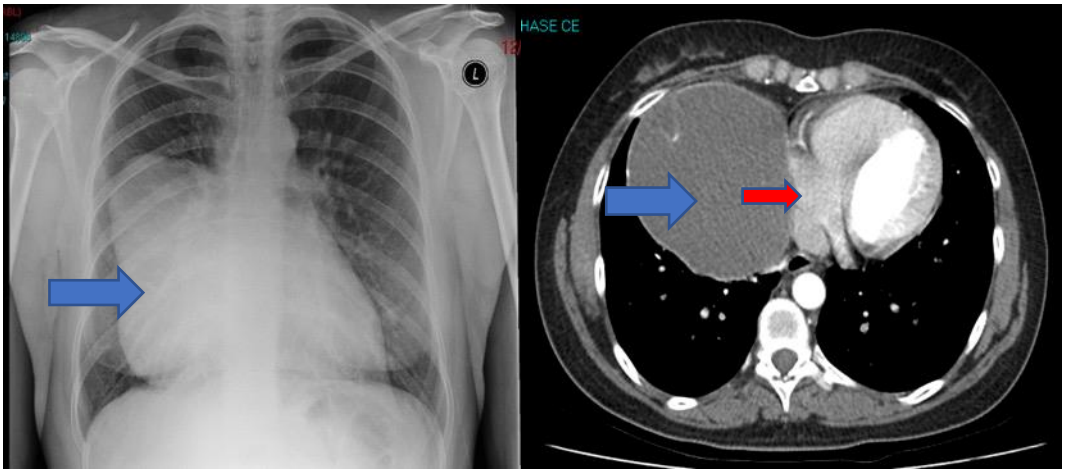

Figure 2: 39 year old female presenting with shortness of breath and chest discomfort. Plain radiographs and CT scan showed a thymic cyst (blue arrow) occupying the right hemithorax. The cyst is compressing the right side of the heart (red arrow)

Thymic epithelial neoplasms include thymoma, thymic carcinoma and thymic neuroendocrine tumours. Thymomas are rare tumours, with the overall incidence of malignant thymoma being less than 0.15 cases per 100,000 person-years (175). However, they are the commonest neoplasm in anterior mediastinum and range from benign to intermediate grade malignant tumours (Figure 3).

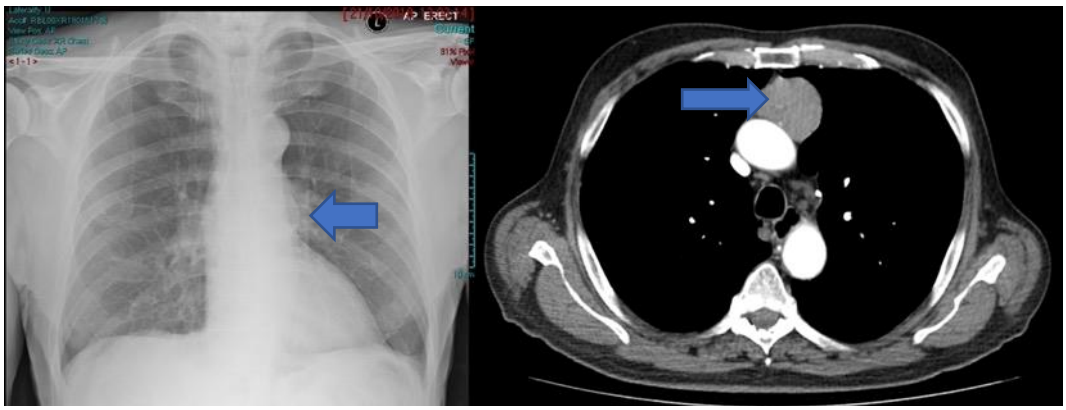

Figure 3: 72 year old male presenting with myasthenia gravis and found to have an anterior mediastinal mass on plain radiograph and CT scan (blue arrow). Surgically resected with post-operative histology confirming a type B3

The average age at diagnosis is around 50 years and there are a range of associated systemic syndromes. The most common is myasthenia gravis, an autoimmune neuromuscular syndrome, which is present in 30- 50% of patients(176). Other frequently seen disorders are hypogammaglobinaemia (5% of cases) and red cell aplasia (5% of cases) (177). Thymomas are grouped by morphology into subtypes A, AB, B1-3 and rarer forms, according to the WHO classification(178). Thymic carcinomas are even less common than thymomas and are well differentiated, high-grade malignant tumours which can develop de novo or within an existing thymoma.

Thymomas are classified using the widely accepted Masaoka staging system (Table 2) (179). TNM staging of thymic neoplasms is a controversial topic, with many proposed systems. However, the International Association for the Study of Lung Cancer (IASLC)/the International Thymic Malignancy Interest Group (ITMIG) staging system as recently been recognised by the American Joint Committee on Cancer (AJCC) (Table 3)(180) .

Stage	Definition
I	Macroscopically encapsulated tumour, with no microscopic capsular invasion
IIa	Macroscopic invasion into surrounding fatty tissue or mediastinal pleura
IIb	Microscopic invasion into the capsule
III	Macroscopic invasion into the neighbouring organs
IVa	Pleural or pericardial metastases
IVb	Lymphogenous or hematogenous metastasis

Table 2: Masaoka Staging System for thymomas

Source: Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer. 1981;48(11):2485-92. PubMed PMID: 7296496.

Category	Description
Tumour (T)	
T1a	Encapsulated or unencapsulated, with or without extension into mediastinal fat
T1b	Invasion of mediastinal pleura
T2	Invasion of pericardium
T3	Involvement of lung, chest wall, phrenic nerve, brachiocephalic vain, SVC or hilar (extra pericardial) pulmonary vessels
T4	Invasion of thoracic aorta, arch vessels, main pulmonary artery, trachea, oesophagus or myocardium
Lymph Node (N)	

N0	No lymph node metastasis
N1	Involvement of anterior (peri thymic) lymph nodes
N2	Involvement of deep intrathoracic or cervical lymph nodes
Metastasis (M)	
M0	No metastasis
M1a	Pleural or pericardial metastatic nodule(s)
M1b	Pulmonary intraparenchymal metastatic nodule or distant-organ metastasis

Table 3: IASLC/ITMIG Staging System for Thymic Epithelial Neoplasms

Source: Carter BW, Benveniste MF, Madan R, Godoy MC, Groot PMd, Truong MT, et al. IASLC/ITMIG Staging System and Lymph Node Map for Thymic Epithelial Neoplasms. RadioGraphics. 2017;37(3):758-76.

The treatment for early stage tumours is surgery, with the aim being complete resection by taking the entire thymus gland together with the peri thymic fat (177). The goal is, therefore, to leave the tumour capsule undisturbed and prevent recurrence. En bloc resection of all affected structures should be carried out in cases of locally advanced disease (T3 and T4 tumours) (181). For those tumours deemed unresectable, neoadjuvant chemotherapy or chemoradiation should be used to downstage the disease and then the resectability of the mass reassessed. The aim being to increase the possibility of achieving resection with wide surgical margins. Complete resection can be achieve great results with high cure rates and the average recurrence rate for Masaoka stage I tumours is around 3%(182) . Recurrence rates increase with stage and 10 year survival rates after complete resection are 90%, 70%, 55%, and 35% for stages I, II, III, and IV, respectively (182). Post-operative chemotherapy is not advised after R0/R1 resection of a thymoma but may be considered in thymic carcinoma of stage II-IV (181, 183). Post-operative radiation tends to be used in thymoma patients with a high risk of local recurrence;

invasion through the tumour capsule (stage IIB), close surgical margins, aggressive histology such as type B or tumour stuck to the pericardium (181). It is not indicated in the case of completely resected stage I-II thymoma, as it offers no survival benefit (184) (185)and the risk of recurrence is similar (186) but is recommended for stage III-IV thymoma and thymic carcinoma (177, 181, 187)

Germ cell tumours

Mediastinal germ cell tumours (MGCT) constitute 10-15% of all mediastinal tumours and most are benign. They can be categorised into teratomas (mature, immature and those with malignant components) and malignant non-teratomatous MGCTs, which comprise of seminomas and non-seminomatous germ cell tumours. The most common MGCTs are teratomas, of which mature teratomas are the most frequent. The majority of MGCTs present in males at 30-40 years of age (188). Many patients are asymptomatic but some present with chest pain, dyspnoea, haemoptysis or cough if the tumour is large (Figure 4 and 5)

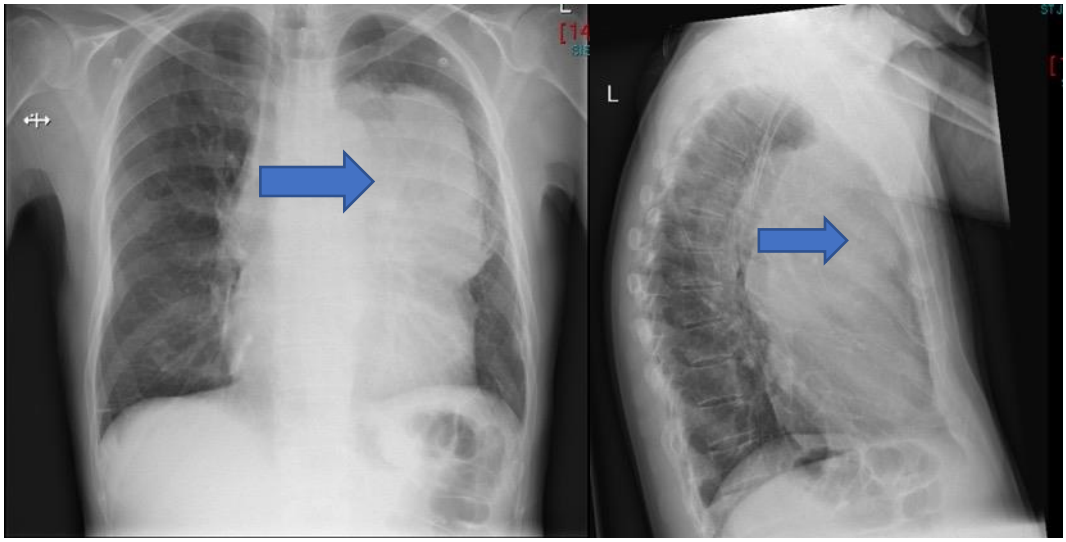

Figure 4: Germ cell tumour. Plain radiographs showing large left-sided mediastinal mass (blue arrow).

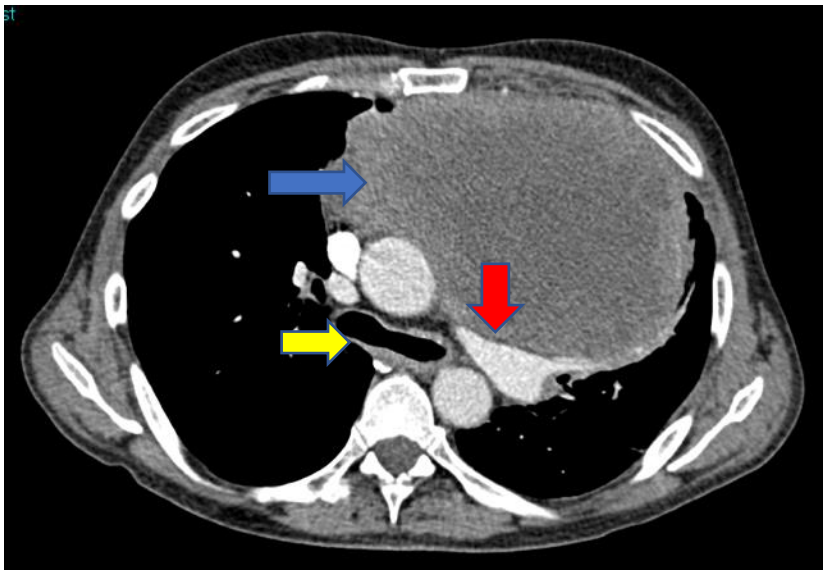

Figure 5: CT showing large germ cell tumour (blue arrow)compressing the carina (yellow arrow) and left main pulmonary artery (red arrow).

Teratomas can be radiologically identified as fatty, fluid filled lesions which may contain bone like structures or teeth and can range from small masses to up to 15cm in diameter (Figure 6) (189). Benign teratomas will have normal serum markers (176) and adequate tissue sampling is needed to differentiate between benign teratoma and those with malignant components. Teratomas are treated by complete surgical resection due to the risk of malignancy (189).

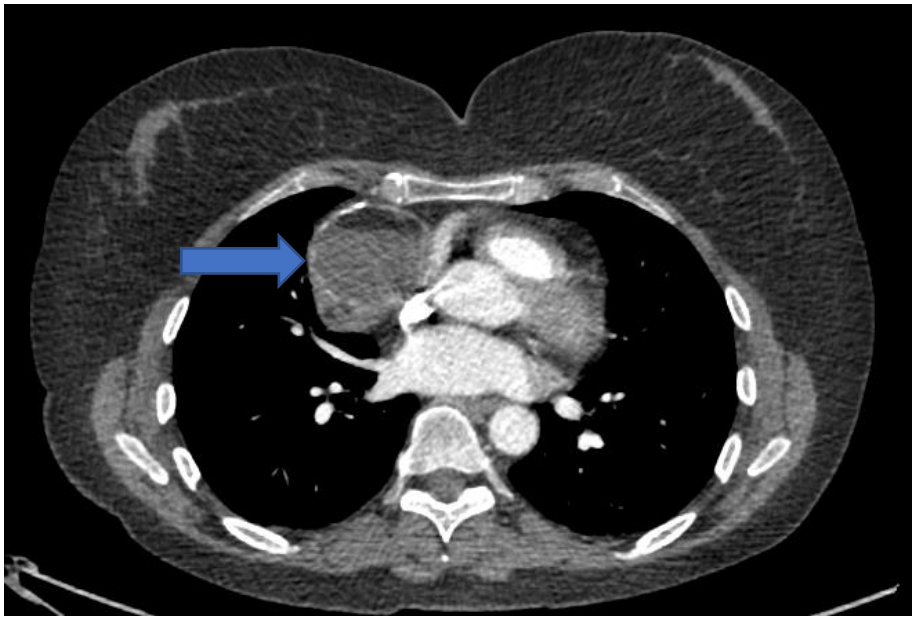

Figure 6: Mature cystic teratoma. CT shows a calcified right-sided anterior mediastinal mass (blue arrow).

All non-teratomatous MGCTs are malignant. Seminomas are a rarity but account for around 37% of MGCTs (189). They often present as large, bulky and solid tumours which are locally invasive and cause symptoms such as cough, dyspnoea and chest pain. Superior vena cava obstruction is also fairly common, occurring in up to a quarter of anterior mediastinal seminomas (176). Certain tumour markers may be tested and a raised serum lactate dehydrogenase (LDH), beta human chorionic gonadotropin (β-hCG) and/or α-fetoprotein (AFP) would increase clinical suspicion of a germ cell tumour. Traditionally these were treated with radiotherapy but with extensive disease this exposed the heart, lung tissue and other structures to large amounts of radiation. Chemotherapy is now the first line therapy for both seminomas and non-seminomatous GCT(176).

Neurogenic tumours

The common masses detected in the paravertebral compartment are neurogenic tumours which originate from nerve sheaths or nerve cells (i.e. those of the autonomic ganglia). They are thought to account for around 10% to 34% of mediastinal tumours in adults (190). The majority in adults are benign and the most frequently seen are schwannomas, ganglioneuromas and neurofibromas. On CT scan these benign tumours present as solid, well-defined, round or lobulated massed adjacent to the vertebral column. They can sometimes be described as "dumbbell" shaped on imaging if the intrathoracic tumour extends into the intervertebral foramen and spinal cord. MR imaging is recommended to assess the extent of involvement of the chest wall and spinal cord (190).

Schwannomas result from the differentiated Schwann cells of the nerve sheath. Most are benign, although, some may show malignant transformation. They are typically found in adults in the third and fourth decade of life (190). Although most occur in the posterior mediastinum but it is important to remember that some have been found in the anterior compartment (191).

Ganglioneuromas arise from the sympathetic ganglion and typically present in young to middle aged adults and are rarely seen in those over the age of 40. The majority of patients are asymptomatic and the mass is found incidentally, although

some exhibit cough, dyspnoea, dysphagia, chest pain or Horner's syndrome if the mass is large (190).

Neurofibromas have a mixture of nerve elements including axons, sheath cells and connective tissue. They are most commonly associated with autosomal dominant disorder neurofibromatosis type 1 and develop in adolescence (191) . Most are cutaneous lesions but thoracic lesions occur in the sympathetic nerve trunks in the paravertebral sulci or rarely from the phrenic and vagus nerves (190). Multiple masses may be found and some present with symptoms of tracheal compression or scoliosis. Malignant transformation to a malignant peripheral nerve sheath tumour (MPNST) should be considered where there is a rapid increase in tumour size or neurological symptoms develop (174). MPNST are more frequently seen in adults compared with other malignant neurogenic tumours such as neuroblastomas and ganglioneuroblastomas.

Benign neurogenic tumours are all treated by surgical excision, which is considered curative, and the risk of recurrence is low. MPNSTs are also resected in order to prevent or relieve spinal cord compression and adjuvant radiotherapy may be given to any local residual tissue (190). However, the risk of 5 year recurrence with these malignant tumours is high at around 53% (192).

Diagnosis and investigations of a mediastinal mass

The location of the mediastinal mass aids in the differential diagnosis at presentation and guides initial investigations. CT imaging is often undertaken in the early stages of investigations, as it is the most useful tool to help localise the mass to the mediastinum and to determine from which compartment the mass originated. Cross sectional CT images also provide information as to the shape and size of the mass and its proximity to other structures in the mediastinum. The character of the mass on CT (vascular, calcified, fatty or fluid-filled) and features such as whether the mass is continuous with the cervical thyroid and can also help to guide diagnosis (Figure 7 and 8). CT is very useful for surgical planning and for assessing the extent of invasion to the surrounding structures, in order to

determine whether minimally invasive techniques are suitable. In the case of thymic neoplasms, IV contrast should be used to assess for invasion of the mediastinal vasculature, particularly the brachiocephalic vein and superior vena cava (SVC) (193).

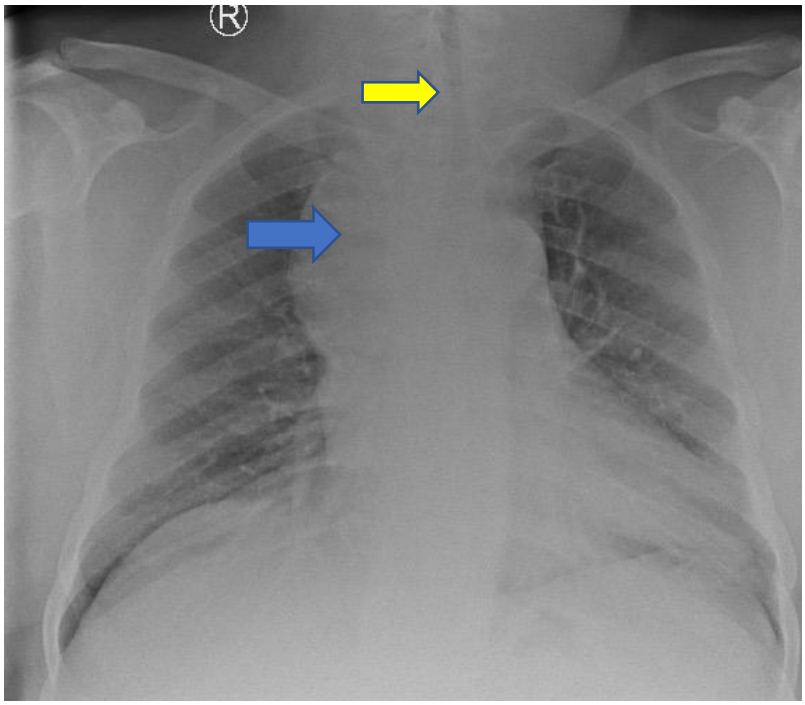

Figure 7: Retrosternal thyroid goitre. Plain radiograph showing widened mediastinum (blue arrow) and narrow trachea (yellow arrow).

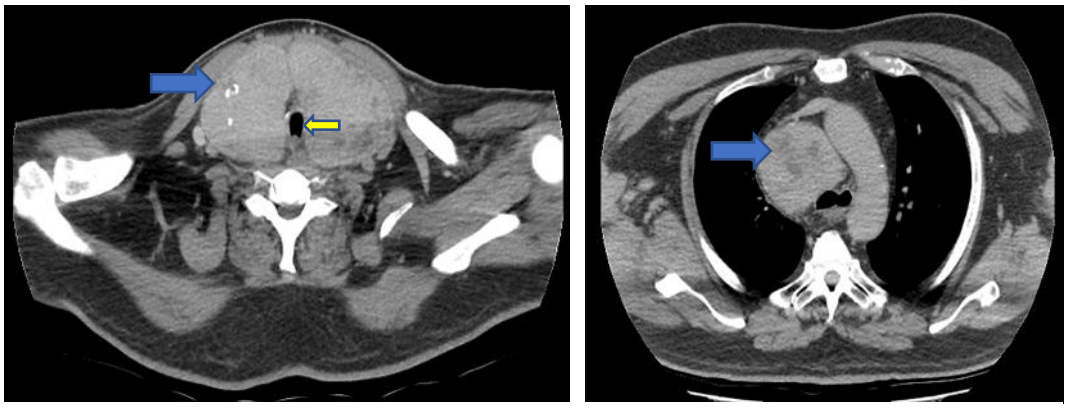

Figure 8: Retrosternal thyroid goitre (blue arrow). CT scans shows cervical thyroid is continuous with the mediastinal mass. Mass was surgical resected via a J-shaped partial sternotomy. The airway is compressed (yellow arrow)

MRI better evaluates soft tissues and is used to further investigate cystic lesions and differentiate cysts from solid neoplastic masses. It is also used to analyse neurogenic tumours in the posterior mediastinal compartment, as neurogenic tumours are often situated next to vertebral bodies and pre-operatively the presence of tumour in the neural foramen or spinal cord needs to be identified. Leaving behind residual tissue in the spinal cord can result in spinal cord compression by direct injury or due to bleeding in the spinal canal (190). Although not routine, positron emission tomography–computed tomography (PET-CT) may also be carried out when primary malignancy, such as lung cancer, lymphoma or oesophageal cancer, or metastatic disease is suspected. It is useful in staging cancers, monitoring response to treatment and detecting disease recurrence (174).

As well as a full blood count, additional blood tests may provide important glues as to the diagnosis or may otherwise give prognostic information. Whilst most serum tumour markers do not hold the specificity or sensitivity needed to make the diagnosis certain, they may add weight to the clinical suspicion (194). In the case of MGCT, immunoassays for serum lactate dehydrogenase (LDH), beta human chorionic gonadotropin (β-hCG) and α-fetoprotein (AFP) may be raised. A significant increase in β-hCG and AFP confirms the presence of a malignancy, although in cases of seminomas β-hCG may be low. It should be noted that AFP is only present if non-seminomatous components are present (176). A raised LDH is also found in the non-Hodgkin lymphoma. In the presence of suspected thymoma, the findings of hypogammaglobinaemia or acetylcholine receptor (AChR) antibodies confirms the incidence of Good's syndrome and myasthenia gravis respectively (194). A QuantiFERON test is also usually performed to exclude an atypical presentation of Mycobacterium tuberculosis.

The most suitable treatment approach depends on the location of the mass, whether it is invasive and should be completely excised or whether histological confirmation should first be established. Radiological imaging is usually sufficient in the diagnosis of thyroid goitres. When considering thymic neoplasms, if the diagnosis is highly probable, based on radiological and clinical features and the tumour is resectable, then tissue sampling is not needed. However, in the case of

non-resectable advanced thymic epithelial tumours or suspected lymphoma, biopsy is needed for tissue diagnosis as treatment plans involve chemotherapy and/or radiotherapy (Figure 9-11). Tissue samples can be obtained by EBUS/endoscopic ultrasound scan (EUS), CT- guided transthoracic needle biopsy, mediastinoscopy, anterior mediastinotomy or VATS.

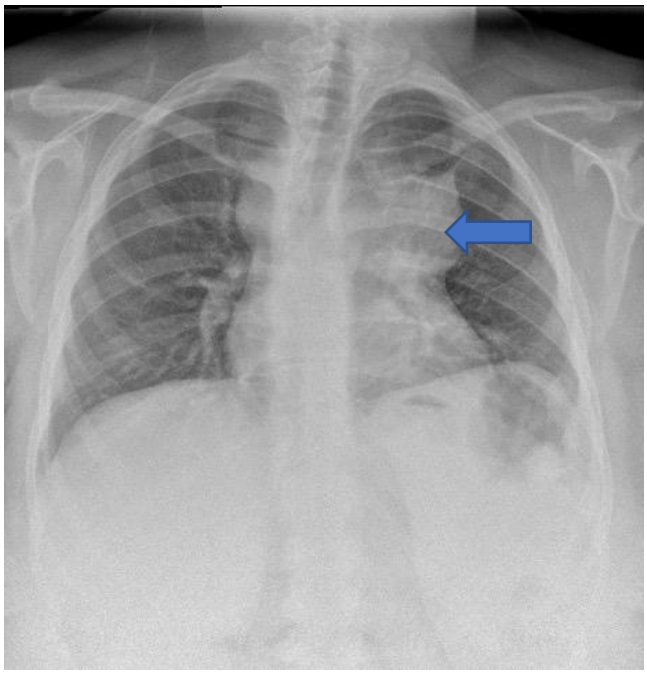

Figure 9: 25 year old female presenting with shortness of breath. Plain radiograph showing a left anterior mediastinal mass (blue arrow).

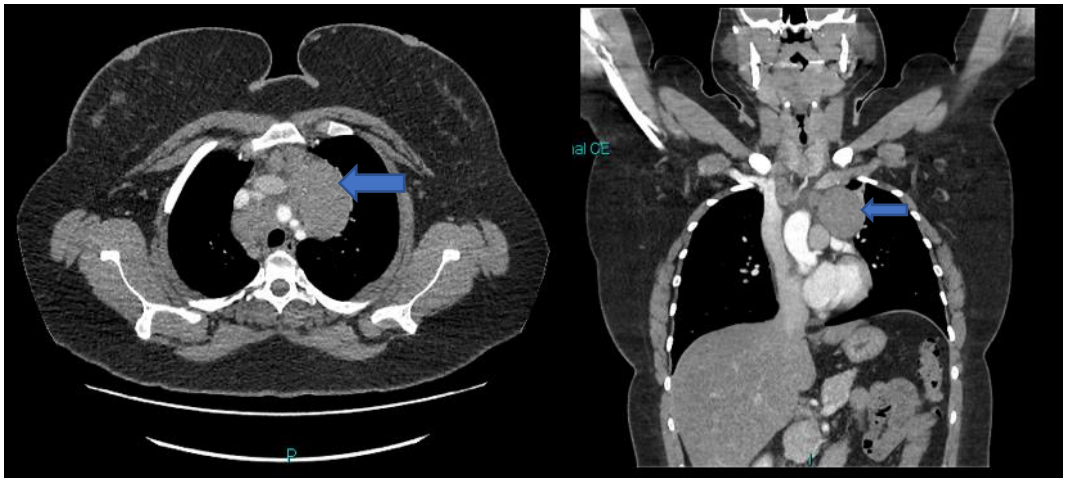

Figure 10: Axial and coronal CT scan showing a left anterior mediastinal mass (blue arrow) in 25 year old female.

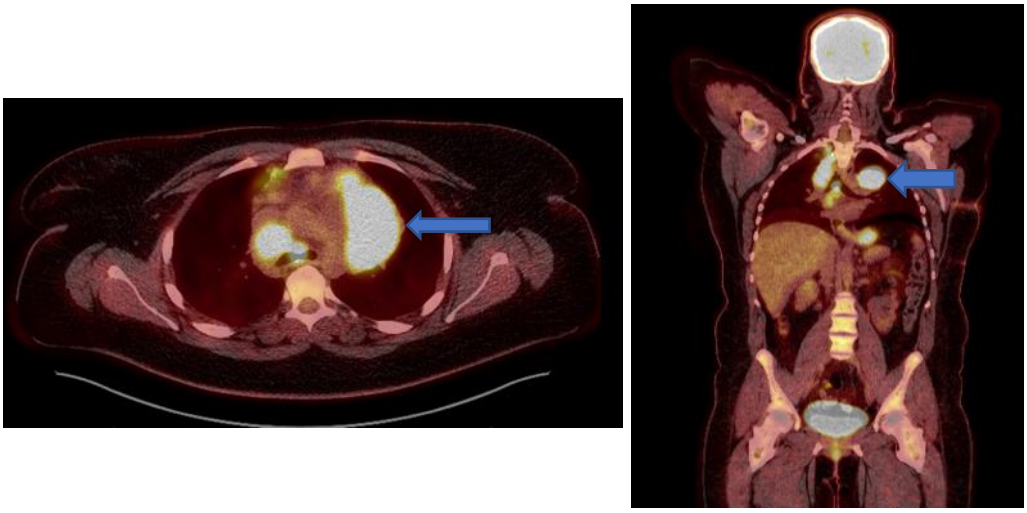

Figure 11: Axial and coronal PET-CT showing PET avid left anterior mediastinal mass (blue arrow) in 25 year old female. EBUS and CT-guided biopsy were both negative and patient subsequently underwent a left VATS biopsy. Histology confirmed the diagnosis to be Hodgkin Lymphoma.

Mediastinoscopy has largely been considered the "gold standard" for staging the mediastinum, although endobronchial ultrasound guided transbronchial needle aspiration (EBUS- TBNA) is a commonly used alternative procedure. Mediastinoscopy has a limited role in providing histological confirmation for anterior mediastinal masses and is used to sample masses which are located or extend into the superior mediastinum. The superior mediastinal lymph nodes are the site of metastasis from the pulmonary disease and tissue samples can help confirm the presence of malignant disease. Mediastinoscopy is performed as an outpatient procedure under general anaesthetic. An incision is made just above the manubrium and a plane is created for the mediastinoscope to be passed anteriorly to the trachea. This provides access to the left and right upper (2R and 2L) and lower (4R and 4L) paratracheal nodes, the subcarinal nodes (7) and the highest mediastinal nodes (1), which can be sampled using biopsy forceps. One of the key complications is vascular injury and haemorrhage, which is usually due to damage of the bronchial arteries, the azygos vein or right upper lobe branch of the pulmonary artery. There is also a risk of injury to the aorta and the brachiocephalic trunk. However, the risk of major haemorrhage is rare and a rate of 0.4% is quoted (195).

EBUS-TBNA is widely used and a less invasive method for sampling mediastinal nodes. In fact, the number of mediastinoscopy and mediastinotomy cases were down 35.1% in 2015-2015 compared with 2010-2011 (45). This is largely thought to be due to the increasing use of EBUS-TBNA and EUS. Following general anaesthetic, an EBUS scope is inserted into the trachea. The ultrasound probe is used to identify the relevant nodes. Unlike, CT guided biopsy, the technique offers real time imaging to help avoid injury to vascular structures, which appear hypoechoic and pulsatile on ultrasound imaging. The biopsy needle can then be passed down the biopsy channel and advanced out of the end of the scope. The needle is quickly used to puncture the lymph node. Suction is applied and the needle is moved in and out of the lymph node multiple times. With the suction released, the biopsy needle is withdrawn from the scope and the samples flushed out of the needle. The process can then be repeated for other lymph node site. This technique enables biopsy of the hilar nodes (10 and 11), which are not accessible with mediastinoscopy(196).
To access the anterior mediastinal compartment, anterior mediastinotomy or VATS is needed. Mediastinotomy involves an incision just lateral to the sternum at the level of the second rib or, alternatively, excision of the 2nd costal cartilage. The lymph nodes at stations 5 and 10 can then be palpated and dissected in a similar way to mediastinoscopy. The VATS technique is not widely used for tissue sampling but may be helpful where masses extend through the pleura or are associated with pleural lesions (197). The technique is described below.

Surgical approach to mediastinal masses

Sternotomy and thoracotomy

Median sternotomy provides the greater exposure for the resection of anterior mediastinal masses (Figure 12). This approach allows for good visualisation if there is invasion of the adjacent lung, pericardium or great vessels and allows for tracheal resection and reconstruction if necessary (197). The patient is placed in a supine position and an incision is made down the midline from the suprasternal notch to the xiphoid process. Electrocautery is used to dissect down the anterior sternal fascia. The xiphoid is divided with scissors and an oscillating sternal saw is then

used to divide the sternum down the middle. Electrocautery or bone wax is used to stem any bone marrow bleeding. A sternal retractor is placed to provide adequate exposure. At the end of the operation one or two chest drains are placed to drain the mediastinum. If the pleural cavities have been opened, then drains are placed into the pleural cavities as well. The sternum is joined back together using interrupted steel sutures, before the fascia, subcutaneous layers and skin are closed.

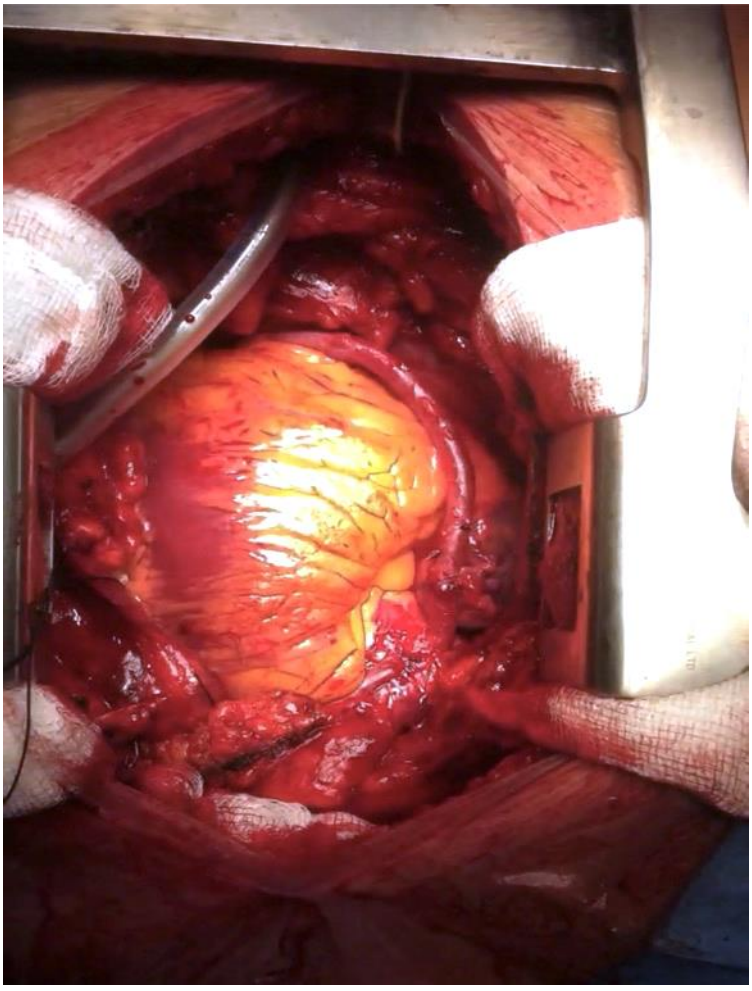

Figure 12: Median Sternotomy in a patient who has undergone coronary artery bypass graft surgery

The standard approach for thymectomy and other mediastinal tumours via a median sternotomy. For thymic tumours a total thymectomy (Figure 13 and 14) is known to provide a greater chance of survival than tumour resection alone (198, 199), and in the presence of extensive disease en bloc resection of the invaded structures should be performed (182). Following sternotomy, the mediastinal pleura is incised to reveal the thymus and left brachiocephalic vein. The mediastinum should be explored for metastatic disease and the phrenic nerves identified. All 4 lobes of the thymus and mediastinal fat up to the left and right phrenic nerves are resected. Care is taken as to not injure the phrenic nerves. Typically, the right superior and inferior horns are dissected off the pericardium and the thyrothymic ligament divided, before the right side is retracted medially and the branches of the internal thoracic artery are ligated. The left lobes are similarly dissected from the surrounding structures and lastly the middle section is freed and the venous drainage to the left brachiocephalic vein is clamped and ligated. If the thymus is found to adhere to any structures, such as the pericardium, this should be resected en bloc with the thymus (200). It is important that the specimen is marked at the time of resection so the pathologist can determine the specimen's orientation and the adjacent structures. Clips should also be used in the operative field to mark the edges where the thymus was resected, in the event that adjuvant radiotherapy is needed (201). Peri-thymic nodes N1 nodes tend to be in the area of resection for complete thymectomy. The ITMIG recommends these are resected in localised disease and that in the case advanced thymomas (Masaoka Stage III and IV) or thymic carcinoma intrathoracic N2 lymph nodes are also sampled (202).

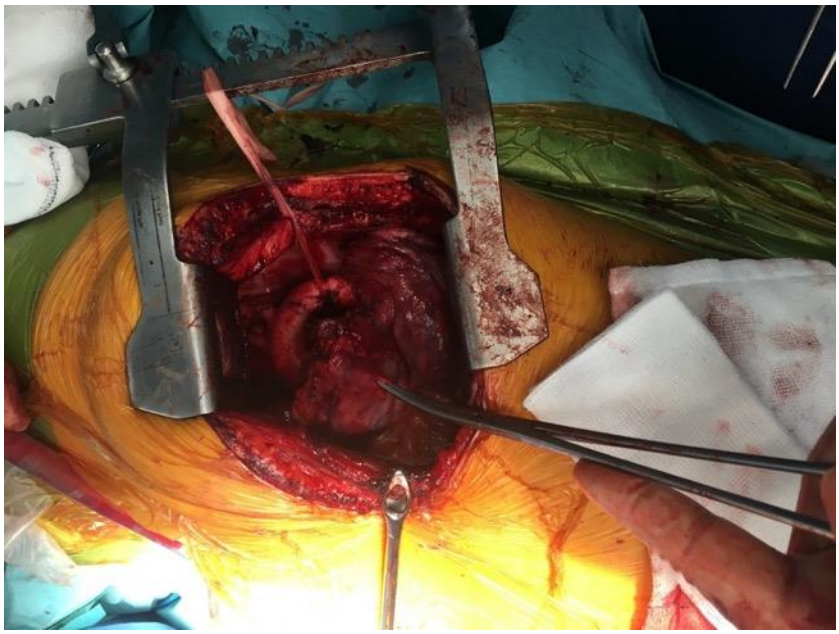

Figure 13: Median sternotomy for total thymectomy for a thymoma.

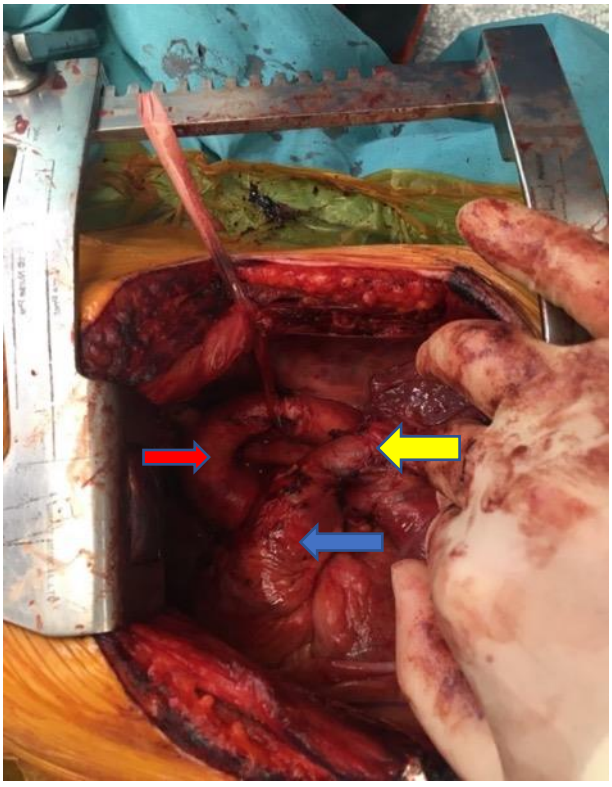

Figure 14: Mediastinum post thymectomy. The arch of aorta is clearly seen (red arrow) and left main pulmonary artery (yellow arrow) arising from the pulmonary trunk (blue arrow)

A less invasive approach is to use a mini-sternotomy. With this incision the sternum upper sternum is divided down the midline and the body of the sternum divided horizontally to the side the mass extends (Figure 15). This approach is less painful and gives a better cosmetic result but does not give as good access to the pleural cavities and lower anterior mediastinum. This approach is of particular use for the excision of retrosternal thyroid glands when they cannot be removed via a cervical excision.

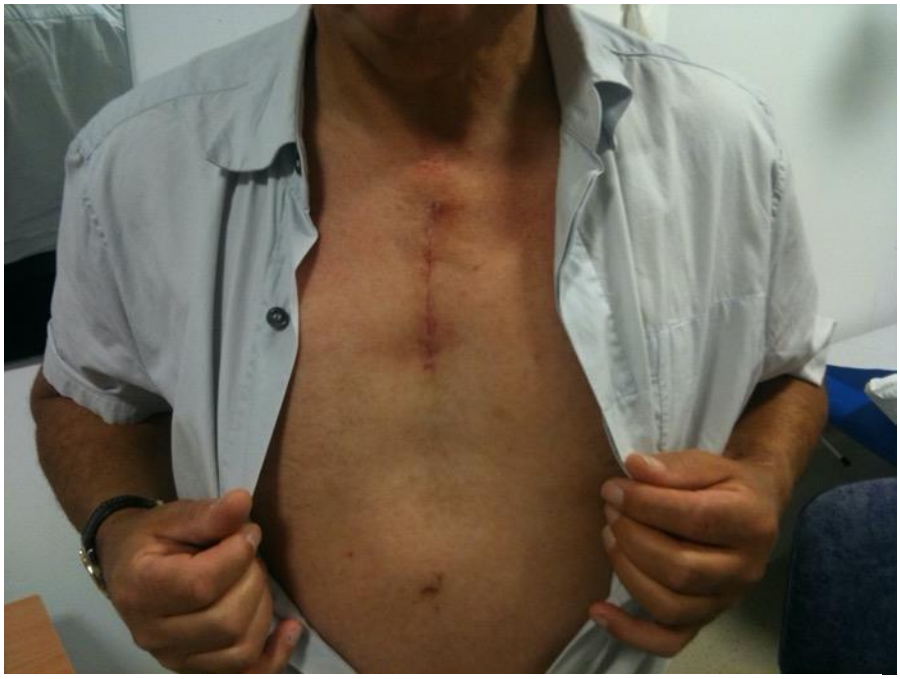

Figure 15: Mini-sternotomy scar

Thoracotomy provides limited exposure to the anterior mediastinum and is used for the resection of posterior mediastinal or paravertebral sulcus tumours. Most of these tumours are benign and so rarely tend to extend into the surrounding structures, such as the oesophagus. The posterior mediastinum contains the descending thoracic aorta, the inferior vena cava, the azygous vein, the thoracic duct and the oesophagus, any of which the malignant tumour may be adherent to. The best approach to the posterior mediastinum is a posterolateral thoracotomy. This technique is previously described in chapter 1.1.3. The level of the intercostal space (ICS) entered will be determined by the position of the lesion to be excised.

For neurogenic tumours, if the tumour extends into the spinal canal, a combined approach with a neurosurgeon is needed. The intraspinal component is resected by posterior laminectomy first before the intrathoracic portion, in order to avoid direct injury or bleeding into the spinal cord. In the case of malignant "dumbbell" tumours such as neuroblastoma, chemotherapy is usually recommended pre-operatively to reduce the extent of spinal cord involvement (190).

VATS for mediastinal masses

A VATS approach has been utilised in the excision of mediastinal masses since its rise in the 1990s. The generally recognised advantages of VATS are less operative trauma leading to reduced post-operative pain, morbidity and length of hospital stay (95, 203). In the case of the resection of benign mediastinal masses, the benefit of surgery is not well studied and therefore it seems appropriate that the morbidity of surgery should be minimised with the use of minimally invasive techniques. VATS is the preferred technique for excising neurogenic tumours and mediastinal cysts as most are benign, well-defined and rarely invade local structures, and thus it is less likely that major structures will need to be resected and repaired. This approach is also favourable as it provides good visualisation of posterior mediastinal tumour. It has also even been shown that "dumbbell" tumours can be successfully resected by laminectomy followed by VATS (204, 205). Additionally, minimally invasive surgery may be beneficial in the case of MGCTs. Most MGCTs present in young patients with recurrence tending to occur late on and, therefore, avoiding open surgery and limiting adhesions can be helpful if they require future thoracic surgery (206).

The role of VATS in the resection of thymic epithelial tumours is a more divisive topic. Some recent studies have supported the use of VATS, describing less intraoperative blood loss (203) and a shorter hospital stay (207) as well as similar rates of postoperative complications and overall and recurrence free survival (207-209). However, this evidence largely comes from small, retrospective studies. Traditional thoughts are that an open approach allows for a greater chance of

achieving clear surgical margins and is safer when approaching tumours invading into the pericardium, phrenic nerves or major vessels. It should be noted that around half of all thymomas have invaded local structures at the time of diagnosis (182). However, from systematic reviews it has shown that open approaches do not allow for more complete resection and, in fact, there was no significant difference in the rate of R0 resection (210, 211). At the present time, surgical approach depends on surgeon preference and experience and there is still a place for open techniques in the case of larger tumours, multiple adhesions, or invasion of vascular structures.

For this reason, VATS is the preferred technique for both cystic and benign solid posterior mediastinal masses (204, 212-214). However, in the case of larger malignant tumours the best approach is open thoracotomy.

Robotic-assisted surgery for mediastinal masses

The benefits of VATS for the resection of mediastinal masses are evident in terms of less intraoperative blood loss, faster recovery and reduced postoperative hospital stay (203, 207-209). Minimally invasive techniques have also been shown to be comparable with open surgery in terms of complete resection and early oncological outcomes for thymic epithelial tumours (210, 211). Although studies analysed in these reviews included robotic assisted thymectomy, most provided limited or no data on the long-term clinical or oncological outcomes of robotic surgery (209, 210, 215, 216). VATS is not considered the ideal approach for resecting masses of the mediastinum as the 2D imaging provides no perception of depth, the instruments are bulky and the range of movement is limited. A robotic surgical approach may be better suited to the resection of mediastinal masses. With high-definition 3D visualisation and wristed surgical instruments which offer greater degrees of freedom, the Da Vinci Surgical System is well-suited for working in the small mediastinal space.

Robotic surgery for thymectomy is thought to hold similar advantages to VATS over open surgery, in terms of peri-operative outcomes. Length of hospital stay and

postoperative complications have been shown to be significantly reduced in robotic cases compared to open, with no difference in positive margin rates (217). A true difference in operative time is difficult to determine as this was calculated from different points in different studies. However, there is a steep learning curve associated with robotic surgery (218) and it seems likely that the longer robotic operative times mentioned in the literature (219) will decrease as the experience of both the surgeon and operating department staff increases (220).

The results of robotic thymectomy are comparable to those completed by VATS. Meta-analysis reports no significant difference is seen in the rate of intraoperative complications, conversions, length of hospital stay, mortality or operative time (217, 221). However, the included studies may be underpowered to detect a small difference in the groups (217). Some single institutions have noted a reduction in length of hospital stay and pleural drainage with the use of robotic techniques compared to VATS (222).

Studies looking at mediastinal masses collectively have shown the feasibility and safety of using robotic surgery to resect mediastinal masses regardless of their mediastinal compartment (223-226). Single institutions have reported that robotic surgery provides an excellent approach to resecting posterior mediastinal masses (227, 228). One of the other potential benefits of robotic surgery is that the learning curve is thought to be less than with VATS. Additionally, the adoption of robotic surgery for mediastinal masses may result in an increase in the number of cases suitable for minimally invasive surgery as more complex cases can be undertaken with the robot.

So far data seems to suggest that both VATS and robotic surgery for the resection of mediastinal masses are associated with good post-operative outcomes, but data is limited to retrospective single institution reports and there is little evidence of the long-term clinical and/or oncological outcomes. Furthermore, the main concern with robotic surgery is the high cost of precuring the robotic system and the maintenance costs. Cost benefit analysis is needed to determine the place for robotic surgery in mediastinal mass resection.

The Liverpool Heart and Chest Hospital performed its first robotic mediastinal mass resection in November 2017. As robotic technology is not widely available in thoracic centres and mediastinal masses only account for a small amount of the thoracic case load, it is important that outcomes are reported.

4.2 Aims and Objectives

The aim of this study was to evaluate the impact of introducing robotic surgery for the resection of mediastinal masses at Liverpool Heart and Chest Hospital.

Our primary objective was to compare outcomes in the pre-robotic and robotic era. Our primary outcomes were rates of minimally invasive surgery, length of hospital stay and postoperative admission to critical care.

Our secondary objective was to compare in-hospital outcomes between the two minimally invasive techniques. Our secondary outcomes in regard to the VATS and robotic cases were operative time, residual tumour status, post-operative admission to critical care, day 1 strong opioid usage and length of stay.

4.3 Methods

Study design

We retrospectively reviewed our experience of robotic assisted mediastinal mass resection since its introduction to the Liverpool Heart and Chest Hospital in November 2017. The hospital's electronic patient record was used to identify all patients that underwent surgical resection for a mediastinal mass in the pre-robotic and robotic era, between November 2015 and September 2019. This start date was chosen as this is when the hospital's electronic patient record was first launched. Tumour size was determined from the pathology report. Where this was not available, it was determined from the pre-operative CT scan. Inclusion and exclusion criteria are listed in Table 1.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Patients undergoing resection of a mediastinal mass at Liverpool Heart and Chest Hospital between November 2015 and September 2019.	All biopsy procedures (including mediastinoscopies)
Patients on Liverpool Heart and Chest Hospital's patient electronic record system	All thyroidectomies
	Thymectomies for non-thymomatous myasthenia gravis

All biopsy procedures (including mediastinoscopies), thyroidectomies and thymectomies for non-thymomatous myasthenia gravis were excluded from this analysis to provide a more homogenous group of patients.

Approvals

All data was collected as part of routine clinical practice and therefore ethical committee approval was not deemed necessary.

Surgical technique

All open surgeries were completed via median sternotomy for anterior mediastinal masses or posterolateral thoracotomy for posterior mediastinal masses.

For VATS resection of anterior mediastinal masses, such as a suspected thymoma, patients were placed in a partial lateral decubitus position with around 30 degrees of upward tilt. Following intubation with a double lumen tube and single lung ventilation, a 10mm camera port is placed in the 4th ICS in the posterior axillary line. Two 5mm trocars are inserted under direct vision, one in the 3rd ICS midaxillary line and one in the 6th ICS anterior axillary line. The lung is retracted posteriorly, and the

phrenic nerve identified. The mediastinal pleura is then incised using a harmonic scalpel. Following resection of the thymus and pericardial fat, the specimen is removed through one of the ports sites using an endobag. A single size 20Ch pleural drain is then inserted and once the lung has shown adequate expansion, the port sites are closed in layers. Port sites were infiltrated with 20ml of 0.25% chirocaine.

Typically, a three port technique was used for posterior mediastinal masses with port placement similar to that of a Copenhagen technique for a VATS lobectomy (see chapter 1.1.4). The exact port position varies depending on the exact site and size of the lesion to be resected. CO_2 insufflation was used for lesions lower down in the chest cavity to push the diaphragm down.
All robotic surgeries were undertaken using the Da Vinci X Surgical System. Patients were anaesthetised with a double lumen tube in a supine positioned. A 30-degree 3D robotic camera and generally a 3 arm approach was used. For an anterior mediastinal lesion, the patient was positioned in a semi-supine position with 30 degrees of tilt away from the side of surgical approach. An 8mm camera port was positioned in the 5th ICS anterior axillary line, followed by two instrument ports: one in the 5th ICS mid-clavicular line and the other in the 3rd ICS in the anterior axillary line. For access to the middle and posterior mediastinum, the patient was placed in the lateral decubitus position. The intercostal space the ports were placed in depended on the site of the lesion. Following, resection the mass was removed from the chest in an endobag. The port sites were closed in layers and infiltrate with 20 ml of 0.25% chirocaine.

<u>Post-operative care</u>

All patients were extubated in theatre post-operatively before sent to the recovery bay. From here patients were either discharged to critical care or the ward. Standard post-operative care was given including adequate analgesia and physiotherapy. Pleural drains were removed when the drainage of any haemoserous fluid was less than 200ml per 24 hours.

Statistical analysis

Data was grouped according to operative period in which they took place, the pre-robotic or robotic era, as well by the planned surgical approach. Continuous variables were presented as median and interquartile range and categorical data as the relative percentage. Statistical analysis was undertaken to compare median values. T-tests were used for normally distributed continuous variables and chi-squared tests for normally distribution categorical variables. For continuous variables of non-normal distribution Mann-Whitney tests were used. A *p* value less than or equal to 0.05 was considered statistically significant.

4.4 Results

Between November 2015 and November 2017, before the introduction of robotic surgery 49 patients underwent 51 operations for excision of mediastinal masses. One patient had a VATS excision of what was thought to be an anterior mediastinal metastasis from a previous hepatocellular carcinoma. The lesion turned out to be a squamous cell carcinoma of the thymus gland. It was a possible R1 resection therefore he underwent a median sternotomy and thymectomy a few weeks later. The other patient who had two operations was a young gentleman who had teratoma metastasis excised from the anterior and posterior mediastinum. A patient who underwent excision of a 2cm thymic cyst at the same time as an aortic valve replacement, mitral valve and tricuspid valve repair was excluded from the analysis as were 8 patients with thymic hyperplasia (six patients with myasthenia gravis, one following chemotherapy for breast cancer, one idiopathic).

Between December 2017 and September 2019, after the introduction of robotic surgery, 42 patients underwent excision of mediastinal masses. Six patients who had thymectomy for thymic hyperplasia associated with myasthenia gravis but no masses were excluded. One patient included in the study had previously undergone excision of a thymoma many years previous who had an excision of a recurrence was included in the study.

Table 2. Pre-operative characteristics in pre-robotic and robotic era

	Pre-robotic	**Robotic era**	**p value**
Number of procedures	51	42	-
Sex = Male (n (%))	22 (43%)	16 (38%)	p=0.62
Age (median [IQR])	55 [46-70]	53.5 [39-70]	p=0.54
Tumour maximum diameter, mm (median [IQR])	74.5 [49.75-100]	60 [43-82.5]	p=0.28
ASA grade	1 n=9 2 n=29 3 n=11 4 n=2	1 n=13 2 n=22 3 n=6 4 n=1	p=0.45
Smoking status	Non-smoker n=33 Ex-Smoker n=11 Current smoker n=7	Non-smoker n=23 Ex-Smoker n=15 Current smoker n= 4	p=0.31
Neoadjuvant chemotherapy or radiotherapy (n (%))	7 (13.7%)	4 (9.5%)	p=0.53
Surgical approach	Minimally n= 10 Open n= 41	Minimally n= 19 Open n= 23	p=0.0079

Procedures in the pre-robotic and robotic era

The pre-robotic and robotic groups were evenly matched in terms of age, sex, ASA grade, lesion size, smoking status and neoadjuvant treatment (see Table 2).

The percentage of masses resected by a minimally invasive technique increased from 20% prior to the introduction of the robotic assisted surgery to 45% following the introduction of robotic surgery. This was a statistically significant increase (p=0.0079). There was no significant difference in the size of lesions removed robotically (median 52.5mm (IQR 37.25-60)) compared to VATS (47.5 (IQR 27.5-60)) (p=0.32).

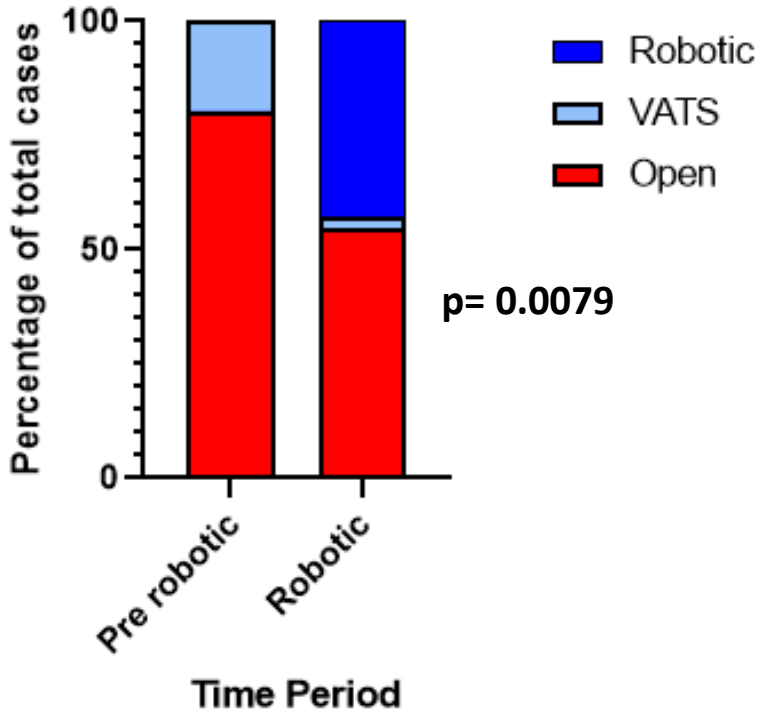

Figure 16: Bar chart showing different operative approaches in the pre-robotic and robotic periods

During the initial time period, 8 patients had a thymectomy for thymic hyperplasia: 2 (25%) via a VATS approach and 6 via an open approach. Following the introduction of the robotic mediastinal programme, 6 patients have had a thymectomy for thymic hyperplasia: 2 open and 4 (66%) robotically.

Length of stay was shorter following the introduction of robotic surgery with a median length of stay of 3 days (IQR 2-5) compared to 4 days (IQR 3-5) prior to the

introduction of robotic surgery. However, this did not quite reach statistical significance(p=0.068).

There was no difference in post-operative admission to critical care between the pre-robotic and robotic time period (78.43% v 64.29%, p= 0.1304). However, significantly fewer minimally invasive cases went to critical care post-operatively compared with the open cases (88.64% v 27.59%, p <0.0001).

There was only 1 in-hospital death throughout the entire period studied. This patient was admitted for urgent surgery due to a large extragonadal germ cell tumour compressing the patient's airway and main pulmonary artery. The patient died 62 days post-operatively due to multiorgan failure.

VATS versus robotic surgery for mediastinal mass resection

Pre-operative characteristics for the VATS and robotic procedures in the robotic period are shown in Table 3. There was one patient converted from a robotic excision to an open excision and one converted from a VATS approach to an open operation, due to adhesions between an infected cyst and the mediastinum. These patients were excluded from the analysis as the aim was to compare VATS to robotic, not to look at conversion reasons or rates. Both groups were evenly matched in terms of age, sex, ASA grade, pre-operative treatment and lesion size.

Table 3. Pre-operative characteristics for VATS and robotic cases in the robotic period

	VATS	**Robotic**	**p value**
Number of procedures	11	18	-
Age (median [IQR])	51 [33-69]	57 [35-71]	p=0.5397
Sex = male (n (%))	2 (18%)	6 (33%)	p=0.3757

ASA grade	1-2 10 3-4 1	1-2 16 3-4 2	p=0.8624
Lesion size mm (median [IQR])	47.5 [27.5-60]	52.5 [37.25-60]	p=0.3119
Smoking status	Non-smoker 5 Ex-smoker 5 Smoker 1	Non-smoker 9 Ex-smoker 8 Smoker 1	p=0.9257
Pre-operative chemotherapy or radiotherapy (n (%))	2 (18.1%)	2 (11.1%)	p=0.5921

Post-operative characteristics for the VATS and robotic cases in the robotic period are summarised in Table 4. The operative time in the VATS group was significantly less than in the robotic group (p=0.015). There was no difference in post-operative critical care use or number of R1 resections between the two groups.

There was a trend towards decreased post-operative strong opioid use when the robotic group (median 24mg) (IQR 4-33) was compared to the VATS group (median 32mg) (IQR 18-40) (p=0.14). However, this did not reach statistical significance (p=0.072).

When comparing the 3 different techniques, both VATS (p<0.0001) and robotic mediastinal surgery (p<0.0001) had significantly shorter length of stay than open surgery, but there was no significant difference between VATS and robotic (p=0.718) (Figure 17).

Table 4. Post-operative characteristics for VATS and robotic cases in the robotic period

	VATS	**Robotic**	**p value**
Operative time (median [IQR])	82.5 [64-100.5]	128 [101-199.3]	p=0.0151
Post-op destination	Ward 10 Critical care 1	Ward 12 Critical care 6	p=0.1388
First 24 hour IV strong opioid usage, mg (median [IQR])	35.8 [23-41]	24 [4.25-33.25]	p=0.073
Length of stay (median [IQR]	2 [1-3]	2 [1-3]	p=0.7184
Residual tumour status	R0 9 R1 or R2 2	R0 16 R1 or R2 2	p=0.5921

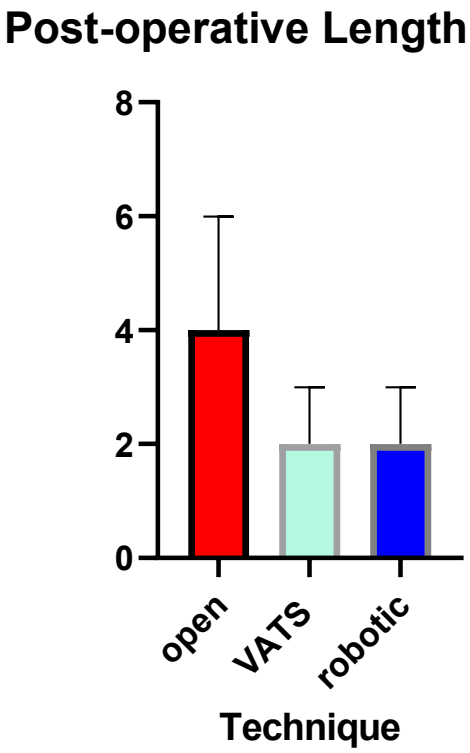

Figure 17: Bar chart showing post-operative length of stay by operative technique. Bars represent median length of post-operative stay with error bars showing the 75th centile.

4.5 Discussion

In this chapter we evaluated the impact of introducing robotic mediastinal surgery at Liverpool Heart and Chest Hospital. The main outcome measures were rates of minimally invasive surgery, length of hospital stay and postoperative admission to critical care in the pre-robotic and robotic era. We also compared in-hospital outcomes between the two minimally invasive techniques, VATS and robotic surgery.

Mediastinal masses are rare and represent a heterogenous group of conditions. This makes comparison of different operative techniques difficult. Robotic surgery is well-matched to the excision of mediastinal masses as it is a relatively small and confined space. The high definition, magnified 3D vision along with wristed instruments of robotic surgery are ideally suited to mediastinal surgery.

Following the introduction of robotic mediastinal surgery, we have found that a significantly higher number of patients have undergone minimally invasive resection of a mediastinal mass. The exact reasons for this are not clear. In a retrospective analysis it is difficult to determine the exact reasons why a surgeon opted for a minimally invasive approach rather than an open approach. There was no difference in size of the lesion between the VATS group or robotic groups, which matches that seen in other studies(222). This suggests that the increase in minimally invasive resections is not due to a willingness to operate on larger tumours robotically, compared to VATS. Other possible explanations may be the position of the tumour and its relationship to other major structures. It is also difficult to compare our rates of minimally invasive surgery to other studies, as may report on thymectomy and resection of other mediastinal masses separately.

Significantly more minimally invasive cases were managed on the ward post-operatively compared to those undergoing open surgery. This suggests a reduced level of care needed post-operatively following minimally invasive surgery. Yet, we cannot exclude the possibility is that our study was subject to selection bias, as there more open procedures in the pre-robotic group and post-operative protocol may have changed over time.

We found that as expected both VATS and robotic mediastinal surgery had a significantly shorter length of post-operative stay than open surgery, although there was no significant difference between VATS and robotic (Table 4). Other centres have found similar results. Minimally invasive techniques tend offer a shorter length of stay compared to open surgery (203, 207, 216) but both VATS and robotic surgery are similar in this regard (221).

One of the possible benefits of robotic mediastinal surgery is the decrease in pain compared to VATS. There was a trend towards a decreased morphine requirement in the robotic group, although this was not quite statistically significant and may represent a type II error due to the small sample size (Table 4). We were unable to find comparable data on post-operative pain following minimally invasive mediastinal mass resection.

The robotic resections also took significantly longer than the VATS cases (Table 4). It is difficult to determine the exact cause of this, however this may reflect the learning curve associated with robotic mediastinal surgery as it was recently introduced to Liverpool Heart and Chest Hospital in November 2017. Due the heterogenous group of cases and with each operation being slightly different, the setup time may be longer and perhaps multiple instruments changes were required during the procedure. These are confounding factors which were not controlled for in our study design. On the other hand, as we found more cases were being performed minimally invasively in the robotic era, it is possible that more complex cases were being performed robotically. Other studies have also reported a longer operative time with robotic surgery (219). However, a trend has been seen in decreasing operative time with an increasing number of cases (223). As studies have shown, the operative time for robotic resection may, therefore, prove to be similar to VATS (221, 222).

A number of limitations have been identified in this study, most notably its retrospective single institution nature. However, as this study aimed to report on the initial experience of robotic mediastinal surgery at Liverpool Heart and Chest Hospital it was only conducted in one centre. Due to the nature of this MPhil, long-term outcomes such as disease recurrence, chronic pain and cost were not

available. A randomised trial to compare robotic and VATS excision of mediastinal masses would be preferable, however in this situation it would be very difficult to design due to the heterogenicity of the lesions.

4.6 Conclusions

In conclusion, the introduction of a robotic mediastinal surgery programme has led to more patients getting a minimally invasive resection of their mediastinal mass. The advantage of this is that minimally invasive surgery is associated with fewer post-operative complications, a reduced length of hospital stay and less pain. We found minimally invasive resection to be associated with a significantly shorter post-operative length of stay and fewer post-operative critical care admissions than an open procedure. There was a non-significant trend towards lower morphine requirements in the first 24 hours in the robotic group compared to the VATS group. However, a larger patient group would be required to identify whether this is a major advantage of robotic surgery over VATS.

Chapter 5: Robotic assisted lung volume reduction surgery: pilot data on introducing a robotic LVRS programme to Liverpool Heart and Chest Hospital

5.1 Background

Lung volume reduction for Chronic Obstructive Pulmonary Disease (COPD)

Lung Volume Reduction (LVR) is a procedure designed to reduce breathlessness and improve exercise tolerance in patients with severe emphysema, by reducing the size of over-inflated lungs and improving mechanical function of the respiratory system. COPD is a respiratory disease characterized by the chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible(229). It consists of two main patterns which may co-exist: chronic bronchitis and emphysema.

In developed countries, it is largely caused by prolonged tobacco smoking, although other causes such as occupational exposure to coal, dust or silica and inherited forms like alpha 1 anti-trypsin deficiency have been noted. Exposure to these particles initiates an inflammatory response in the small airways and prolonged exposure results in a chronic inflammatory state which leads to the destruction of the lung. The main pathological features of emphysema are permanently enlarged airspaces distal to the terminal bronchioles with damaged alveoli walls and no obvious fibrosis (230). Some patients develop bullae, thin-walled air-filled spaces which do not contribute to gas exchange and compress the surrounding lung, reducing its effectiveness. Work of breathing is, therefore, markedly increased in emphysema due to air trapping, reduced gas exchange, reduced elastic recoil and hyperinflation. Hyperinflation of the lungs places the respiratory muscles at a mechanical disadvantage as it flattens the diaphragm and brings the intercostal muscles into a more horizontal position(230).

An obstructive pattern is seen on spirometry with a reduced percentage predicted FEV_1 and a FEV_1/FVC <70%. The common symptoms are productive cough with white/clear sputum, breathlessness and wheeze. Exacerbations of the disease are often caused by viral/bacterial respiratory infections or environmental pollutants. As this chronic disease progresses, a decline in lung function, increased exacerbations and a deterioration of symptoms is seen. Pulmonary hypertension, weight loss, muscle wasting, hypertension and osteoporosis may also be seen in those with advanced disease. COPD is associated with significant morbidity and mortality and, in 2016, was the third leading cause of death globally(231). Pharmacological and non-pharmacological treatments focus on controlling symptoms, delaying disease progression and preventing exacerbations. Surgical management is only suitable for a small subset of patients who fulfil set criteria which are discussed below and who are still breathless after optimal medical management(232).

Physiology of Lung Volume Reduction

Lung hyperinflation in emphysema results from the expiratory airflow limitation that occurs due to small airway collapse and reduced elastic recoil. This leads to air trapping and an increase in residual volume (RV) and total lung capacity (TLC). As a result the inspiratory capacity (IC) of the lungs is reduced (233). In patients where hyper expansion of the lungs is one of the main causes of shortness of breath, lung volume reduction surgery (LVRS) aims to remove areas of severe emphysematous change in the lung, reducing the over-inflation, thus improving the mechanics of breathing and the elastic recoil of the lung. Post-operatively a decrease in residual volume should be seen as well as an increase in FEV_1 and transfer factor of the lung for carbon monoxide (TLCO).

History of Lung Volume Reduction Surgery

Bullectomy was the original operation performed for severe emphysema. Today NICE recommends referral for assessment for bullectomy in COPD patients that are breathless and have a CT scan showing a bulla occupying at least one third of the

hemithorax (Figure 1 and 2), as this is when the most marked increase in pulmonary function are seen(232).

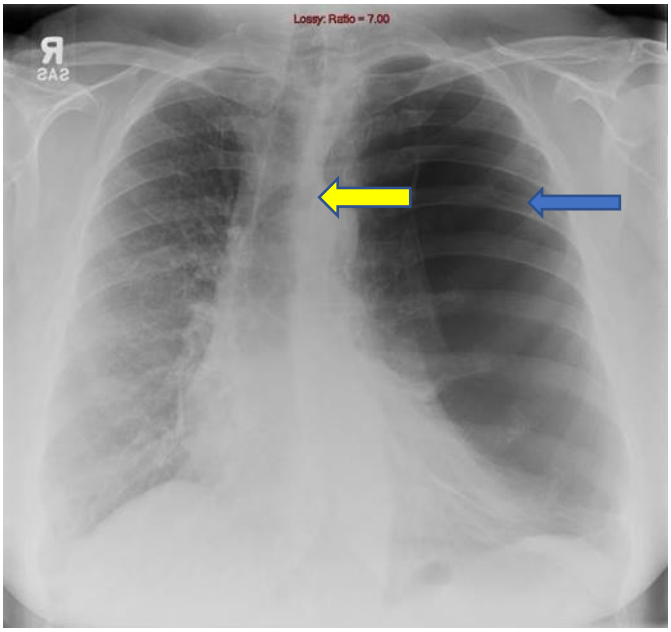

Figure 1: Plain radiograph of a patient at Liverpool Heart and Chest Hospital demonstrating a large bulla in left hemithorax (blue arrow) causing mediastinal shift. (yellow arrow)

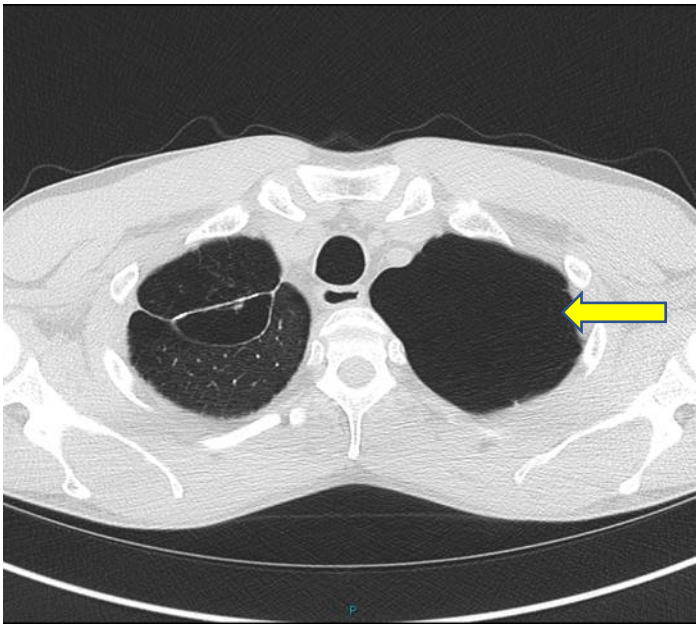

Figure 2: CT scan of a patient at Liverpool Heart and Chest Hospital showing bullae in the left upper lobe (yellow arrow).

In the mid 1900s, looking for treatments for severe emphysema, attention turned to experiments for lung transplantation. It was whilst observing the results of these procedures, that Otto Brantigan noted that after transplantation the hyperexpanded chest reverted back to its normal size (234). In 1957, he advocated for resections for non-giant bullous or generalized emphysema, based on the idea that reducing the volume of a hyperexpanded lung would improve ventilation and this could lead to better gas exchange(234). Brantigan performed his operations via posterolateral thoracotomy and removed multiple wedges of the "worst" emphysematous tissue until 20-30% of the lung tissue was taken. Whilst improvement was seen in nearly all patients, his high mortality rate of 15-20% meant little support for the practice (235).

The idea was later taken up by Joel Cooper, who in 1995 described results of 20 patients who had undergone bilateral LVRS for severe emphysema. His technique differed in the respect that it was performed via a median sternotomy, linear staplers were used to removed peripheral sections of lung and bovine pericardial strips were used to buttress the staple lines. From 18 patients, the mean increase in FEV_1 was 82% with no post-operative deaths(236). Following this many centres began performing LVRS, but literature from the early era (1993-1997) of LVRS was difficult to interpret. Most data came from small case series not randomised trials and the results of surgical management were not compared with that of medical therapies (237). Conclusions regarding outcomes such as increased pulmonary function and mortality rates could not confidently be made as numbers were small, inclusion criteria and surgical approaches varied and follow up was short or incomplete. There would undoubtably have been publication bias as well.

With concern for the rapid increase in LVRS and the inconsistences in reported data, the Health Care Financing Administration (HCFA) in the United States issued a national policy declining insurance coverage for LVRS. Furthermore, its internal evaluation concluded that the mortality rates seen were higher than recorded in the literature and, of 711 Medicare beneficiaries undergoing LVRS between 1995-

1996, 26% had died within the one year post-operatively (238). It was clear that questions regarding the benefit of LVRS, long-term outcomes, patient safety, patient suitability criteria, and financial consequences on health care systems needed to be answered. In response, the National Heart, Lung, and Blood Institute, the Agency for Healthcare Research and Quality (AHRQ) and HCFA agreed to sponsor a multicentre randomised trial comparing medical treatment and LVRS to medical treatment alone in patients with severe emphysema (National Emphysema Treatment Trial (NETT)).

Evidence for Lung Volume Reduction Surgery

In 1998, the NETT was set up. The key inclusion criteria were as follows: history of emphysema, $FEV_1 \leq 45\%$ ($\geq 15\%$ if over age 70), TLC $\geq 100\%$, RV $\geq 150\%$ and CT evidence of emphysema $\pm$ heterogeneous. Before randomisation, all patients underwent pulmonary rehabilitation. Those randomised to LVRS underwent bilateral stapled wedge resection through a median sternotomy or video-assisted thoracic surgery, aiming to remove 20-30% of each lung. Those in the medical group continued pulmonary rehabilitation, smoking cessation and optimal medical treatment. Primary outcomes were survival and maximum exercise capacity at 2 years post randomisation. Secondary outcomes were to identify selection criteria for LVRS, assess the effect of LVRS on pulmonary function, 6-minute walk distance, health related quality of life and the degree of dyspnea and determine cost effectiveness. From 1998 to 2003, 1218 patients underwent randomisation (608 to surgery and 610 to medical therapy) in one of the largest randomised trials ever to take place in thoracic surgery (239).

Initial results of the trial identified a high-risk group of patients, those with FEV_1 <20%, DLCO <20% or homogenous disease, who had high risk of dying post LVRS surgery and a low probability of functional benefit(240). These patients were excluded from randomisation in May 2001.The main trial showed that at 24 months exercise capacity improved in 15% (54/371) of patients in the surgery group and only 3% (10/378) of patients in the medical group (P<0.001). Additionally, quality of

life at 24 months had also improved in 33% (121/371) of patients that had surgery versus 9% (34/378) of patients in the medical group. 90 day mortality was significantly higher for the surgery group than the medical group (7.9% vs 1.3%), with no significant difference between VATS and open groups. However, during follow up (mean 29.2 months) no difference in overall mortality was seen between the groups and overall mortality was 0.11 deaths per person-year. Furthermore, although the effect of LVRS varied amongst patients, those who received LVRS were generally more likely to function better at 2 years than those who only received medical treatment. The subgroup with predominantly upper lobe emphysema and low exercise capacity made the greatest improvements in exercise capacity and quality of life and even showed survival benefit at 2 years(239).

Post-operative air leak was very common, occurring in 90% of patients, and tended to be long in duration, with a median duration of 7 days. Post-operative air leak is a key complication following LVRS and can result in an increased length of hospital stay, increased in hospital complications and readmission to intensive care. From analysis of NETT, prolonged air leak was associated with upper lobe emphysematous disease, lower diffusion capacity and pleural adhesions. Importantly, surgical approach, buttressing, stapler brand, and other adjunctive procedures did not result in fewer or less prolonged air leaks(241).

In a cost effectiveness evaluation of 531 patients in the surgery group and 535 patients randomised to maximal medical therapy alone (242), the cost effectiveness of LVRS vs medical therapy was $140,000 per quality-adjusted life-year (QALY) gained. This was projected to fall to $54,000 per QALY at 10 years but there was a high degree of uncertainty around this estimate as it was difficult to predict the participants costs and quality of life after 5 years. The subgroup with upper lobe emphysema and low exercise capacity displayed the most favorable cost effectiveness per QALY at 5 years.

Assessment for LVRS and current guidance

Following the results of NETT, many centres started to perform both unilateral and bilateral LVRS, either by median sternotomy, clamshell, bilateral thoracotomies or VATS. Current NICE guidelines emphasise that LVR procedures should be considered in patients with severe COPD patients (FEV1 <50% (243)), only after the completion of pulmonary rehabilitation and optimisation of medical treatment, if breathlessness is affecting quality of life. Patients must not smoke and must be able to complete a 6-minute walk distance of at least 140 metres(232). Additionally, currently used criteria for LVRS are based on those from the NETT and include the presence of heterogenous emphysema morphology, RV $\geq$ 150%, total lung capacity $\geq$ 100% and an FEV_1 or TLCO >20%, due to the high risk of mortality(240). Furthermore, the British Thoracic Society recommends simultaneous lung volume reduction during lung cancer resection, in patients who meet current criteria and whose tumours are located in areas of severe heterogenous emphysema. They note the benefit of improved symptoms and curative resection(31).

Pre-operative assessments include a full history and examination, routine bloods, spirometry and diffusion capacity, alpha 1 antitrypsin levels, chest radiograph (Figure 3) and high resolution CT scan (Figure 4).

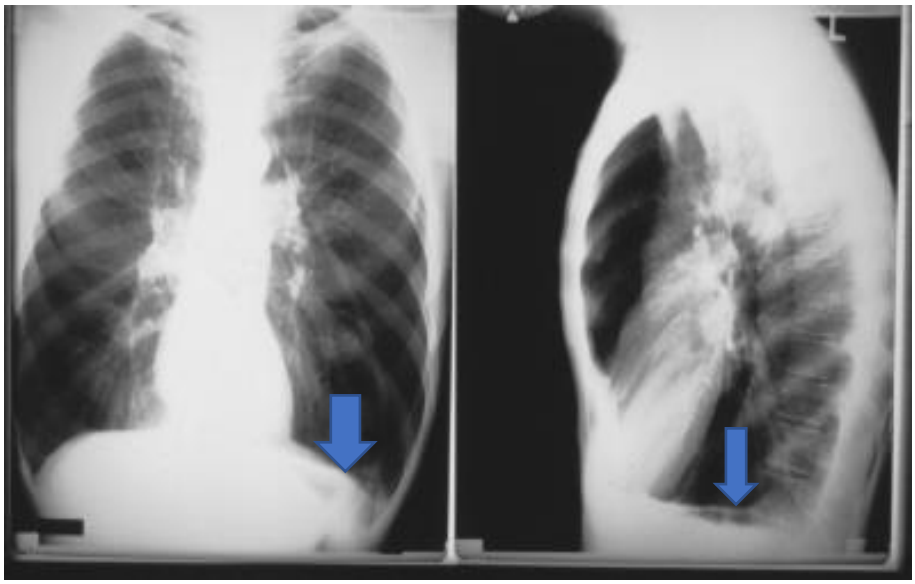

Figure 3: Plain radiograph taken of a patient undergoing lung volume reduction procedures at Liverpool Heart and Chest Hospital showing hyperexpanded chest with flattened diaphragm (blue arrow).

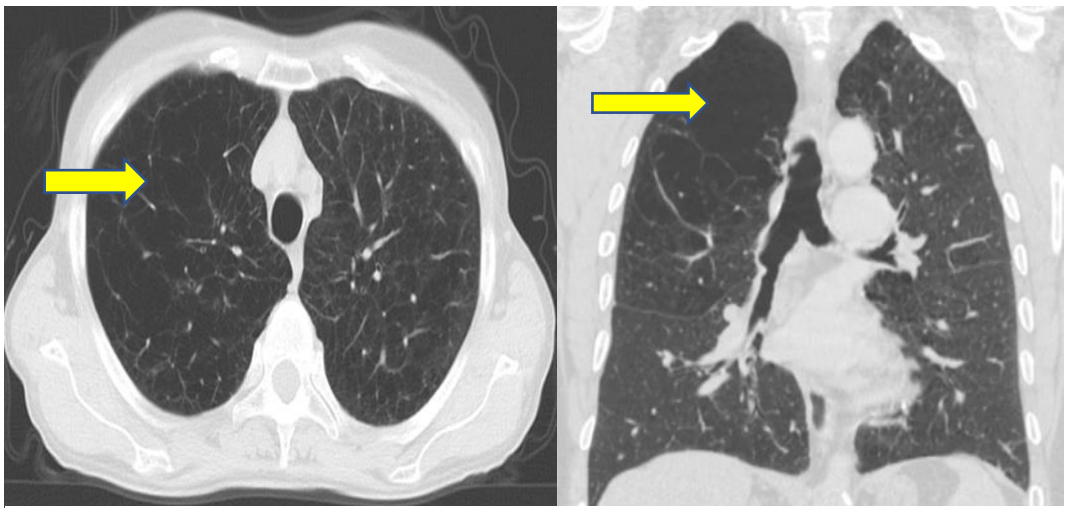

Figure 4: CT scan of a patient at Liverpool Heart and Chest Hospital, demonstrating right upper lobe emphysema (yellow arrow)

High- resolution CT allows for assessment of the distribution of emphysematous changes and software such as Stratx can quantify the density of each lobe of the lung (Figure 5). Quantitative VQ scanning can be used to quantify the function of various areas of the lung, however this has largely been replaced by CT scanning.

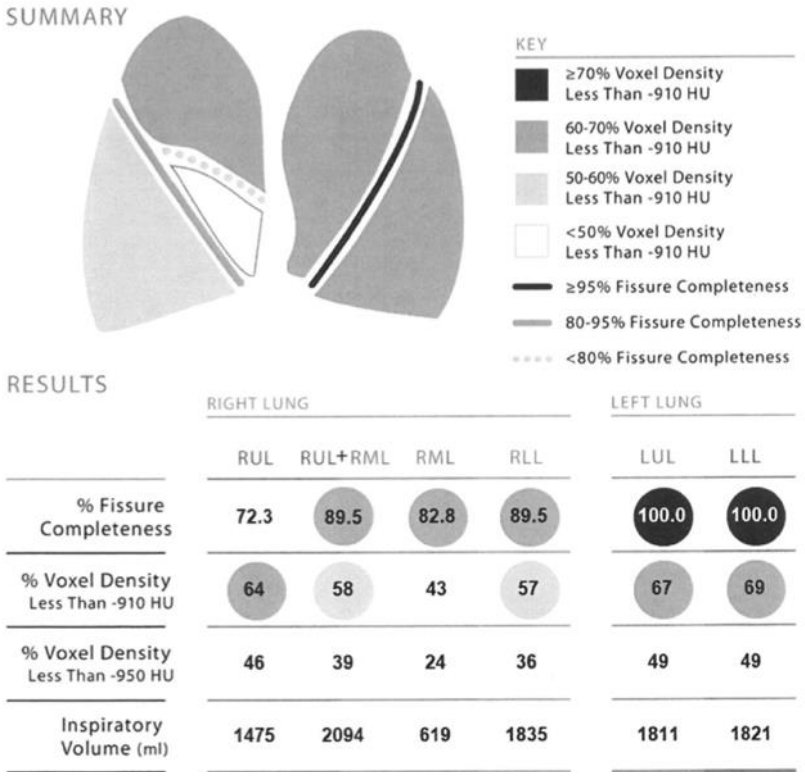

Figure 5: Stratx summary report for a patient undergoing pre-operative assessment for consideration for lung volume reduction surgery at Liverpool Heart and Chest Hospital.

Body plethysmography is the preferred technique to measure lung volumes such as total lung capacity and residual volume in this group of patients. In the presence of emphysema, gas (helium) dilution may underestimate total lung capacity and residual volume due to air trapping (Figure 6).

	Actual	Pred	%Pred	LLN
---- SPIROMETRY ----				
FVC (L)	2.16	3.45	62	2.45
FEV1 (L)	0.79	2.63	29	1.79
SVC (L)	2.57	3.45	74	2.44
FEV1/FVC (%)	36.53	74.13	49	62.34
FEV1/SVC (%)	30.66	76.23	40	
FEF Max (L/sec)	3.19	7.34	43	5.35
FEF 25-75% (L/sec)	0.27	2.83	9	1.12
---- GAS TRANSFER ----				
DLCOunc (mM/min/kPa)	3.19	7.84	40	5.52
VA (L)	4.29	6.08	70	4.71
DL/VA (mM/min/kPa/L)	0.74	1.29	57	
DLCOcor (mM/min/kPa)		7.84		5.52
RV/TLC (SB) (%)	46.54	42.30	110	31.38
TLC (SB) (L)	4.44	6.34	70	5.19
RV (SB) (L)	2.07	2.57	80	1.90
---- LUNG VOLUMES ----				
TGV (L)	9.18	3.50	262	2.51
RV (Pleth) (L)	7.97	2.57	310	1.90
TLC (Pleth) (L)	9.79	6.34	154	5.19
RV/TLC (Pleth) (%)	81.43	42.30	192	31.38

Figure 6: Lung function tests from a patient at Liverpool Heart and Chest demonstrating how TLC and RV can be underestimated with the use of gas dilution.

The growth of minimally invasive techniques for LVRS

A sub-analysis of the NETT data compared outcomes of different surgical techniques. It included 511 patients across 17 centres who underwent median sternotomy (359) or VATS (152) for bilateral LVRS(244). Similar mortality rates, post-operative complications, improvements in FEV1 and quality of life up to 24 months follow up were noted. 90 day mortality was low at 5.9% for median sternotomy and 4.6% for VATS (P = 0.67). Additionally, the VATS approach was favourable in terms of length of hospital stay and cost. Looking at centres which in themselves randomised to median sternotomy (75 patients) and VATS (67 patients),

median length of stay was 15 days for median sternotomy patients and 9 days for VATS patients ($P < .001$). From data of 489 Medicare patients, the mean in-hospital costs were $8207 less for VATS patients and mean total costs in the 6 months following surgery were also $10,428 less (244).

The total number of LVRS cases in the UK remains low. In fact, according to figures from the Third National Thoracic Surgery Activity & Outcomes Report, there were only 654 LVRS cases in England between 2010-2015, of which Liverpool Heart and Chest Hospital contributed 21 cases (45). Nonetheless, LVRS activity has grown and today VATS is the most commonly used technique. An 80% increase was noted between 2010-2011 and 2014-2015 and this was entirely due to the increase in VATS cases (Figure 7) (45). Cases have continued on an upwards trajectory, with a total of 311 operations taking place in the period 2019-2020(245).

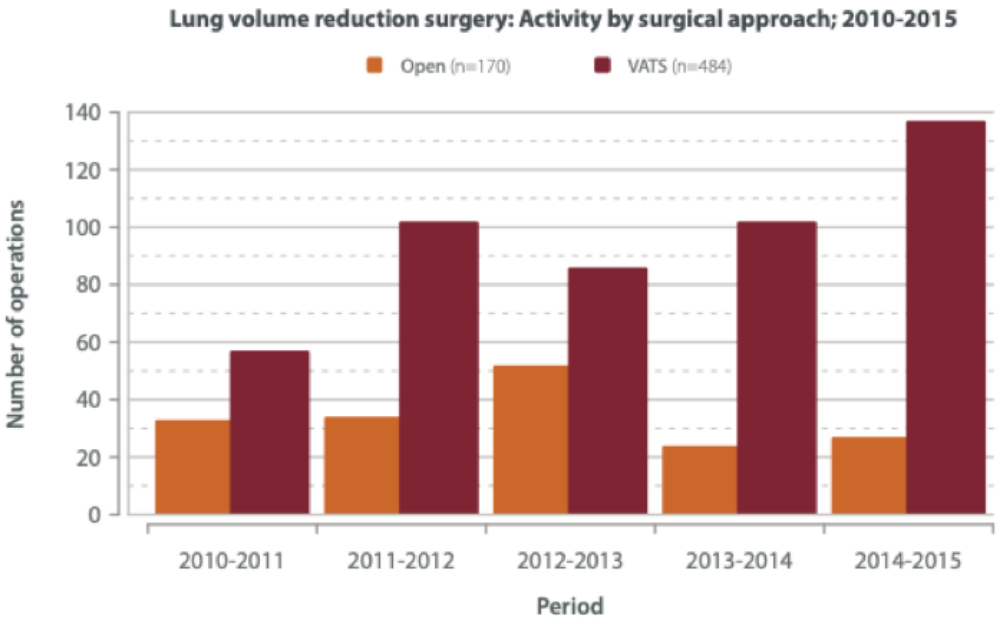

Figure 7: Lung volume reduction surgery: Activity by surgical approach;2010-2015. An increase in LVRS activity of just over 80% is noted between the period 2010-2011 and 2014-2015.

Source: Society for Cardiothoracic Surgery in Great Britain & Ireland. Third National Thoracic Surgery Activity & Outcomes Report. Dendrite Clinical Systems Ltd; 2018.

Various surgical units have shown that the mortality argument against LVRS holds little weight as long as patients are selected according to strict criteria (246, 247). In fact, in hospital survival rates in the UK from 2010-2015 were 99% for VATS and 96.5% for open(45).

There is no official guidance on whether LVRS should be performed by open or minimally invasive techniques. However, with the benefits of reduced hospital stay, post-operative pain and improved cost-effectiveness seen with the use of VATS, minimally invasive techniques seem to be a favourable option. Additionally, when considering the group eligible for LVRS, with severe COPD and likely poor performance status, a technique which offers reduced tissue trauma, shorter time under general anaesthesia and a chance for faster recovery seems appropriate.

In an effort to provide less invasive procedures for LVR, various endobronchial techniques were developed. These include the placement of one-way valves, endobronchial coils and the use of thermal vapour ablation. There has been an exponential increase in endobronchial LVR of which the main technique of benefit and with the greatest evidence base is endobronchial valves (EBVs)(248-251). Randomised controlled trials have shown a greater response to EBV placement in those with heterogenous emphysema and complete interlobar fissures, a surrogate measure for a lack of interlobar contralateral ventilation(252) .The main complication is pneumothorax which this occurs in around 6.2% of cases (253). Mortality rates compared to standard care were similar at 12 months (248, 252). In 2013, NICE approved the use of EBVs for LVR in emphysema(254). There has been an industry driven promotion of LVR techniques and an increase in LVR multidisciplinary team meetings. Figures for the period 2019-2020 show that 311 LVRS operations and 255 EBV procedures took place in hospitals in England, with 15 cases at Liverpool Heart and Chest Hospital (245).

Introduction of robotic techniques for LVRS

Robotic LVRS may hold some advantages over the commonly used VATS technique. Unlike a healthy lung, which will collapse down when not ventilated, an emphysematous lung does not compress down easily due to the air trapping. This makes the lung difficult to move and there is a risk of damaging the lung during surgery. The use of CO_2 insufflation in robotic surgery aids in the compression of the emphysematous lung, creating greater space in the thoracic cavity in which to manipulate the lung. Additionally, the robot's 3D visual system and articulated instruments allow for good visualisation and a greater freedom of movement, which may result in less mobilisation of lung, fewer lung tears and subsequently a reduction in the frequency and duration of post-operative air leaks. Another benefit of the robot is that the robotic instruments are good for removing pleural adhesions and, as previously noted, the presence of pleural adhesions is associated with prolonged air leak(241). During LVRS, in an effort to reduce post-operative air leaks, staple lines are often re-enforced with either pericardial strips, glues or sealants, as some benefit is seen in patients with severe emphysema (255, 256). However, robotic staplers (Figure 8) may be superior to endostaplers and may result in fewer post-operative air leaks, although this has yet to be determined.

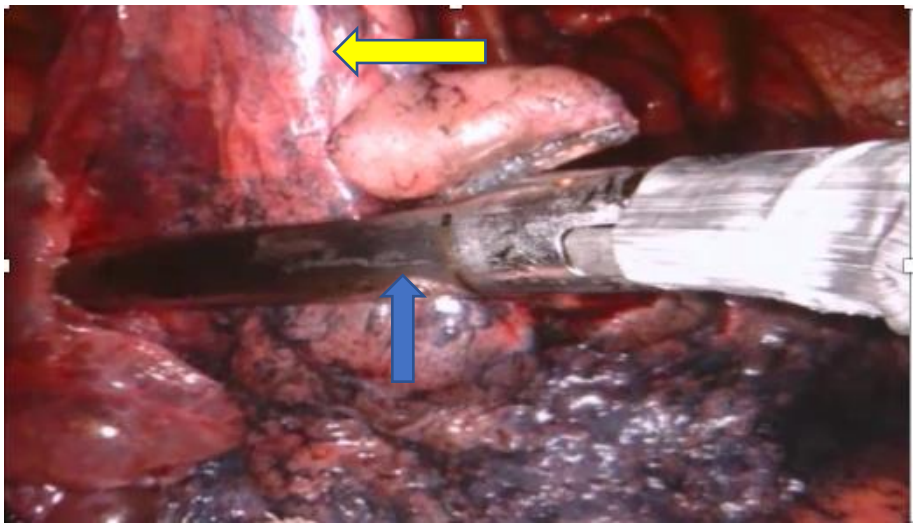

Figure 8: Image captured from video showing robotic stapling (blue arrow) of emphysematous lung tissue in right upper lobe (yellow arrow) during robotic lung volume reduction surgery. Ports are positioned inferiorly, with the camera pointing towards the lung apex and a horseshoe shaped wedge of lung being resected.

Although not used routinely at Liverpool Heart and Chest Hospital, the other benefit of robotically performed LVRS is the option to use the Da Vinci integrated fluorescence imaging system (Firefly) intraoperatively (257). With the use of an indocyanine green tracer, the technology developed by Intuitive Surgical, Inc. can help identify areas of emphysematous lung, which have a poor blood supply in comparison with healthy lung tissue.

Robotic surgery may also have the benefit of reducing tissue trauma and subsequently post-operative pain. The Da Vinci robot uses smaller ports than the standard 10mm VATS ports, with two 8mm ports and a 12mm stapler port. These ports are placed with the fixed point around which the cannula pivots between the ribs, thus minimising the force exerted on the thoracic wall, especially the intercostal nerves.

Table 1. Advantages and disadvantages of robotic LVRS

Advantages of robotic LVRS	**Disadvantages of robotic LVRS**
Use of CO2 insufflation	High cost of procuring a robot and servicing costs
3D visualisation	Potentially longer operating time
Endowrist instruments	
Well-suited to removing pleural adhesions	
Robotic staplers with potential to reduce air leaks	
Intra-operative Firefly perfusion assessment	
Smaller ports compared to VATS, that are designed to minimize force on chest wall	

In January 2019, the robotic programme at Liverpool Heart and Chest Hospital was expanded to include LVRS. The world of robotics is new to the area of lung volume reduction surgery. In fact, the first US robotic LVRS case was performed in January 2019 at NorthWestern Memorial Hospital. The proposed benefits of robotic

techniques for LVRS have been summarised in Table 1. Robotics may be a well-suited choice for LVRS as the operation is concentrated in a small area and does not require great manipulation of the lung tissue.

5.2 Aims and objectives

The aim of this study is to look at the effect of introducing robotic LVRS at Liverpool Heart and Chest Hospital on patient outcomes and costs.

Our primary objective was to prove that robotic LVRS was safe in terms of providing similar in-hospital outcomes to VATS LVRS, the gold standard technique. The primary outcomes of this study are 90-day mortality, length of post-operative stay and rates of respiratory complications.

Our secondary objective was to assess the impact of robotic LVRS on post-operative pain and changes in pulmonary function as well as to conduct a basic cost analysis. Our secondary outcomes were day 1 strong opioid usage, changes pulmonary function at 6 weeks to 3 months follow up and in-hospital costs.

5.3 Methods

Study design

We conducted a single centre retrospective analysis of all patients undergoing VATS and robotic LVRS between November 2015 and October 2019 at Liverpool Heart and Chest Hospital. The inclusion and exclusion criteria are listed in Table 2.

The start date was chosen as November 2015 as this is when the hospital's electronic patient records was set up. The hospital's electronic patient record system was used to search for all patients that had undergone lung volume reduction surgery. Patient characteristics such as age, sex, BMI, pre-operative spirometry, co-morbidities and alcohol and smoking status were recorded, along with operation date, and surgical technique. Post-operative details were recorded for in hospital outcomes, including post-operative complications, analgesic requirements, intensive care admissions and length of hospital stay.

Table 2. Inclusion and exclusion criteria

Inclusion criteria	**Exclusion criteria**
Patients undergoing LVRS at Liverpool Heart and Chest Hospital between November 2015 and October 2019	Patients undergoing LVRS in conjunction with lung cancer resection
Patients on Liverpool Heart and Chest Hospital's patient electronic record system	Patients undergoing bullectomy
Patients undergoing LVRS by robotic and VATS techniques	

Approvals

All data was collected as part of routine clinical practice and therefore ethical committee approval was not deemed necessary.

Surgical technique

VATS LVRS was performed as a unilateral procedure with the patient placed in the lateral decubitus position, after intubation with a double lumen tube. A single shot paravertebral block was performed pre-operatively and postoperatively the wounds were infiltrated with 20ml of 0.25% chirocaine. Following isolation of the lung, a 10 mm port for the 30-degree angled HD video-thoracoscope was made in the 9^{th} or 10^{th} intercostal space in the mid-axillary line. The procedure was carried out with a 10mm camera port and two instrument ports. A horseshoe shaped wedge was resected using endostapler reloads. Following the positioning of apical chest drain(s), the ports are closed.

Robotic LVRS was completed with the da Vinci X surgical system, created by Intuitive Surgical, Inc (258). The patient was positioned the same as in VATS, and similar anaesthetic and analgesic techniques were used. Three ports were

positioned in the 7th intercostal space: an 8mm camera port in the midclavicular line, another 8mm port posteriorly and a 12mm anterior port for the robotic stapler. There needs to be a distance of at least 10cm between ports. A 30-degree 3D robotic camera was used. CO2 insufflation was then connected and the robot was docked. The thoracic space was first assessed for adhesions which were then divided. Substantial bullae and blebs were then located, and a horseshoe shaped wedge of lung was removed using the robotic staplers green 45mm reloads. The robot was de-docked and a single 28Ch apical drain placed. Wounds were infiltrated with 20ml 0.25% chirocaine and closed.

Post-operative care

In both VATS and robotic LVRS, all patients were extubated immediately in theatre and sent to recovery. They were then sent to the ward or critical care depending on their condition. Routine post-operative analgesia and physiotherapy was given. Drains were removed when there was no air leak or were placed on flutter bags to allow patients to be discharged home if they were ready for discharge prior to an air leak ceasing.

Cost analysis

Cost per procedure were calculated based on the following costings laid out in Table 3. It is assumed that all other costs relating to patient care such as investigations, anaesthetic costs, drug costs, and other theatre and ward consumables are similar in both groups. It is also assumed that like in this case, the LVRS programme is added to an already existing robotic programme and therefore costs due to capital expenditure and maintenance are not added. This assumption was made as the number of LVRS cases is small and robotic LVRS would complement an already existing robotic surgery programme. Robotic programmes also vary by centre, with some centres sharing their robot between various specialities.

Table 3. Costs per procedure for robotic and VATS LVRS

Robotic LVRS costs	**VATS LVRS costs**
Theatre time = £7 per minute	
1 night critical care stay= £619	
1 night ward stay= £407	
Consumables	
Arm drapes= 3 x £46.35	Trocar= 1 x £30
Central column drape = £16	Diathermy hook= 1 x £43
Diathermy spatula= 1/10 x £1780	Minimally invasive stapler and 12 reloads=£1480
Fenestrated bipolar forceps= 1/10 x £241	
Robotic stapler with 12 reloads= £1539	

Statistical analysis

Statistical analysis was undertaken, using the GraphPad Prism software (259), to compare outcomes between patients in the VATS and robotic LVRS groups. The median and interquartile range was reported for patient characteristics and outcomes, due to the small sample size. Differences between the median values were evaluated using t-tests for normally distributed continuous variables and chi-squared tests for normally distribution categorical variables. For continuous variables of non-normal distribution Mann-Whitney tests were used. A *p* value less than or equal to 0.05 was considered statistically significant.

5.4 Results

Between November 2015 and October 2019, 31 patients underwent 36 LVRS operations at LHCH. In total 12 robotic and 24 VATS were performed. The first

robotic LVRS took place in January 2019. No LVRS case was converted in either the VATS or the robotic group.

Pre-operative characteristics are shown in Table 4. 11 (45.8%) of the VATS patients and 5 (41.7%) of the robotic patients were male. The groups were similar in terms of age and pre-operative lung function.

Table 4: Pre-operative characteristics for 34 patients undergoing VATS and robotic LVRS

Characteristic	**VATS**	**Robotic**	***p* value**
Number of procedures completed	24	12	-
Sex = Male (n (%))	11 (45.8)	5 (41.7)	1.000
Age (median [IQR])	57.50 [51.00, 62.00]	59.50 [54.75, 64.75]	0.347
FEV_1 - % of predicted value (median [IQR])	30.93 [27.11, 47.73]	31.84 [27.30, 37.09]	0.859
FVC - % of predicted value (median [IQR])	76.42 [71.42, 97.50]	76.24 [64.96, 79.80]	0.271
TLC- % of predicted value (median [IQR])	126.80 [119.95, 139.30]	120.90 [115.80, 131.75]	0.286
RV- % of predicted value (median [IQR])	214.50 [192.00, 252.55]	200.00 [190.50, 215.40]	0.277
DLCO - % of predicted value (median [IQR])	39.40 [32.60, 51.30]	37.00 [31.15, 38.50]	0.211

Operative Characteristics are shown in Table 5. The median operation time was 64 minutes in the VATS group and 81 minutes in the robotic group. There did appear to be a learning curve with regards time taken for the robotic cases. The median time for the first 6 robotic cases was 98 minutes and 76 minutes for the later 6. The time taken for the VATS case did not appear to change significantly with time. After 12 cases the moving averages for the operative time were similar for both groups (Figure 9).

None of the operations in the VATS group were converted to open and none of the robotic cases were converted to VATS or open procedures. The median number of chest drains inserted was 2 in the VATS group and 1 in the robotic group, with a single drain used in all the robotic cases. 17 patients in the VATS group and 1 patient in the robotic group was sent to critical care post-operatively.

Table 5: Operative characteristics for 24 VATS and 12 robotic LVRS operations taking place at LHCH between November 2015 and October 2019.

Characteristic	**VATS**	**Robotic**	***p* value**
Operation time, minutes (median [IQR])	64.00 [54.50, 70.50]	80.50 [78.00, 98.00]	<0.001
Conversion to open (n (%))	0 (0)	0 (0)	-
Number of drains (median [IQR])	2.00 [2.00, 2.00]	1.00 [1.00, 1.00]	<0.001
Post-op destination = ward (n (%))	7 (29.2)	11 (91.7)	0.001

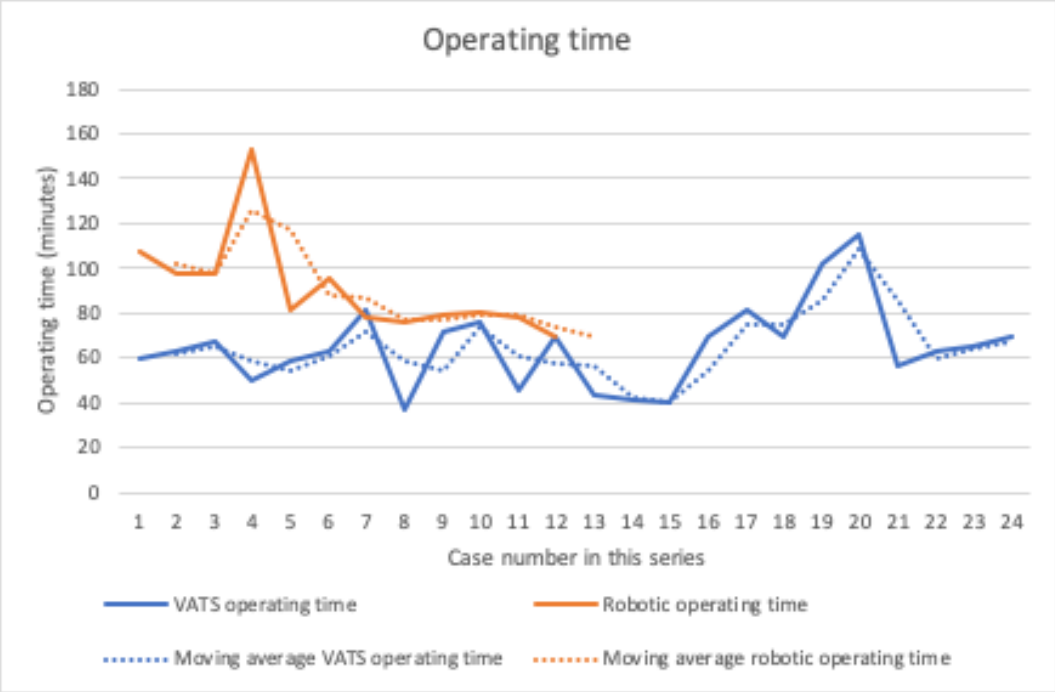

Figure 9: Line graph showing operating times for VATS and robotic LVRS

Post-operative outcomes are shown in Table 6. The median post-operative length of stay was 8 days in the VATS group and 6.5 days in the robotic group. 3 patients in the VATS group and 2 patients in the robotic group were discharged home with a chest drain. The median day chest drains were removed was between post-operative day 7 and 8 in the VATS group and day 4 in the robotic group (Figure 10). 14 patients in the VATS group and 6 in the robotic group experienced a respiratory complication post-operatively. There was a 2.78% 90-day mortality rate overall.

Intravenous (IV) strong opioid usage in the first 24 hours was compared between the two groups. In the VATS group the following were excluded from the analysis; two patients did not have data available, four patients had thoracic epidurals, and one patient had a fentanyl PCA. In the robotic group two patients did not required any strong opioids, and four patients required just oral strong opioids in the first 24 hours. The median intravenous strong opioid requirement in the first 24 hours in the robotic group was 1mg (IQR 0-27mg) and 58mg (IQR 28-68mg) in the VATS group (p=0.0008). Patients in the robotic group who had oral strong opioids only were reported as having 0mg IV strong opioid use. The analysis was repeated excluding the patients in the robotic group who had only oral strong opioids. The

median intravenous opioid usage excluding these patients was 14mg (IQR 1-38mg). This remained significantly lower than in the VATS group (p=0.0260) (Figure 11).

Table 6: Post-operative outcomes for 24 VATS and 12 robotic LVRS operations taking place at LHCH between November 2015 and October 2019.

Characteristics	**VATS**	**Robotic**	***p* value**
Post-operative day chest tube removed (median [IQR])	7.5 [3.25 - 14.75]	4 [2.5-13.25]	0.469
Discharged home with chest drain (n (%))	3 (12.5)	2 (16.7)	0.733
IV PCA strong opioid usage in first 24 hours (mg), oral strong opioids included (median [IQR])	58.0 [28.0-68.0]	1 [0.0 -26.6]	<0.001
IV PCA strong opioid usage in first 24 hours, oral strong opioids excluded (median [IQR])	58.0 [28.0 – 68.0]	13.8 [0.5 – 37.5]	0.026
Post-operative length of stay (median ([IQR])	8.00 [5.00, 11.25]	6.50 [3.75, 12.00]	0.626
Critical care re-admission (n (%))	1 (4.2)	2 (16.7)	0.218

Respiratory complication (n (%))	14 (58.3)	6 (50.0)	0.537
90-day mortality rate (n (%))	0 (0%)	1 (8.3%)	0.1515

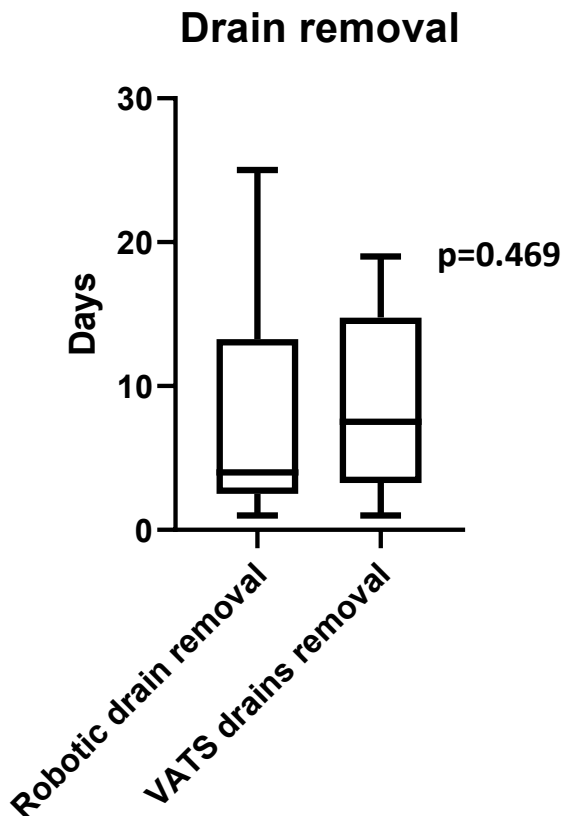

Figure 10. Boxplot showing day of drain removal post-operatively. Boxes represent the median and interquartile range with bars depicting the range of values observed.

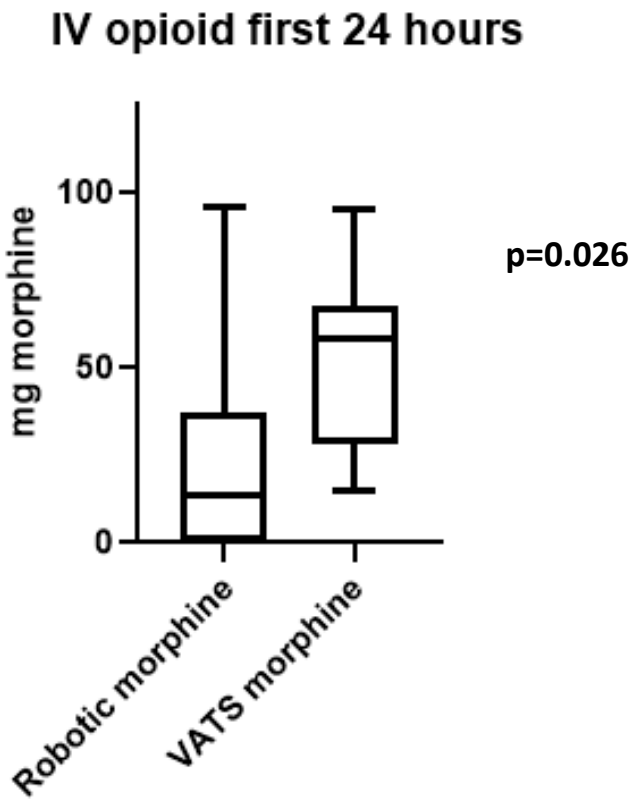

Figure 11: Boxplot showing IV strong opioid usage in the first 24 hours post-operatively. Boxes represent the median and interquartile range with bars depicting the range of values observed. Patients that had just oral opioids were excluded.

Change in pulmonary function at 3-12 months was available in 62.5% of VATS cases and 50% of robotic cases. A lot of patients are reviewed in District General Hospitals where body plethysmography cannot be performed therefore post-operative data is not available in all patients. Change in pulmonary function tests are shown in Table 7. Both groups showed an increase in FEV_1 and TLCO, and a decrease in RV at follow up as expected.

Table 7: Post-operative change in pulmonary function for follow up patients at 3/6 weeks

Characteristics	**VATS**	**Robotic**	***p* value**
Follow up available (n (%))	15 (62.5)	6 (50.0)	0.453
FEV1- Change in % predicted value (median [IQR])	10.71 [4.87, 12.68]	12.00 [7.03, 19.05]	0.484
DLCO- Change in % predicted value (median [IQR])	0.40 [-1.1, 8.25]	11.00 [3.75,14.5]	0.041
TLC- Decrease in % of predicted value (median [IQR])	6.20 [1.6, 11.9)	9.00 [3.55, 38.2]	0.461
RV- Decrease % predicted value (median [IQR])	42.20 (10,74.6)	49.80 [19, 158]	0.763

We performed a basic cost analysis on our data concentrating on theatre time, theatre disposable, post-operative destination and post-op length of stay. Median values were used for each group. The following costs were used; critical care stay was high dependency with a cost of £619 per day, ward bed per day £407 and operating room time £7 per minute. It is assumed all theatre consumable costs were the same apart from those shown in Table 8. We took the average number of stapler reloads per case to be 12. As it anticipated a robotic LVRS programme would complement an already existing robotic programme, capital purchase and maintenance costs have not been included.

Table 8. Basic cost analysis for robotic and VATS procedures

Robotic consumables	
Arm drapes 3 x £46.35	£139.05
Central column drape	£16
Canulae seal x 3	£48
Diathermy spatula	£178
Fenestrated bipolar forceps	£241
Robotic stapler	£1539
Total	**£2161.05**

VATS consumables	
Minimally invasive stapler and reloads	£1480
Canula x1	£30
Diathermy hook	£43
Total	**£1553**

Item	**VATS**	**Robotic**
Theatre time	64 x £7 = £448	80.5 x £7 = £563.50
Consumables	£1553	£2161.05
Average HDU cost per patient	£438.46	£51.58
Ward cost per patient	£3256	£2645.50
Total	**£5695.46**	**£5421.63**

5.5 Discussion

This is the first published series on robotic lung volume reduction surgery, to our knowledge. Robotic surgery was advantageous and there was a significant decrease in critical care stay and post-operative morphine requirements in the first 24 hours.

Post-operative outcomes

A trend was seen towards a shorter post-operative length of stay and chest drain duration in the robotic group compared to the VATS group, however this was not statistically significant and likely the result of a type II error due to a small sample size. Fewer post-operative respiratory complications were also seen in the robotic group than the VATS group, but again this was not seen to be statistically significant. A similar number of critical care re-admissions were seen between the groups (p=0.218). However, overall fewer patients in the robotic group (2/12) had any admissions to critical care compared to the VATS group (17/24). This may reflect hospital protocols rather than the fact the robotic patients required a reduced level of clinical care compared to VATS patients. An increase in FEV1 and decrease in RV was seen in both groups post-operatively and was similar to that seen in the literature (244, 247, 260).

Our post-operative outcomes were comparable to those reported in other unilateral LVRS case series. Rates of those discharged with a chest drain were similar (247), as were rates of respiratory complications (260) and length of hospital, with reported figures ranging from a mean of 9 – 16 days (247, 261, 262).

90-day mortality

There is very limited evidence of robotic LVRS in the literature. The NETT trial reported a 90 day mortality rate of 4.6% in the VATS group (244). In comparison, we observed a 90-day mortality rate 2.78%, with a 0% 90-day mortality rate in the VATS group. A true judgement on patient outcomes cannot be made as the NETT data is historic and patients underwent bilateral rather than unilateral LVRS. Our case numbers are also small and, therefore, it is not surprising that our mortality rate is better. More recent unilateral LVRS case series have also suggested that

mortality is lower in current practice than reported in NETT, with some studies reporting a 30-day mortality of 0-3% (260, 262) and others a 90-day mortality of 0 - 1.03% (247, 261).

Post-operative pain

One of the rationales for and potential benefits of robotic surgery is that it causes less tissue trauma compared with VATS and open surgery and thus is thought to lead to a reduction in post-operative pain. In thoracic surgery there has been a move away from the use of thoracic epidurals. This was seen in our patients; four patients early in the series (VATS group) had thoracic epidurals while none in the latter period had one. As none of the patients in the robotic group had an epidural, this perhaps suggests the need for stronger analgesia in the VATS group. However, as epidurals are placed pre-operatively, this more likely demonstrates a time related change. Although epidurals are considered the gold standard for pain management, they can cause fluid shifts and reduce mobility and have never been shown to improve outcomes.

Some of the patients in the robotic group were managed with oral opioids in the first 24 hours rather than intravenous opioids. It is difficult to say whether this is because the robotic group experienced less pain or whether it merely reflects a change in practice. We found that the robotic LVRS patients required significantly less intravenous strong opioid in the first 24 hours than the VATS group. This was the case when those managed only on oral strong opioids were (IV strong opioid requirement = 0mg) included and were not included.

One of the limitations of the analysis is that we do not have pain scores. However, if patients are given adequate analgesia, then one would expect pain scores to be similar. Intravenous strong opioid requirement may therefore be a better measure of how painful the operation is. Post-operative pain was difficult to compare to other studies as analgesic techniques vary between units and studies use different measures to record pain.

Operative time

The main perceived disadvantages of robotic surgery are thought to be the increased operating time and increased costs. Operative time was significantly longer in the robotic group. There was, however, a decrease in operative time over the 12 robotic cases suggesting a learning curve. The time taken for the robotic cases towards the end of the series was similar to that of the VATS cases.

Costs

In this basic cost analysis, the cost of robotic and VATS LVRS were similar and actually slightly lower in the robotic group. Theatre time and consumable were greater in the robotic group, but HDU requirement and ward stay were longer in the VATS group. As VATS LVRS has been found to be cost effective compared to open surgery(244), results therefore indicate that robotic LVRS is cost-effective and may potentially more cost-effective due to the reduction in critical care stay and length of hospitalisation. However, the amortized cost of the robot was not included and larger studies would be needed to validate this.

Post-operative care

The majority of robotic LVRS patients did not go to the critical care unit post-operatively. This may well be due to a change in practice over time, rather than a reflection that the robotic LVRS patients require a lower level of care than the VATS LVRS patients. To try and see whether this was the case, we compared the VATS LVRS cases in the year prior to commencing robotic LVRS. In this year only 45.5% of patients went back to the ward which is significantly lower than in the robotic group (91.7%). This suggests that either robotic LVRS require a lower level of post-operative care or a conscious decision was made to avoid critical care admission at the start of the robotic LVRS programme. As our mediastinal mass study (chapter 4) reported no difference in post-operative critical care admission between VATS and robotic cases, it would suggest that this observed difference was not due to a general change in hospital policy, but rather reflects the reduced level of post-operative care required for patients undergoing robotic LVRS.

Benefits of robotic surgery

In robotic LVRS some groups have used injection of indocyanine green and autofluorescence to target the poorly perfused areas of lung to be removed (257). We have not adopted this technique as we feel that the aim of lung volume reduction is to reduce the volume of the lung, not to remove areas of ventilation/ perfusion mismatch.

Some of the potential benefits of robotic LVRS could actually be replicated in VATS LVRS. This could perhaps result in improved patient outcomes, whilst eliminating the need for surgeons to undertake robotic training and the need for the capital expenditure required to purchase a robot. For example, CO_2 insufflation, a single chest drain and smaller 5mm thoracoscopes could all be used in a VATS setting. Additionally, whereas the majority of patients in the VATS group were sent to critical care post-operatively, nearly all of the patient in the robotic group were sent back to the ward. The robotic group has shown that patients can safely be managed on the ward post-operatively and that nearly all these patients did not require an admission to critical care during their hospital stay.

Study limitations

The main limitation of this study is its retrospective nature. Data fields were predetermined and we must consider the impact of possible information bias. The sample size was small and much larger numbers are required to determine whether any true differences exist between VATS and robotic LVRS. No quality of life analysis was undertaken. As lung volume reduction surgery is performed to improve quality of life this would be an important aspect to consider in any prospective study.

5.6 Conclusions

In conclusion, robotic lung volume reduction surgery appears as safe and at least as cost effective as traditional VATS LVRS. Robotic LVRS patients require significantly less IV opioids in the first 24 hours post-operatively. Further prospective studies are

required to determine whether there is a benefit of one technique over the other and, due to the relatively small number of cases performed, this would have to be a multicentre trial. Any prospective studies should include a quality of life analysis. Currently data on LVRS and bronchoscopic lung volume reduction (BLVR) is being collected in a registry as part of the UK Lung volume reduction study (ISRCTN16371361), a multicentre observational study. As robotic LVRS numbers increase, it would be of value to expand the study to include robotic LVRS so that a comparison can be made with VATS LVRS.

Chapter 6: Discussion & Conclusions

6.1 The key findings identified in Chapters 2-5

1. Retrospective analysis suggests robotic lobectomy is safe and possibly has fewer overall complications, a shorter length of stay and lower critical care requirements than VATS lobectomy. (Chapter 2)

2. The COLT pilot study identified that a high-quality, detailed prospective dataset could successfully be collected on all patients undergoing anatomical lung resection at Liverpool Heart and Chest Hospital. Data completeness was 98.1%. (Chapter 3)

3. Rates of minimally invasive anatomical lung resection (75.6%) at Liverpool Heart and Chest Hospital are higher than the national average. (Chapter 3)

4. The COLT pilot study revealed smaller clinical differences between VATS and open anatomical lung resection in terms of median length of hospital stay (4 vs 3 days, p= 0.1548) and post-operative pain scores (2 vs 2 on day 1, p=0.8528) than in the literature. (Chapter 3)

5. The percentage of anatomical lung resections performed by open (14.4%) and robotic (3.3%) surgery were lower than expected (Chapter 3).

6. The introduction of robotic surgery has led to an increase in the percentage of mediastinal masses being resected by a minimal invasive surgery from 20% to 45%. (Chapter 4)

7. Minimally invasive resection of mediastinal masses is associated with a shorter median length of stay (4 vs 2 vs 2 days, open vs VATS vs robotic, $p<0.0001$) and fewer post-operative admissions to critical care (88.64% v 27.59%, $p <0.0001$) compared to open surgery. Robotic surgery showed a

trend in reduced morphine use in the first 24 hours post-operatively compared to VATS (24mg vs 35.8mg, p=0.073). (Chapter 4)

8. Robotic lung volume reduction surgery (LVRS) is safe and there was less IV morphine use in the first 24 hours post-operatively (13.8mg vs 58.0mg, p=0.026) and fewer patients sent to critical care (8.3% vs 70.8%, p=0.001) compared to VATS. (Chapter 5)

9. Robotic LVRS was associated with a short learning curve and after 6 cases operative time fell and plateaued at a time similar to that taken for VATS LVRS. (Chapter 5)

10. Robotic lung volume reduction surgery is cost effective when compared to VATS LVRS (£5421.63 vs £5695.46). (Chapter 5)

Robotic assisted surgery for early-stage lung cancer: a retrospective study

On retrospective analysis of robotic lobectomy since its introduction to Liverpool Heart and Chest Hospital in 2017, robotic lobectomy was found to be at least as safe as VATS lobectomy. The robotic lobectomy group had a significantly less complications (25.0% v 17.2%, p=0.0093), significantly shorter length of stay (4 v 3 days, p=0.0063) and required significantly less critical care admissions post-operatively (85.5% v 19.0%, p<0.0001), suggesting the potential benefit of robotic surgery.

COLT pilot study

The prospective COLT pilot study showed that a detailed dataset can be collected on all anatomical lung resections for suspected and confirmed cases of lung cancer at Liverpool Heart and Chest Hospital. Despite COVID-19, the dataset showed 98.1% completeness, which is promising for the future COLT trial. Rates of minimally invasive surgery (75.6%) were higher than the national average (21). The majority of planned procedures were by VATS (82.2%), demonstrating that Liverpool Heart and Chest Hospital is a leading centre in the UK for VATS. Patients that underwent

VATS were significantly more likely to be managed on the ward post-operatively. The number of open and robotic cases included in the pilot study was low. When designing future studies this will need to be taken into account to ensure that trials are sufficiently powered. For recommendations on future studies see Chapter 6.3.

Robotic mediastinal mass surgery

On review of the introduction of robotic mediastinal surgery at Liverpool Heart and Chest Hospital, we observed an increase in the percentage of patients receiving minimally invasive surgery for mediastinal mass resection from 20% to 45%. Minimally invasive resection was also associated with a significantly reduced length of hospitalisation compared with open surgery and patients undergoing minimally invasive surgery were more likely to be managed on the ward post-operatively. The robotic group showed a trend towards reduced morphine requirements in the first 24 hours post-operatively compared to the VATS group.

Robotic lung volume reduction surgery

From the initial experience of robotic lung volume reduction surgery at Liverpool Heart and Chest Hospital, we found the robotic approach to be safe and at least as cost effective as VATS LVRS. Patients that underwent robotic LVRS had fewer chest drains, had their drains removed earlier and were significantly less likely to be admitted to critical care post-operatively compared with those undergoing traditional VATS LVRS. Robotic LVRS patients also required significantly less IV opioids in the first 24 hours post-operatively compared to VATS LVRS. Operative time was higher for robotic LVRS but over 12 cases the moving average decreased and was similar to that of VATS LVRS.

6.2 Discussion

Advantages of robotic surgery

Robotic technology allows surgeons to perform complex and intricate operations via a minimally invasive approach. The da Vinci surgical system provides 3D high

visualisation with magnification and endowrist instruments which permit greater precision, dexterity and control than VATS. The proposed benefits are reduced tissue trauma and post-operative pain due to smaller incisions, reduced port site trauma and no rib spreading (75, 124, 125, 134). In addition, it has been suggested that robotic surgery provides a shorter length of hospitalisation, fewer complications and less time on critical care, all resulting in a faster recovery and improved patient experience (71, 72, 75, 82, 118, 123).

In an ageing population that present with more co-morbidities, one of the benefits of robotic surgery may be in increasing the rates of minimally invasive surgery. Looking to the future, lung cancer screening programmes may be rolled out in the UK, increasing the detection of early-stage lung cancers which are ideally suited to minimally invasive resection (12).

The advantages of robotic surgery were evident in our studies. Robotic LVRS resulted in a decrease in critical care stay post-operatively and a trend in shorter hospital stay compared to patients undergoing traditional VATS LVRS (Chapter 5). Minimally invasive mediastinal mass resection showed a reduction in hospital stay and critical care admissions compared to open surgery (Chapter 4). Patients undergoing robotic LVRS experienced less pain and had a significantly reduced morphine requirement in the first 24 hours after surgery compared with the VATS group. A similar trend in reduced morphine requirement after surgery was seen with robotic mediastinal mass resection.

Robotic surgery is less invasive than open and VATS approaches and appears at least as safe as VATS lobectomy (Chapter 2). The robotic lobectomy group had significantly fewer overall complications (25.0% v 17.2%, $p=0.0093$), significantly shorter median length of stay by one day (4 v 3 days, $p=0.0063$) and patients required significantly less critical care admissions post-operatively (85.5% v 19.0%, $p<0.0001$). This suggests that there may be potential benefit of robotic surgery.

When comparing retrospective data (Chapter 2), the two interventions occurred over different time periods. The VATS lobectomy group had operations between 2013-2018, in order to increase the numbers, and the robotic group over a more

recent period. It is therefore difficult to control for other changes in practice over time. There has been a move in thoracic surgery towards enhanced recovery programmes in thoracic over the last few years (263). This has led to shorter length of hospital stays. When comparing our retrospective VATS cohort (Chapter 2) to the prospective COLT pilot (Chapter 3), the median length of stay and critical care bed usage was less in the COLT pilot, which took place over a more recent time period. This suggests that there has been a change in practice over time. In the COLT pilot, both length of stay and critical care bed usage for robotic lobectomy are similar to that in the retrospective study.

Studies have suggested that robotic surgery is easier to learn compared to VATS and has a shorter learning curve (76, 78). A short learning curve was observed with robotic LVRS and after 6 cases operative time had fallen and plateaued at a time similar to that taken for VATS LVRS. Robotic surgery provides high-definition visualisation and wristed instruments and may be suitable for more complex cases which would usually be contraindicated for VATS. The introduction of robotic mediastinal surgery led to a significant increase in the number of patients receiving minimally invasive surgery for mediastinal mass resection. The benefits of minimally invasive surgery are described in Chapter 1 and include less post-operative pain and a faster recovery compared to open surgery. With this in mind, robotic surgery seems to be of patient benefit.

Post-operative pain following robotic surgery

There is no consensus on how best to measure post-operative pain. If all patients are given adequate analgesia, we would expect patient reported pain scores to be similar for all surgical approaches. We observed no difference in pain scores or the number of patients taking strong opioids post-operatively between open and VATS approaches for lobectomy. Pain was measured on a scale of 0-3, which may have been too crude and perhaps the visual analogue scale of 0-10, which has been seen to be more sensitive, should be used (264). It is not clear how big a difference would need to be observed in order to determine a meaningful difference between

surgical techniques. Furthermore, perhaps it is not enough to record the number of patients taking strong opioids and measurements of dose should be included in further studies.

There was a significant decrease in intravenous morphine use in the robotic LVRS group compared to the VATS group, suggesting patients had less pain. A similar trend was seen for robotic mediastinal surgery. However, we observed no difference between open and VATS lobectomy. This does not fit with the literature, which has shown VATS to be less painful than open surgery(73, 101). In addition, little is known regarding chronic pain following VATS and robotic surgery. Pain is an important outcome for patients and further studies need to be carefully designed to measure post-operative pain.

Cost effectiveness of robotic surgery

The main caveat to the adoption of robotic thoracic surgery is the high capital cost, instrument costs and maintenance fees. Studies which have shown robotic surgery to be cost effective, have found this was largely due the decrease in hospitalisation and favourable post-operative outcomes(114). Cost analysis was only undertaken in our robotic LVRS study (Chapter 5) and showed robotic LVRS to be at least as cost effective as VATS LVRS (£5421.63 vs £5695.46). This was largely due to a reduction in the length of stay and critical care admissions. In future studies, cost would be an important outcome to evaluate. As with other studies(133, 142), we saw a longer operative time with robotic surgery compared to VATS. However, as robotic surgery has only recently been introduced in thoracic centres, it is likely that set up time is longer and that surgeons are still early on in the learning curve. In our robotic LVRS study, we observed a fall in operative time over the 12 cases, at which point the robotic operative times were similar to those of VATS LVRS.

Study limitations

This report contains a mix of prospective and retrospective studies. These studies were non-randomised and unblinded, and therefore were predisposed to selection

bias. To measure the effect of this, we recorded pre-operative patient characteristics and determined if there was a statistically significant difference between the groups. Despite this, there are likely to be patient characteristics which we could not control for. A major limitation was the small case numbers which may have resulted in the possible type II errors seen in these studies. Similarly, if any difference exists between robotic and VATS lobectomy it is likely small and large numbers will be needed to show a statistically significant difference. Furthermore, small single centre studies are unable to yield reliable estimates and results are not generalisable. As the number of robotic lobectomy cases were low in the COLT pilot study and LVRS and mediastinal mass surgery are generally rare, future studies should be multicentre. At this centre, there was a limited number of surgeons performing robotic operations, and thus we were unable to control for differences in surgical expertise or assess the effect of learning curves. Results may not be a reliable reflection of the average level of technical proficiency in robotic surgery that is present nationally.

Our retrospective studies required few resources to conduct and could produce results quickly. However, these studies were limited by the data fields collected and we were unable to control for information bias. This was a major issue in the analysis of the data. Confounding variables such as trainee involvement, presence of incomplete fissures and surgeon expertise could not be controlled for. In addition, to increase our sample size study groups were selected from different time periods e.g. pre-robotic and robotic. Hospital protocols and clinical practice changes over time and this was a potential source of sampling bias. Endpoints such as post-operative destination and length of hospital stay were likely influenced by this.

The COLT pilot study was conducted prospectively, allowing for the design of a study protocol and pre-determined outcomes. This highlighted the weakness of our retrospective evidence and complication rates appeared to have been underreported when compared to our prospective data. Although participants were not randomised, the study had scarce exclusion criteria and was pragmatic in

nature which allowed for the assessment of current clinical practice. For example, rates of VATS lobectomy were much higher than previously thought and this should be considered when planning future studies.

6.3 Future work

Robotic mediastinal mass surgery

Current literature suggests that there is a benefit to robotic surgery for mediastinal mass resection (217, 221-223). Surgeons at Liverpool Heart and Chest Hospital have indicated that the robot is well suited to mediastinal surgery and suggest there is an advantage. Evidence for robotic mediastinal surgery is limited to small retrospective studies and there is little evidence regarding long-term clinical outcomes, oncological outcomes or cost effectiveness.

Mediastinal masses are a very heterogenous group and a randomised trial comparing robotic mediastinal surgery to VATS would be extremely difficult to design. A similar group of cases which were not included in the current study were patients undergoing resection for benign thymic hyperplasia. This is a more homogenous group of patients and a randomised control trial comparing VATS and open surgery with robotic resection may be possible in this group of patients.

Robotic lung volume reduction surgery

We have reported the first published series on robotic LVRS. Further evidence is now needed to determine if robotic LVRS provides a benefit, based on a number of parameters discussed in Chapter 5, over traditional VATS LVRS and is also cost-effective. The number of LVRS cases performed nationally every year is fairly small, however, this is a very homogenous group of patients which would lend itself to a randomised control trial.

Currently data is being collected in a registry as part of the UK Lung volume reduction study (ISRCTN16371361) on LVRS and bronchoscopic lung volume

reduction. This could be expanded to include robotic LVRS so data can be compared to VATS LVRS.

Robotic lobectomy

Currently there are no prospective randomised trials comparing robotic surgery for lung cancer resection to VATS or open surgery and the place of robotic surgery for lobectomy is unknown. There is, therefore, a need for well-designed and conducted trial to provide the evidence base for the uptake and delivery of this surgical approach. Currently, the proportion of robotic assisted lobectomies performed in the UK remains low, thus a randomised trial of robotic surgery would be difficult to undertake at present for the following reasons:

1. Full results of the VIOLET trial (VATS vs open lobectomy) are awaited (65), therefore the gold standard has still to be determined.

2. UK surgeons are still on the robotic surgery learning curve (defined as the first 50 cases in the VIOLET trial).

3. Most centres only have limited access to a robot thus randomisation would be difficult.

A large prospective cohort study would enable accurate and comprehensive data collection allowing comparison of open, VATS and RATS lobectomy. This data could then be used to design and power a randomised control trial, which is urgently needed to inform current NHS practice and health policy as well as individual surgeon and patient decision-making.

The COLT pilot included a high proportion VATS cases, suggesting that surgeons are taking on more complex cases by VATS and accepting that some may require conversion to open surgery. This is one of the reasons a large cohort study may have an advantage over a randomised trial. For example, a surgeon may decide not to randomise a patient who they think has a high risk of conversion to open in a randomised trial.

The disadvantages of a prospective cohort trial are that they require a large sample size and are costly. As the study would not be randomised or blinded, any selection bias would be difficult to control for. Open lobectomy is rare and thus an open comparison group would be potentially difficult. There are a large number of minimally invasive cases at Liverpool Heart and Chest Hospital thus there would be sufficient cases to compare robotic surgery to VATS.

Recommendations from the COLT pilot study

1. The pilot study was used to inform the design of the larger COLT trial (**C**ohort study comparing **o**utcomes for different **l**obectomy **t**echniques in units performing robotic thoracic surgery). This prospective cohort study aims to compare the outcomes and cost effectiveness of robotic lobectomy for early lung cancer resection to open surgery and VATS.

2. In preparation for the COLT trial, a study protocol, patient information leaflet, consent form, GP letter and a pilot study case report file were developed as part of this MPhil and will reviewed by the ethics board (see Appendix A-D).

3. The COLT prospective trial will also require an online database overseen by a clinical trials unit, as well as having dedicated research nurses and data manager(s) to ensure the quality of the trial dataset.

4. Recommendations from the COLT pilot study included incorporating details of planned frozen sections, as this may impact on the surgical approach. In addition, a visual analogue score should be used to measure pain.

5. Following the current COVID-19 pandemic, the dataset should include any previous COVID-19 infection and associated long-term sequalae, as the long-term impact on the respiratory system is not yet known.

6. The pilot study only looked at in-hospital outcomes and one of the recommendations for the full COLT trial would be look at morbidity and mortality rates over a 90 day follow up period as well as uptake to adjuvant treatment.

7. There was no assessment of quality of life or cost in the pilot study. As these are both important outcomes when considering the place for robotic surgery, the COLT trial should measure quality of life using validated questionnaires (see Appendix E) and a cost analysis should be conducted, which should include the direct cost of the operation, all in-hospital costs and the sum of standardised healthcare costs for all hospitalisation events in the 90 day follow up period.

COLT trial

The COLT (**c**ohort study comparing **o**utcomes for different **l**obectomy **t**echniques in units performing robotic thoracic surgery) trial, is a prospective study which aims to start recruiting in October 2021. It will compare outcomes for open, VATS and RATS techniques for lobectomy for early-stage lung cancer.

Its primary objective is to assess self-reported physical function (QLQ-C30) at 5 weeks post-surgery.

Its secondary outcomes are assessing the efficacy of the technique in terms of:

1. In-hospital outcomes: length of hospital stay, adverse health events to 3 months, in-hospital morbidity, proportion and time to uptake of adjuvant treatment and the proportion of patients who experience prolonged incision pain.

2. Oncological outcomes: overall survival to 1-year, proportion of patients who undergo complete resection during the procedure and the proportion of patients upstaged to pN2 disease after the procedure.

3. Cost effectiveness: resource use up to 3 months (measured for the duration of post-operative hospital stay until discharge, at 5 weeks and 3 months)

We hypothesise that robotic surgery will lead to less tissue trauma and therefore better recovery of several aspects of health-related quality of life in the early post-operative period than open surgery and similar to VATS, but that surrogate clinical outcomes of survival will be similar in all types of surgery.

Appendices

Appendix A - COLT Pilot Study: Case Report File

COLT Pilot Study– **C**ohort study comparing **O**utcomes for different **L**obectomy **T**echniques in units performing robotic thoracic surgery

CRF Folder Contents

Section 1	**Patient information** A1 - Patient details
Section 2	**Baseline information** B1- B4 - Baseline clinical details B5 - Baseline analgesia Baseline HrQol
Section 3	**Operative details** C1-C4
Section 4	**Post-op details** D1-3 - In Hospital complications D4-6 – In Hospital pain scores D7- Post-op analgesia D8- Analgesia on discharge D9- Discharge information D10 -11 – Pathology/ Histology
Section 5	**SAE forms** S0 – SAE master form S1-2 SAE initial report form S3- SAE follow up form

PATIENT DETAILS **A1**

PATIENT DETAILS

Patient's title: (*Please tick one*) Dr ☐ Miss ☐ Ms ☐ Mrs ☐ Mr ☐

Patient's name:_____ Patient's DOB: _ _ / _ _ / _ _ _ _

Patient's address: _____

_____

_____

_____

Patient's postcode: _____

Patient's NHS number: ☐☐☐☐☐☐☐☐☐☐

Patient's Sex: M ☐ F ☐

PATIENT CONTACT DETAILS

Patient's home phone number:

Patient's mobile phone number:

Patient's email address:

Can answer machine message's be left? Yes ☐ No ☐

Can the patient be contacted by *(please tick all appropriate)*:

Phone ☐ Post ☐ Text ☐

Would the patient like to receive a summary of the trial results? Yes ☐ No ☐

GP CONACT DETAILS

GP name:

GP practice and address: _____

_____

_____

_____

BASELINE CLINICAL DETAILS **B1**

BASELINE CLINICAL MEASURES (taken within 1 month prior to surgery)

DOB: _____

Sex: M ☐ F ☐

Ethnicity:

- ☐ White or Caucasian
- ☐ Mixed / Multiple ethnic groups
- ☐ Asian / Asian British
- ☐ Black / African / Caribbean / Black British
- ☐ Other ethnic group

Height: ☐☐☐ cm

Weight: ☐☐☐ . ☐ kg

ECOG Performance Status (0-5): ☐

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

(info for facing page)

Haemoglobin: ☐☐ . ☐ g/dl

White cell count: ☐☐ . ☐ x 10^9 / l

Platelet count: ☐☐☐ x 10^9 / l

Date bloods taken: _ _ / _ _ / _ _ _ _

PULMONARY FUNCTION

Was spirometry performed pre-op? ☐ Yes ☐ No

If YES, provide date: _ _ / _ _ / _ _ _ _

% predicted FEV1 ☐☐☐ . ☐

% predicted FVC ☐☐☐ . ☐

% predicted TLCO ☐☐☐ . ☐

SMOKING STATUS

Current smoking status:

- Never smoked
- Ex-smoker >3 months
- Ex-Smoker <3 months
- Current smoker

If patient has ***ever smoked please complete the following:***

The average number of cigarettes smoked **per day**

Age patient started smoking ☐☐☐

Age stopped (if applicable) ☐☐

MEDICAL HISTORY

Respiratory comorbidity[1] Yes ☐ No ☐

Neurological dysfunction[2] Yes ☐ No ☐

Diabetes mellitus Yes ☐ No ☐

Alcoholism[3] Yes ☐ No ☐

Any previous lung surgery Yes ☐ No ☐

If YES, specify date _ _ / _ _ / _ _ _ _

Type of surgery: _____

Side of previous surgery:

CVA / TIA s Yes ☐ No ☐

Cardiovascular comorbidity[4] Yes ☐ No ☐

Chronic pain syndrome[5] Yes ☐ No ☐

Deep Vein Thrombosis (DVT) Yes ☐ No ☐

Previously treated malignancy *(other than basal cell skin cancer)*

If YES, give date of diagnosis _ _ / _ _ / _ _ _ _

Specify malignancy: _____

Family history of lung cancer[6] Yes ☐ No ☐

Other medical conditions: _____

_____

[1] *Respiratory comorbidity: Any history of treated chronic obstructive pulmonary disease, asthma, interstitial lung disease or bronchiectasis.*
[2] *Neurological dysfunction: Any history of persistent disease of the central or peripheral nervous system diagnosed by a medical practitioner*
[3] *Alcoholism: As defined by daily consumption of >10 units for men or >5 units for women.*

[4] *CV comorbidity: Any history of treated angina, myocardial infarction, heart failure, heart valve disease, hypertension, pulmonary embolism, peripheral vascular disease.*
[5] *Chronic pain syndrome: As defined by pain experienced >6 months after the onset of the initial acute injury or illness.*
[6] *Family history of lung cancer: Any history of lung cancer in patient's children, siblings, parents, uncles, aunts or grandparents*

PRE-OPERATIVE IMAGING

What pre-operative imaging has been performed?

CT Yes ☐ No ☐

If YES, date performed: _ _ / _ _ / _ _ _ _

Stage: T (1-4) (-/a/b/c) N (0-3) M (0-1) (-/a/b/c)

PET-CT Yes ☐ No ☐

If YES, date performed: _ _ / _ _ / _ _ _ _

Stage: T (1-4) (-/a/b/c) N (0-3) M (0-1) (-/a/b/c)

CURRENT MALIGNANCY – LOCATION

Please specify the location of the ***primary tumour*** within the lung (*note: can have multiple selections)*

Left Upper Lobe ☐

Left Lower Lobe ☐

Right Upper Lobe ☐

Right Middle Lobe ☐

Right Lower Lobe ☐

IASLC 8th edition staging lung cancer

T: Primary tumour

- **Tx:** primary tumour cannot be assessed or tumour proven by the presence of malignant cells in sputum or bronchial washings but not visualised by imaging or bronchoscopy
- **T0:** no evidence of a primary tumour
- **Tis:** carcinoma in situ - tumour measuring 3 cm or less and has no invasive component at histopathology
- **T1:** tumour measuring 3 cm or less in greatest dimension surrounded by lung or visceral pleura without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e. not in the main bronchus)
  - **T1a(mi):** minimally invasive adenocarcinoma
    - tumour has an invasive component measuring 5 mm or less at histopathology
  - **T1a ss:** superficial spreading tumour in central airways (spreading tumour of any size but confined to the tracheal or bronchial wall)
  - **T1a:** tumour ≤1 cm in greatest dimension
  - **T1b:** tumour >1 cm but ≤2 cm in greatest dimension
  - **T1c:** tumour >2 cm but ≤3 cm in greatest dimension
- **T2:** tumour >3 cm but ≤5 cm or tumour with any of the following features:
  - involves the main bronchus regardless of distance from the carina but without the involvement of the carina
  - invades visceral pleura
  - associated with atelectasis or obstructive pneumonitis that extends to the hilar region
  - involving part or all of the lung
  - **T2a:** tumour >3 cm but ≤4 cm in greatest dimension
  - **T2b:** tumour >4 cm but ≤5 cm in greatest dimension
- **T3:** tumour >5 cm but ≤7 cm in greatest dimension or associated with separate tumour nodule(s) in the same lobe as the primary tumour or directly invades any of the following structures:
  - chest wall (including the parietal pleura and superior sulcus)
  - phrenic nerve
  - parietal pericardium
- **T4:** tumour >7 cm in greatest dimension or associated with separate tumour nodule(s) in a different ipsilateral lobe than that of the primary tumour or invades any of the following structures
  - diaphragm
  - mediastinum
  - heart
  - great vessels
  - trachea
  - recurrent laryngeal nerve
  - oesophagus
  - vertebral body
  - carina

N: regional lymph node involvement

- **Nx:** regional lymph nodes cannot be assessed
- **N0:** no regional lymph node metastasis
- **N1:** metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
- **N2:** metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- **N3:** metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M: Distant metastasis

- **M0:** no distant metastasis
- **M1:** distant metastasis present

- **M1a:** separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusions
- **M1b:** single extrathoracic metastasis, involving a single organ or a single distant (nonregional) node
  - a single extrathoracic metastasis has a better survival and different treatment choices, reason why it has now been staged separately
- **M1c:** multiple extrathoracic metastases in one or more organs

BASELINE CLINICAL DETAILS **B3**

CURRENT MALIGNANCY – HISTOLOGY

Has a biopsy of their lung cancer been attempted? Yes ☐ No ☐

Biopsy modality:

Bronchoscopy/ EBUS ☐ If YES, give date of biopsy: _ _ / _ _ / _ _ _ _

CT- guided ☐ If YES, give date of biopsy: _ _ / _ _ / _ _ _ _

Thoracotomy/VATS ☐ If YES, give date of biopsy: _ _ / _ _ / _ _ _ _

Was the biopsy conclusive?

Yes ☐ If yes→ complete outcome

No ☐ If no → biopsy inconclusive (not diagnostic) or biopsy failed (no cells obtained)

Outcome of biopsy:

SCLC ☐

Squamous cell carcinoma ☐ Adenocarcinoma ☐ Large cell carcinoma ☐

Carcinoid ☐

Other ☐ *If OTHER, please specify:* _____

DETAILS OF THE **PLANNED** RESECTION

Please indicate the lobe(s) of the lung that will be resected during the procedure: *(may have multiple selections)*

Left Upper Lobe ☐

Left Lower Lobe ☐

Right Upper Lobe ☐

Right Middle Lobe ☐

Right Lower Lobe ☐

PRE-OPERATIVE TREATMENT
Has the patient undergone any pre-operative treatment? Yes ☐ No ☐ If ***YES***, has the patient undergone: Radiotherapy Yes ☐ No ☐ *If **YES**, specify date finished:* _ _ / _ _ / _ _ _ _
Chemotherapy Yes ☐ No ☐ *If **YES**, specify date finished:* _ _ / _ _ / _ _ _ _

BASELINE ANALGESIA

CLASS OF ANALGESIA	Yes/No		PRN/REGULAR		EXAMPLES
Paracetamol	Yes	No	PRN	REGULAR	Paracetamol
NSAIDs	Yes	No	PRN	REGULAR	Ibuprofen, naproxen, diclofenac
Mild opioids	Yes	No	PRN	REGULAR	Codeine, cocodamol, dihydrocodeine, tramadol
Strong opioids	Yes	No	PRN	REGULAR	Morphine, oxycodone, fentanyl patch
Adjuvants	Yes	No	PRN	REGULAR	Gabapentin, pregabalin, lidocaine patch, amitriptyline, corticosteroids,

OPERATION DETAILS **C1**

BASIC OPERATION DETAILS

Operation date: _ _ / _ _ / _ _ _ _ Consultant initials: ☐☐☐

First operator classification: Consultant surgeon ☐ Trainee surgeon ☐

Operation start time (knife to skin): ☐☐ : ☐☐ (24 hr clock)

Finish time (dressings on) : ☐☐ ☐☐ (24 hr clock)

OPERATIVE STRATEGY

Was a frozen section biopsy ATTEMPTED? Yes ☐ No ☐

If YES, was malignancy confirmed? Yes ☐ No ☐

DRAIN LOCATIONS

Specify the number of drains inserted ☐

Were all drains located at the port/incision sites? Yes ☐ No ☐

OPERATION DETAILS

C2

INTRA-OPERATIVE ANALGESIA

Analgesia type	Given Yes	No
Single shot Paravertebral block	☐	☐
Epidural	☐	☐
Paravertebral catheter	☐	☐
Intercostal block	☐	☐

DETAILS OF RESECTION

Provide details of the type/extent of surgery:

	Yes	No				
Open & Close	☐	☐	If YES, skip remaining "C" forms			
Resection of airway without removal of lung parenchyma	☐	☐				
Pneumonectomy	☐	☐				
Lobectomy/Bilobectomy	☐	☐	If YES, specify lobe (s)	☐	& ☐	1= Right upper lobe 2= Right middle lobe 3=Right lower lobe 4= Left upper lobe 5=Left lower lobe
Segmentectomy	☐	☐	If YES, specify lobe (s)	☐	& ☐	
Wedge resection	☐	☐	If YES, specify lobe (s)	☐	& ☐	

Was any extended resection performed? Yes / No
(If yes please select → chest wall resection, sleeve , trachea, pericardium, diaphragm, other)

OPERATION DETAILS

C3

THORACOTOMY

Please provide details of the type of the thoracotomy performed: *(drop down options)*

	Yes	No		Yes	No
Anterior thoracotomy	☐	☐	Axillary thoracotomy	☐	☐
Posterolateral thoracotomy	☐	☐			
Was a muscle sparing technique used?	☐	☐			

If YES, specify:

Serratus muscle "spared" ☐ Latissimus muscle "spared" ☐

Specify number of staples used:

Bronchus ☐☐

Lung ☐☐

Vein ☐☐

Artery ☐☐

ROBOTIC

Number of arms used ___ 3 or 4 *(drop down option)*

Was a utility port used? Yes / No

Instruments used: *(drop down, may have multiple selection)* cadier forceps, maryland dissector, fenestrated bipolar, tip up, diathermy hook

Was the robotic stapler use? Yes/No
Number of staplers used:
Bronchus __
Lung __
Vein __
Artery __

Was the operation converted to: VATS / Open
→ If YES, please specify reason (bleed, adhesions, unable to identify anatomy, equipment failure, tumour/lymph nodes)

→ if either please complete relevant section in op details

VATS

Specify the number of ports / incisions used ☐ *1-4 options*

Was rib-spreading performed? Yes ☐ No ☐

Specify number of staples used

Bronchus ☐☐

Lung ☐☐

Vein ☐☐

Artery ☐☐

Was the operation converted to open? Yes / No
→ If YES, please specify reason (bleed, adhesions, unable to identify anatomy, equipment failure, tumour/lymph nodes)

→ if either please complete relevant section in op details

INTRA-OPERATIVE COMPLICATIONS

	Yes	No
Bronchus injury	☐	☐
Bleeding from vascular injury	☐	☐

Did the patient survive the operation? Yes ☐ No ☐

OPERATION DETAILS

LYMPH NODE MANAGEMENT

Identify locations from which lymph nodes sampled were taken:

LEFT		ZONE	RIGHT	
		Upper Mediastinal Zone		
#2	Yes ☐ No ☐	Upper Paratracheal	Yes ☐ No ☐	
#3a	Yes ☐ No ☐	Pre-vascular	Yes ☐ No ☐	
		Retrotracheal #3p Yes ☐ No ☐		
#4a	Yes ☐ No ☐	Lower paratracheal	Yes ☐ No ☐	
		Aorta-Pulmonary Zone		
		Sub-aortic #5 Yes ☐ No ☐		
		Para-aortic #6 Yes ☐ No ☐		
		Subcarinal Zone		
		Subcarinal #7 Yes ☐ No ☐		
		Lower Mediastinal Zone		
#8	Yes ☐ No ☐	Paraoesophageal	Yes ☐ No ☐	
#9	Yes ☐ No ☐	Pulmonary ligament nodes	Yes ☐ No ☐	
		Hilar / Interlobar Zone		
#10	Yes ☐ No ☐	Hilar	Yes ☐ No ☐	
#11	Yes ☐ No ☐	Interlobar	Yes ☐ No ☐	

POST OPERATIVE DETAILS **D1**

POST OPERATIVE CARE

Where was the patient admitted after surgery → ward / HDU / ICU

Date discharged from HDU/ICU:

Re-admission to ICU ? Yes / No
If yes→ total re-admission days on ICU ___

IN HOSPITAL COMPLICATIONS

PULMONARY COMPLICATIONS:	Yes	No		CTCAE Grade v5*	SAE** Yes	SAE** No
Acute respiratory failure	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Pulmonary collapse (requiring intervention- CPAP)	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Empyema[1]	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Surgical emphysema (requiring intervention)	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Bronchopleural fistula	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Post-drain pneumothorax requiring intervention[2]	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Chylothorax	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Acute Respiratory Distress Syndrome[3]	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Acute lung injury[4]	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Pulmonary embolus	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Insertion of a mini-tracheostomy tube	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Bronchoscopy	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
If YES, please specify reason _____						
Pleural effusion	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Prolonged air leak[5]	☐	☐	If yes give date drain removed _ _ / _ _ / _ _ _ _	☐	☐	☐

*CTCAE grade v5 – please report events according to CTCAE (v5) and provide details of **worst** grade patient experienced during in-hospital stay .. add classification score on opposite side

** The above events are all "expected" and therefore **do not** require an SAE form to be completed

[1] Defined as needing antibiotics or drainage

[2] Other post drain pneumothorax requiring intervention

[3] ARDS: Acute onset of respiratory failure, defined by bilateral infiltrates on chest radiograph, hypoxia defined by Pa02/ FiO2 ratio ≤200mmHg and no evidence of left atrial hypertension or pulmonary capillary pressure <18mmHg to rule out cardiogenic odema.

[4] Acute Lung Injury, defined as above but a 200 < Pa02/FiO2 ≤300mmHg

[5] Air leak persisting for > 5 days

CTCAE v5

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated. Grade 5 Death related to AE.

IN-HOSPITAL COMPLICATIONS

D2

CARDIAC COMPLICATIONS	Yes	No		CTCAE v5*	SAE** Yes	SAE** No
Myocardial infarction	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Arrhythmia (requiring treatment or lasting more than 24 hours)	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐

RENAL COMPLICATIONS	Yes	No		CTCAE v5 *	SAE** Yes	SAE** No
Acute Kidney Injury	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Haemofiltration	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐

Acute Kidney Injury is defined by a rise in serum creatinine >50% preoperative value to any rise above the reference range in previously normal values.

GASTRO-INTESTINAL COMPLICATIONS	Yes	No		CTCAE v5*	SAE** Yes	SAE** No
Peptic ulcer/ GI bleed/ perforation	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Pancreatitis	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Other GI complication	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐

If OTHER, please specify_____

INFECTIVE COMPLICATIONS				CTCAE v5*	SAE** Yes	SAE** No
Infection[1]	Yes ☐	No ☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐

If YES, specify site:
Pneumonia/ Chest infection[1] ☐ Wound infection[1] ☐

Other infection[1] ☐ If OTHER, please specify:_____

[1]Defined as needing antibiotic treatment for suspected infection

NEUROLOGICAL COMPLICATIONS	Yes	No		CTCAE v5*	SAE** Yes	SAE** No
Transient ischaemic attack (TIA)	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Stroke	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐
Acute psychosis	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐	☐

*CTCAE grade v5 – please report events according to CTCAE (v5) and provide details of **worst** grade patient experienced during in-hospital stay

** The above events are all "expected" and therefore **do not** require an SAE form to be completed.

IN-HOSPITAL COMPLICATIONS

D3

OTHER COMPLICATIONS	Yes	No		CTCAE v5 *	SAE**
				Yes	No
Wound dehiscence requiring treatment	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐ ☐
If YES, specify treatment:	Yes	No			
Suture/Staple	☐	☐	Other	Yes ☐	No ☐
Vacuum assisted closure	☐	☐	If OTHER, please specify _____		
Laryngeal nerve damage	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐ ☐
Deep vein thrombosis	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐ ☐
Haematoma	☐	☐	If yes give date recognised _ _ / _ _ / _ _ _	☐	☐ ☐

RE-OPERATION	Yes	No		CTCAE v5 *	SAE**
				Yes	No
Re-operation	☐	☐	If yes give date of operation _ _ / _ _ / _ _ _ _	☐	☐ ☐
If YES, please identify reason:					
Bleeding	☐	☐	Other	Yes ☐	No ☐
Prolonged air leak	☐	☐	If OTHER, please specify_____		

*CTCAE grade v5 – please report events according to CTCAE (v5) and provide details of **worst** grade patient experienced during in-hospital stay

** The above events are all "expected" and therefore **do not** require an SAE form to be completed.

UNEXPECTED COMPICATIONS
Any other events not listed on CRFs D1-3 are "unexpected" and **DO** require an SAE form to be completed, if they meet the SAE criteria.
Did the patient experience any OTHER events NOT listed on CRFs D1-3 that meet the SAE criteria[1]? Yes ☐ No ☐
If YES, complete SAE form (SAE S1-2) for each event
[1] SAE criteria: i) increased length of hospital stay, ii) life threatening, iii) persistent or significant disability, iv) caused death, v) Other serious (important medical event)

IN-HOSPITAL PAIN SCORES **D4**

Please complete pain scores daily from post-op till discharge on daily ward round

PAIN SCORE: DAY 1

TO COMPLETED BY STAFF ON BEHALF OF THE PATIENT ON DAY 1 POST-OP:

NB: DAY OF SURGERY= DAY 0

Was the patients pain score recorded at 1 day post-op? Yes ☐ No ☐ If NO, provide reason: ☐

1: Patient refused, 2:Patient unwell , 3:Patient upset, 4: Inconvenient, 5: Administrative failure, 6: Patient discharged, 7: Other

If YES, complete the following:

Date of assessment _ _ / _ _ / _ _ _ _ Time: ☐☐ : ☐☐ (24 hr clock)

Please ask the patient to choose a number that reflects their current pain, where 0= no pain and 10=worst pain possible:
(Please circle)

0	**1**	**2**	**3**
NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

PAIN SCORE: DAY 2

TO COMPLETED BY STAFF ON BEHALF OF THE PATIENT ON DAY 2 POST-OP:

NB: DAY OF SURGERY= DAY 0

Was the patients pain score recorded at 2 day post-op? Yes ☐ No ☐ If NO, provide reason: ☐

1: Patient refused, 2:Patient unwell , 3:Patient upset, 4: Inconvenient, 5: Administrative failure, 6: Patient discharged, 7: Other

If YES, complete the following:

Date of assessment _ _ / _ _ / _ _ _ _ Time: ☐☐ : ☐☐ (24 hr clock)

Please ask the patient to choose a number that reflects their current pain, where 0= no pain and 10=worst pain possible:
(Please circle)

0	**1**	**2**	**3**
NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

IN-HOSPITAL PAIN SCORES **D5**

Please complete pain scores daily from post-op till discharge

PAIN SCORE: DAY 3

TO COMPLETED BY STAFF ON BEHALF OF THE PATIENT ON DAY 3 POST-OP:

NB: DAY OF SURGERY= DAY 0

Was the patients pain score recorded at 3 day post-op? Yes ☐ No ☐ If NO, provide reason: ☐

1: Patient refused, 2:Patient unwell , 3:Patient upset, 4: Inconvenient, 5: Administrative failure, 6: Patient discharged, 7: Other

If YES, complete the following:

Date of assessment _ _ / _ _ / _ _ _ _ Time: ☐☐ : ☐☐ (24 hr clock)

Please ask the patient to choose a number that reflects their current pain, where 0= no pain and 10=worst pain possible:
(Please circle)

0	**1**	**2**	**3**
NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

PAIN SCORE: DAY 4

TO COMPLETED BY STAFF ON BEHALF OF THE PATIENT ON DAY 4 POST-OP:

NB: DAY OF SURGERY= DAY 0

Was the patients pain score recorded at day 4 post-op? Yes ☐ No ☐ If NO, provide reason: ☐

1: Patient refused, 2:Patient unwell , 3:Patient upset, 4: Inconvenient, 5: Administrative failure, 6: Patient discharged, 7: Other

If YES, complete the following:

Date of assessment _ _ / _ _ / _ _ _ _ Time: ☐☐ : ☐☐ (24 hr clock)

Please ask the patient to choose a number that reflects their current pain, where 0= no pain and 10=worst pain possible:
(Please circle)

0	**1**	**2**	**3**
NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

IN-HOSPITAL PAIN SCORES **D6**

Please complete pain scores daily from post-op till discharge

PAIN SCORE: DAY ___

TO COMPLETED BY STAFF ON BEHALF OF THE PATIENT ON DAY __ POST-OP:

NB: DAY OF SURGERY= DAY 0

Was the patients pain score recorded at day__ post-op? Yes ☐ No ☐ If NO, provide reason: ☐

1: Patient refused, 2:Patient unwell , 3:Patient upset, 4: Inconvenient, 5: Administrative failure, 6: Patient discharged, 7: Other

If YES, complete the following:

Date of assessment _ _ / _ _ / _ _ _ _ Time: ☐☐ : ☐☐ (24 hr clock)

Please ask the patient to choose a number that reflects their current pain, where 0= no pain and 10=worst pain possible:
(Please circle)

0	**1**	**2**	**3**
NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

PAIN SCORE: DAY ___

TO COMPLETED BY STAFF ON BEHALF OF THE PATIENT ON DAY __ POST-OP:

NB: DAY OF SURGERY= DAY 0

Was the patients pain score recorded at day__ post-op? Yes ☐ No ☐ If NO, provide reason: ☐

1: Patient refused, 2:Patient unwell , 3:Patient upset, 4: Inconvenient, 5: Administrative failure, 6: Patient discharged, 7: Other

If YES, complete the following:

Date of assessment _ _ / _ _ / _ _ _ _ Time: ☐☐ : ☐☐ (24 hr clock)

Please ask the patient to choose a number that reflects their current pain, where 0= no pain and 10=worst pain possible:
(Please circle)

0	**1**	**2**	**3**
NO PAIN	MILD PAIN	MODERATE PAIN	SEVERE PAIN

POST-OP TO DISCHARGE ANALGESIA **D7**

IN HOSPITAL (POST- OPERATIVE) ANALGESIA

CLASS OF ANALGESIA	Yes/No	PRN/REGULAR	EXAMPLES
Paracetamol	Yes No	PRN REGULAR	Paracetamol
NSAIDs	Yes No	PRN REGULAR	Ibuprofen, naproxen, diclofenac
Mild opioids	Yes No	PRN REGULAR	Codeine, cocodamol, dihydrocodeine, tramadol
Strong opioids	Yes No	PRN REGULAR	Morphine, oxycodone, fentanyl patch
Adjuvants	Yes No	PRN REGULAR	Gabapentin, pregabalin, lidocaine patch, amitriptyline, corticosteroids,
Patient controlled analgesia	Yes No		

ANALGESIA PRESCRIBED AT DISCHARGE **D8**

ANALGESIA PRESCRIBED AT DISCHARGE

CLASS OF ANALGESIA	Yes/No		PRN/REGULAR		EXAMPLES
Paracetamol	Yes	No	PRN	REGULAR	Paracetamol,
NSAIDs	Yes	No	PRN	REGULAR	Ibuprofen, naproxen, diclofenac
Mild opioids	Yes	No	PRN	REGULAR	Codeine, cocodamol, dihydrocodeine, tramadol
Strong opioids	Yes	No	PRN	REGULAR	Morphine, oxycodone, fentanyl patch
Adjuvants	Yes	No	PRN	REGULAR	Gabapentin, pregabalin, lidocaine patch, amitriptyline, corticosteroids,

DISCHARGE INFORMATION **D9**

:

DISCHARGE DETAILS
Date medically fit for discharge: _ _ / _ _ / _ _ _ _ (insert definition from protocol) Date of discharge: _ _ / _ _ / _ _ _ _
Were all drains removed prior to discharge? Yes ☐ No ☐ If no give date last drain removed: _ _ / _ _ / _ _ _ _
Discharge destination:
Home ☐ Nursing Home ☐ Residential home ☐ Patient died ☐ Other hospital ☐
Other ward in hospital ☐ Intermediate care ☐ Other ☐ *If **OTHER**, specify:* _____

D10

PATHOLOGY/HISTOLOGY

SAMPLE DETAILS

Has the primary tumour been taken for analyses? Yes ☐ No ☐

If NO, please specify the reason why: _____

If YES, has the primary tumour been Formalin Foxed & Paraffin Embedded (FFPE)? Yes ☐ No ☐

TUMOUR STAGE AND TYPE

Please classify the pTNM stage of the primary tumour by post-surgical/pathological findings:

T (1-4)	(-/a/b/c)	N (0-3)	M (0-1)	(-/a/b/c)
☐	☐	☐	☐	☐

No cancer/benign findings ☐

Specify the size of the primary tumour: ☐☐ . ☐ cm

Please identify the tumour type of the primary tumour:

SCLC ☐ Squamous cell carcinoma ☐ Adenocarcinoma ☐ Large cell carcinoma ☐

Carcinoid ☐ Other ☐ *If OTHER, please specify:* _____

RESECTION COMPLETENESS

Please provide details of the resection completeness below (tick one):

R0 (no residual tumour) ☐ R1 (microscopic residual tumour) ☐

R2 (macroscopic residual tumour) ☐

D11

PATHOLOGY/HISTOLOGY

+ve = positive lymph node -ve = negative lymph node NS= not sampled

LYMPH NODE INVOLVEMENT			
	LEFT	ZONE	RIGHT
		Upper Mediastinal Zone	
#2	+ve ☐ -ve ☐ NS	Upper Paratracheal	+ve ☐ -ve ☐ NS ☐
#3a	+ve ☐ -ve ☐ NS	Pre-vascular	+ve ☐ -ve ☐ NS ☐
		Retrotracheal #3p +ve ☐ -ve ☐ NS ☐	
#4a	+ve ☐ -ve ☐ NS	Lower paratracheal	+ve ☐ -ve ☐ NS ☐
		Aorta-Pulmonary Zone	
		Sub-aortic #5 +ve ☐ -ve ☐ NS ☐	
		Para-aortic #6 +ve ☐ -ve ☐ NS ☐	
		Subcarinal Zone	
		Subcarinal #7 +ve ☐ -ve ☐ NS ☐	
		Lower Mediastinal Zone	
#8	+ve ☐ -ve ☐ NS ☐	Paraoesophageal	+ve ☐ -ve ☐ NS ☐
#9	+ve ☐ -ve ☐ NS ☐	Pulmonary ligament nodes	+ve ☐ -ve ☐ NS ☐
		Hilar / Interlobar Zone	
#10	+ve ☐ -ve ☐ NS ☐	Hilar	+ve ☐ -ve ☐ NS ☐
#11	+ve ☐ -ve ☐ NS ☐	Interlobar	+ve ☐ -ve ☐ NS ☐
		Peripheral	
#12	+ve ☐ -ve ☐ NS ☐	Lobar	+ve ☐ -ve ☐ NS ☐
#13	+ve ☐ -ve ☐ NS ☐	Segmental	+ve ☐ -ve ☐ NS ☐
#14	+ve ☐ -ve ☐ NS ☐	Subsegmental	+ve ☐ -ve ☐ NS ☐

An SAE report should be completed for each event that fulfils the following criteria and that is not listed as expected in the CRFs D1-3.

i) increases length of hospital stay ii) causes hospitalisation iii) is life-threatening iv) results in persistant significant disability v) results in death

For each event that meets the above criteria, please complete a line in the table below. An initial report S1&2 should be completed for each event and follow up forms should be complete every five days until event is considered resolved or until patient has died.

Please ensure all SAE reports are identifies with the correct SAE reference, which is derived by the table below.

SAE ref	Brief description	Onset date	Date of intial report	Date of follow-up 1	Date of follow-up 2	Date of follow-up 3	Event resolved?
1							
2							
3							
4							
5							
6							
7							
8							

SAE INITIAL REPORT FORM **S1**

SAE ref: ____

SAE report page___ of ___

1. PARTICIPANT DETAILS

Patient initials : ☐☐ Male ☐ Female ☐ Date of Birth: _ _ / _ _ / _ _ _ _

2. SAE CLASSIFICATION

	Yes	No		Yes	No
Prolonged ongoing hospitalisation	☐	☐	Required in in patient hospitalisation	☐	☐
Resulted in persistent or significant disability/incapacity	☐	☐	Is/was life-threatening	☐	☐
Resulted in death	☐	☐	If YES, give date of death _ _ / _ _ / _ _ _ _		
Other serious (important medical event)	☐	☐	If YES, please specify: _____		

If the event RESULTED IN DEATH, was this due to disease progression? Yes ☐ No ☐

3. EVENT DETAILS

Full description of event (including body site, reported signs and symptoms and diagnosis where possible):

Specify the adverse event term and CTCAE grade:

Adverse Event Term:	CTCAE grade		CTCAE grade
e.g. Atrial fibrillation	4	3. _____	☐
1._____	☐	4. _____	☐
2._____	☐	5. _____	☐

4. DETAILS OF ONSET AND OUTCOME

Date of onset _ _ / _ _ / _ _ _ _ Time of onset ___ ___ : ___ ___ (24 hour)

Resolved no sequelae ☐ Resolved with sequelae ☐ Ongoing ☐ Died ☐

If RESOLVED, specify end date and time: date _ _ / _ _ / _ _ _ _ time ___ ___ : ___ ___ (24 hour)
If resolved with sequelae, ongoing or died, please give details:

SAE INITIAL REPORT FORM **S2**

SAE ref: ____

SAE report page___ of ___

5. DETAILS OF RESEARCH INTERVENTION
Date of intervention: _ _ / _ _ / _ _ _ _
6. ACTION TAKEN AND FURTHER INFORMATION
Please describe action taken: Provide any other relevant information e.g. medical history, test results:
7. WITHDRAWAL
Has the patient been withdrawn? Yes ☐ No ☐ If YES, please give date: _ _ / _ _ / _ _ _ _
8. RELATEDNESS
In the opinion of the PI or delegated dcotor was the event related to the study intervention? Not related ☐ Unlikely to be related ☐ Possibly related ☐ Probably related ☐ Definitely related ☐ Please provide justification:
9. DETAILS OF PRNCIPAL INVESIGATOR OR DELEGATED DOCTOR
The completed SAE form must be singed by the **PI or delagted doctor.** I confirm that the contents of this form (pages S1 and S2) are accurate and complete: Name_____ Signature_____ Date _ _ / _ _ / _ _ _ _
<u>FOR CTEU USE ONLY</u> Does the event reporting to REC? Yes ☐ No ☐ If NO, please give reason: _____ Does the Chief investigaror disagree with the assessment fo relatedness? Yes ☐ No ☐ If YES, please give reason:_____

SAE FOLLOW-UP FORM **S3**

SAE ref: ____

SAE report page___ of ___

1. PARTICIPANT DETAILS
Patient initials : ☐☐ Male ☐ Female ☐ Date of Birth: _ _ / _ _ / _ _ _ _
2. SAE DETAILS
Date of onset _ _ / _ _ / _ _ _ _ Time of onset ___ ___ : ___ ___ (24 hour)
3. EVENT DETAILS
Specify the maximum intensity o of event:
Adverse Event Term: e.g. Atrial fibrillation — CTCAE grade: 4
1._____ CTCAE grade: ☐
2._____ CTCAE grade: ☐
3. _____ CTCAE grade: ☐
4. _____ CTCAE grade: ☐
5. _____ CTCAE grade: ☐
Additional actions/further information since initial report:
4. DETAILS OF ONSET AND OUTCOME
Resolved no sequelae ☐ Resolved with sequelae ☐ Ongoing ☐ Died ☐
If RESOLVED, specify end date and time: date _ _ / _ _ / _ _ _ _ time ___ ___ : ___ ___ (24 hour)
If resolved with sequelae, ongoing or died, please give details:
If long term SAE that is possibly/probably/defintiely related to intervention and new follow up schedule has been agreed, give date of next follow up _ _ / _ _ / _ _ _ _
5. WITHDRAWAL
Has the patient been withdrawn? Yes ☐ No ☐ If YES, please give date: _ _ / _ _ / _ _ _ _
6. DETAILS OF PRNCIPAL INVESIGATOR OR DELEGATED DOCTOR
The completed SAE form must be singed by the **PI or delagted doctor.**
I confirm that the contents of this form (pages S1 and S2) are accurate and complete:
Name_____ Signature_____ Date _ _ / _ _ / _ _ _ _

Appendix B - COLT Trial: Patient Information Leaflet

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Patient Information Leaflet

COLT STUDY

Cohort study comparing Outcomes and cost effectiveness of different Lobectomy Techniques of lung cancer resections

You are being invited to take part in a research study. Before you can make a decision on whether to join our study, you need to understand why we are carrying out this research and what taking part would involve. Please take time to read through the information carefully and feel free to talk to your friends and/or family about it.

A member of our research team will be happy to go through the information leaflet with you and answer any questions you may have. If you would like more information or feel that anything is not clear then you can also contact a member of our research team (see contact details on page 1).

Take time to decide whether you wish to take part or not. Please remember that taking part is voluntary and, if you do choose to join us, you can withdraw at any time by letting a member of the research team know, you will not have to give a reason. There will be no effect on your future care or treatment from your doctors or this hospital if you decide not to take part.

What is the purpose of this study?

We are carrying out this research because we want to compare the different surgical techniques used to treat lung cancer. There are 3 different techniques currently used to perform a lobectomy (remove the part of the lung containing the tumour). These are open surgery and two types of key hole surgery: video assisted thoracoscopic surgery (VATS) and robotic assisted surgery.

Surgery can be associated with complications such as those related to the chest and the wound sites. There has been a large increase in key hole surgery in the UK, which aim to reduce these complications as well as make improvements to post-operative pain, length of hospital stay and quality of life. The use of robotic surgery has been shown to be cost effective and may provide better short term outcomes than open surgery. However, the number of robotic assisted lobectomies performed in the UK remains low. Surgical approach is driven by availability of a robot and surgeon preference rather than informed by evidence.

The aim of our study at Liverpool Heart and Chest Hospital is to compare patient outcomes and experiences associated with the types of surgery (VATS, robotic and open). In the future, this data would be used to design and power a larger multi-centre study or a randomised control trial.

Why have I been chosen?

You are being asked to take part in this study because you have been offered surgery to treat your diagnosed or suspected lung cancer. Our research team at Liverpool Heart and Chest Hospital would like to collect information on your outcomes and recovery following lobectomy and compare the different surgical techniques used.

What will I have to do?

If you decide to take part in our research study, you will meet with one of our research team and have the opportunity to ask any questions. You will also be asked to sign a consent form, stating that you agree to take part in the study. The type of surgery and other treatments you receive will be decided on by your surgeon using his/her own knowledge and experience. This study has no influence over the type of surgery or any other treatments you will have.

We will collect information about your lung cancer diagnosis and medical history prior to the operation and ask you to fill in quality of life questionnaires.

After your operation, your surgeon will record the type of surgery you had, your diagnosis and any complications you may have experienced. This information is already routinely collected by the hospital. From your hospital records, the research team will note your general health after surgery, post-operative pain scores, types of pain medication, length of hospital stay and any other associated treatments you receive.

You will be followed-up by the research team at 2 weeks, 5 weeks and 3 months. At these points, the team will check up on your recovery and will ask you to complete a quality of life questionnaire. These can be completed online or sent via post.

The 2- week follow-up will be via telephone. The 5-week follow-up has been scheduled to coincide with your routine post-operative follow-up appointment. If your follow-up is at a local hospital (i.e. not Liverpool Heart and Chest Hospital), study follow-up will be via telephone.

Follow-up at 3 months will be via a telephone call with a study research nurse, who will contact you at mutually agreed times.
We will access your medical records up to 5 years following your operation.

Do I have to take part?

Please remember that taking part in a research study is voluntary and your standard of care will not be affected if you decide not to take part. Additionally, if after joining the study you do not wish to continue, then you may withdraw at any time without giving a reason. At this point, we may ask your permission to keep the information we have already collected as it may be of use to our research.

How will my information be used and will my taking part in the study be kept confidential?

All information which is collected about you during this research study will be kept strictly confidential and will only be seen by our research team and authorised NHS staff involved in your care. We will need access to your hospital medical notes in order to record information about your health after the operation. All information collected will be stored securely.

With your permission, your data will be stored and shared with other medical databases for future cancer and surgical research. Your information will only be passed to researchers in a way that protects your identity.

What will happen to the results of the research study?

The results of the research will reported in medical journals and presented at meetings. The data will be anonymised and your identity will not be disclosed. If you wish we can send you a copy of the results for your own reading. Please let a member of the research team know.

Who is organising and funding the research?

This study is being organised by Liverpool Heart and Chest Hospital funded by Intuitive Surgical. The purpose of these grants is to support technology research in the field of surgical robotics, or related fields.

What if there is a problem?

If you have a problem you should speak to a member of the research team who will do their best to answer the question. Contact details can be found at the end of this information sheet.

If you have any concerns about the way you have been approached or treated as part of this study, the normal NHS complaints mechanisms are available to you. The Liverpool Heart and Chest Hospital Patient and Family Support Team can be contacted at any time point on 0151 600 1517.

Who do I contact if I have any questions?

Your doctors or a member of the research team will any questions you may have. If you have any questions during the study you may write or speak to:

Mr Michael Shackcloth

Liverpool Heart and Chest Hospital

Thomas Drive

Liverpool L14 3PE

Tel: 0151 600 1616

Sarah Feeney, Research Nurse

Liverpool Heart and Chest Hospital

Thomas Drive

Liverpool L14 3PE

Tel: 0151 600 1427

Appendix C - COLT Trial: Consent Form

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Informed Consent Form

COLT STUDY

Cohort study comparing Outcomes and cost effectiveness of different Lobectomy Techniques of lung cancer resections

Principal Investigator: Mike Shackcloth

Patient Identification Number:

Please ask the patient to complete the following:	*Initials*
1. I have read and understood the Patient Information Leaflet (dated 05/03/2020, version 1)	
2. I have had the opportunity to ask questions about the study and have received satisfactory answers to my questions.	
3. I understand that my participation is voluntary and that I may refuse to participate in this study. I understand that I am free to withdraw from the study at any time without giving a reason and that withdrawing will have no effect on my future care or treatment by my physicians or this hospital.	
4. I have read the information, and have received a copy of this form for my records. I have asked questions and have received satisfactory answers. I consent to participate in this study.	
5. I give permission for members of the research team to gather and store information about my lung cancer treatment from my medical records. I give permission for my questionnaire answers to be looked at by members of the research team and I understand that strict confidentiality will be maintained.	

6. I give permission for my data to be shared with other medical databases for future cancer and surgical research and understand that my information will only be passed to researchers in a way that protects my identity.	☐
7. I agree to being contacted at the intervals specified in the Patient Information Leaflet to complete the study questionnaires.	☐
THE FOLLOWING QUESTION IS OPTIONAL: YOU CAN STILL TAKE PART IN THE STUDY IF YOU DO NOT WISH TO DONATE TISSUE SAMPLES	
8. I agree to donate a sample of my tumour for this study and future approved studies into anti-cancer treatments? *Patient to tick Yes/No and Initial* Yes ☐ No ☐	☐

Name of patient	Signature	Date
Name of person taking consent	Signature	Date

1 copy for patient, 1 for research team (original); 1 to be kept with hospital notes

Appendix D - COLT Trial: GP Letter

Trust study number (local site):
REC No:

Liverpool Heart and Chest Hospital NHS
NHS Foundation Trust

Mr Michael Shackcloth
Liverpool Heart and Chest Hospital NHS Foundation Trust
Thomas Drive
Liverpool
L14 3PE

INFORMATION REGARDING INCLUSION OF YOUR PATIENT IN A CLINICAL STUDY

The COLT Study: A cohort study comparing outcomes and cost-effectiveness for different lobectomy techniques in units performing robotic thoracic surgery

Dear Dr.

Name **DoB**
NHS:
Address:

I am writing to inform you that the above patient has consented to take part in the COLT study. This study involves patients, referred by the MDT for lung resection for known or suspected lung cancer, allowing their data to be collected, answering quality of life questionnaires and donating samples of their resected cancer for future research.

By consenting to take part, your patient has agreed to information from their medical notes being made available for the purposes of the research.

They will also be asked to complete validated quality of life questionnaires at designated time points during the first year of their surgical follow up. These questionnaires will be administered by the study team at the patient's follow up hospital appointments, by telephone calls with the study research nurse or sent by post.

The tissue samples from their resected cancer will be stored at the Royal Liverpool University Hospital pathology department and used for future research.

This study is being organised by Liverpool Heart and Chest Hospital and the results of the research will be reported in medical journals and presented at meetings.

We very much hope you will be able to support the study. If you have any queries or concerns, please do not hesitate to contact me.

Yours sincerely,

Mr. Michael Shackcloth, Consultant Thoracic Surgeon

Appendix E - COLT Trial: Study Protocol

COLT STUDY

Prospective cohort study comparing outcomes and cost effectiveness of different techniques of lung cancer resections in units performing robotic thoracic surgery

Protocol version: 2

Dated: 2nd March 2020

NCT (Clinicaltrials.gov) Number:

Weblink

KEY CONTACTS

Chief Investigator Michael Shackcloth Consultant Thoracic Surgeon Liverpool Heart and Chest Hospital (LHCH) Thomas Drive, Liverpool, L14 3PE, UK	Tel: +44(0) 151 600 1398 Email: michael.shackcloth@lhch.nhs.uk
Trial Sponsor Liverpool Heart and Chest Hospital	Contact: Vicky Wilkinson Email: Vicky.Wilkinson@lhch.nhs.uk
Independent Special Advisor	TBC
Chair Data Monitoring and Safety Committee	TBC

TABLE OF CONTENTS

1 PROTOCOL SUMMARY

Full Title	Prospective cohort study comparing outcomes and cost effectiveness of different techniques of lung cancer resections in units performing robotic thoracic surgery.
Running Title	Does the technique used to perform a lung cancer resection effect Outcomes and Costs?
Acronym	***COLT***
Study Description	A prospective cohort study comparing outcomes and cost effectiveness of different techniques of lung cancer resections in units performing robotic thoracic surgery.
Study Design	Prospective cohort study
Patient Population	**Inclusion Criteria** Patients undergoing a lobectomy for known or suspected lung cancer at Liverpool Heart and Chest Hospital. Participants must be ≥16 years of age and Able to give written consent, . **Key Exclusion Criteria** *Screening phase exclusion criteria* • ≤ 16 years of age • Inability to provide informed consent • Residence outside the UK or other issues limiting the ability to secure clinical follow-up data to 90 days • Life expectancy under 1 year
Trial Objectives	The study will recruit patients undergoing lobectomy for lung cancer or for suspected lung cancer. The study will adopt a pragmatic design to determine 'real-world' differences in the different techniques utilised to perform a lobectomy. The study will have limited exclusion criteria to promote recruitment of a population that represents the clinical norm. The study outcome measures will examine patient reported quality of life, clinical events and costs.

Follow Up Schedule	Outcome measures will be assessed and reported for all patients up to 90 days after recruitment.
Primary Economic Outcome Measure	Resource utilisation as determined by health care costs at 90 days. Resource utilisation will be tracked from surgery and include the direct costs of the operation and all subsequent in-hospital costs. Subsequent costs will be reported as the sum of standardised healthcare costs for all hospitalisation events to 90 days All hospital admissions will be tracked using national hospital episode statistics; the cost of each episode will be derived from a cost model using standard UK tariffs. This analysis will compare the mean (or median) of the total hospital costs recorded for each patient during the 90 day follow-up period.
Primary Quality of Life Outcome Measure	Generic and disease-specific health related quality of life questionnaires will be used: EORTC QLQ-C30, QLQ-LC13 and EQ5D (measured at baseline, 2 weeks, 5 weeks and 3 months post surgery.

Secondary Outcome Measures	• Assessment of efficacy
	  • Time from surgery to hospital discharge
	  • Adverse health events to 3 months
	  • In-hospital morbidity
	  • Proportion and time to uptake of adjuvant treatment
	  • Proportion of patients who experience prolonged incision pain (defined as the need of analgesia > 5 weeks post-surgery)
	• Oncological outcomes
	  • Proportion of patients who undergo complete resection during the procedure
	  • Proportion of patients upstaged to pN2 disease after the procedure

Sample Size	400 - 500 patients (recruitment for 1 year)
Study Centre	The study will be conducted at LHCH

Timelines	First recruitment	March 2020
	End of recruitment	March 2021
	End of 90 day follow-up	June 2021
	HES data complete	September 2021
	Study results	November 2021

2 STUDY FLOW DIAGRAM

3 BACKGROUND AND RATIONALE FOR THE STUDY

Lung cancer is the leading cause of cancer death worldwide and the survival of patients with lung cancer in the UK is amongst the lowest in Europe [1]. In 2018 39205 patients were diagnosed with lung cancer in the UK [2]. The National Lung Cancer Audit (NLCA) reported that 18.4% of patients with non-small cell lung cancer underwent surgical resection as part of their treatment in England and Wales [2]. There has been a steady increase in the proportion of lobectomies performed by VATS [3]. The proportion performed robotically in the UK remain very low.

There is variation in surgical resection rates across the UK. It is noted in the NLCA report, adjusted surgical resection rates varying from 10% to 37%. 52 organisations failed to meet the audit standard of 17% [2]. Despite the Getting It Right First-Time report [4] recommending that patients with early stage lung cancer should be operated on by minimally invasive surgery, geographical disparity is wide between the type of techniques used. Some units achieve minimally invasive surgery rates of 84%, while the lowest unit rate was 10.4% [4]. The approach used for surgery for lung cancer is driven by surgeon preference rather than informed by evidence leading to patient benefit. The VIOLET trial will determine the role of VATS compared to open surgery, but the place of robotic thoracic surgery will remain unknown. With a possible easier adoption, robotic surgery may allow an increase in minimally invasive lung cancer surgery.

Mortality after lobectomy is 2% and common complications include bleeding, chest and wound infections, prolonged air leak and arrhythmia. The mortality rate for resections performed by minimally invasive surgery compares favourably with the open approach [3] and a recent literature review by Cao and colleagues, also reported lower perioperative morbidity, pneumonia, atrial arrhythmia and a shorter hospital stay in patients who underwent VATS lobectomy compared to open surgery [5].

Over the last two years there has been a surge in robotic surgery in thoracic surgical units in the UK. The robotic system enables surgeons to perform delicate and complex operations through a few very small incisions with magnification, high definition visualisation, precision, dexterity and control. This may lead to reduced surgical trauma to a patient's body when

utilising a robot compared to open and VATS techniques. Studies have shown that patients have a reduced length of stay overall, spend less time on critical care, have reduced complications and a faster recovery time. All of these culminating in a better patient experience.

Robotic lung resection has been shown to be cost effective when compared to thoracotomy [6,7]. This is largely due to a shorter hospital stay and lower complication rate. A study by Kent *et al* [8] uses a large national database in America (State Inpatient Database) comparing open lobectomy, VATS lobectomy and robotic lobectomy. In both the unmatched and matched analysis robotic lobectomy compares favourably with both VATS and open lobectomy [8].

However, the proportion of robotic assisted lobectomies performed in the UK remains low. There is therefore a need for well-designed and conducted trial to provide the evidence base for the uptake and delivery of this surgical approach.

A randomised trial of robotic surgery would be difficult at present for the following reasons

1. Results of the VIOLET trial (VATS vs open lobectomy) are awaited, therefore we do not know the gold standard to compare to.
2. Most UK surgeons are still on their learning curve (defined as the first 50 cases in the VIOLET trial)
3. Most centres only have limited access to a robot making randomisation difficult.

The above factors may however change over the next year.

A prospective cohort study would allow accurate and comprehensive data collection allowing comparison of open, VATS and robotic lobectomy. Data would be used to design and power a multi-centre cohort study or randomised control trial.

The aim of this study is to generate high quality evidence to compare a range of clinical and patient-reported outcomes between all types of lung cancer surgery (VATS, robotic and open). Date from this single centre pilot study will be used to design and power a larger multicentre trial. A well designed and conducted study comparing the effectiveness and cost-effectiveness of different techniques is urgently needed to inform current NHS practice, health policy and individual surgeon and patient decision-making.

3.1 **Potential Impact of the Study**

The results of the COLT study will give an overview of potential differences between methods of lobectomy in terms of outcomes and costs. Data would be used to design and power a multi-centre cohort study or randomised control trial.

4 **STUDY OBJECTIVES**

4.1 **Primary Objective**

The primary objective is to assess self-reported physical function (QLQ-C30) at 5 weeks post-surgery. Physical function has been chosen as the primary endpoint because it is a patient-centred outcome that will reflect the anticipated earlier recovery with robotic surgery and has been used in other minimal access surgery trials. The primary endpoint has been chosen to be five weeks (one month post-surgery) to capture the early benefits of minimal access surgery on recovery.

4.2 **Secondary Objectives**

The secondary objectives are to assess the efficacy of the technique in terms of time from surgery to hospital discharge, adverse health events to 3 months, In-hospital morbidity, proportion and time to uptake of adjuvant treatment and generic and disease-specific quality of life to 3-months (measured at 2 week, 5 weeks and 3 months, post surgery)

Oncological outcomes will be assessed by looking at overall survival to 1-year, proportion of patients who undergo complete resection during the procedure and the proportion of patients upstaged to pN2 disease after the procedure.

The cost effectiveness of different surgical techniques will be investigated by looking at resource use to 3 months (measured for the duration of post-operative hospital stay until discharge, at 5 weeks and 3 months.

4.3 **Hypothesis**

We hypothesise that robotic surgery will lead to less tissue trauma and therefore better recovery of several aspects of health-related quality of life in the early post-operative period

than open surgery and similar to VATS, but that surrogate clinical outcomes of survival will be similar in all types of surgery.

5 STUDY DESIGN:

5.1 Brief Description of Study Design

This is a prospective single centre cohort study.

The study will adopt a pragmatic design with limited exclusion criteria to promote recruitment of a population that represents the clinical norm. The study outcome measures will examine resource utilisation, patient reported quality of life and clinical events.

5.2 Patient Consent

Patients will be required to provide written informed consent prior to surgery. Patient information sheets, consent forms (and any subsequent amendments) will be approved by NRES and local hospital process prior to implementation.

The process of consent requires individual discussion with the patient. Information will be provided in a language and at a level of complexity understandable to the subject in both oral and written form.

Patients will not be coerced, persuaded, or unduly influenced to participate or remain in the trial. Patients will understand that they are free to withdraw from the trial at any point and that this decision will not affect the nature of care they will receive. The original signed consent form will be stored in the patient's trial file and a copy will be kept in the patient's medical case notes. An additional copy will be given to the patient.

5.3 Patient Population

All patients undergoing a potentially curative resection for proven or suspected lung cancer resection at Liverpool Heart and Chest Hospital will be invited to take part. A screening log will be kept and compared to NLCA data to confirm accuracy. The consent form will be two parts; the first to allow use of the patients' data, the second to ask the patient to fill in the quality of life questionnaires.

Participants must be ≥16 years of age and able to give written consent,

5.4 Surgical technique

5.4.1 Lobectomy via Open surgery

Conventional open surgery is undertaken through a single incision +/- rib resection and with rib spreading. The operation is performed under direct vision with isolation of the hilar structures (vein, artery and bronchus) which are dissected, ligated and divided in sequence and the lobe of lung resected. The procedures may be undertaken using ligatures, over sewing or with staplers. Lymph node management is undertaken in accordance with the International Association of the Study of Lung Cancer (IASLC) recommendations where a minimal of 6 nodes / stations are removed, of which 3 are from the mediastinum that includes the subcarinal station. The thoracotomy is closed in layers starting from pericostal sutures over the ribs, muscle, fat and skin layers.

5.4.2 Lobectomy via Video Assisted Thoracoscopic Surgery (VATS)

VATS lobectomy is undertaken through one to four keyhole incisions **without** rib spreading. The use of 'rib spreading' is prohibited as this is the key intra-operative manoeuvre which disrupts tissues and causes pain (and is used in open surgery). The procedure is performed with videoscopic visualisation without direct vision. The hilar structures are dissected, stapled and divided. Endoscopic ligation of pulmonary arterial branches may be performed. The fissure is completed and the lobe of lung resected. Lymph node management is the same as described for open surgery. The incisions are closed in layers and may involve muscle, fat and skin layers. This definition of VATS lobectomy is a modification of CALGB 39802 definition.

5.4.3 Lobectomy via Robotic Surgery

Robotic lobectomy is performed using the di Vinci X platform. Four ports for the robot arms and a utility port are made. The hilar structures are dissected, stapled and divided. Endoscopic ligation of pulmonary arterial branches may be performed. The fissure is completed, and the lobe of lung resected. Lymph node management is the same as described for open surgery. Robotic staplers will be used where possible.

5.5 **Post-operative care**

As this is a pragmatic study post-operative care will be what is routinely practiced at Liverpool Heart and Chest Hospital. The criteria for chest drain management and removal at Liverpool Heart and Chest Hospital is similar for all surgical techniques.

5.6 **Analgesia**

Due to the pragmatic nature of this study standardising the use of analgesia is impractical and, if implementable, would produce data unrepresentative of real clinical practice. Accurate details of pain scores and the analgesia used throughout the patients in-hospital stay will be recorded on the trial CRFs.

The degree of post-operative pain experienced by patients undergoing RATS, VATS or open surgery is an important consideration when comparing different surgical techniques. Patients will be asked to verbally report their pain on a visual analogue scale (VAS) at baseline (pre-operatively) and on daily post-operatively.

5.7 **Assessment of discharge suitability**

In order to objectively compare the time from surgery to hospital discharge (a secondary outcome measure) between the different surgical techniques, the following discharge suitability criteria have been developed. Patients will be evaluated against the following criteria to ensure that they are **medically fit-for-discharge**:

1. Patient has achieved satisfactory mobility with,
2. Pain under control with analgesia
3. Satisfactory serum haemoglobin and electrolytes (i.e. does not require intervention)
4. Satisfactory chest-x-ray (which will be performed as part of routine clinical care)
5. No complications that require further / additional treatment

Patients who are considered **medically fit-for-discharge** may not necessarily be discharged immediately; in some instances, social and other factors may necessitate extended

hospitalisation. The time at which patients are considered medically fit-for-discharge and when they are physically discharged from hospital will both be recorded on the trial CRFs.

5.8 Assessment of patient reported study outcomes

Baseline quality of life questionnaires will be performed. Patients will be followed-up at 2 weeks, 5 weeks, and 3 months. At these time-points details of adverse events experienced, resource use, uptake of adjuvant chemotherapy and disease recurrence will be collected.

The 2- week follow-up will be via telephone. The 5-week follow-up has been scheduled to coincide with the patient's routine post-operative follow-up appointment and may or may not be conducted at the hospital where the patient had their surgery. If a patient is to be followed-up at a peripheral hospital (i.e. not the centre where they underwent their surgery), study follow-up will be via telephone. Conversely, patients who attend the hospital at which they had their procedure, will see a member of the local research team. In both cases, follow-up should be conducted by a member of the research team blinded to the patient's treatment allocation.

Follow-up at 3 months will be via a telephone call with a study research nurse, who will contact the patient at mutually agreed times.

6 OUTCOME MEASURES

6.1 Primary Economic Outcome Measure

The primary economic outcome measure will be a comparison of health care costs, observed over the 3-month follow-up period. The case record form will be designed to capture key elements of resource utilisation during the index operation and up to hospital discharge. Subsequent costs for each patient will then be calculated for hospitalisation events, reported by the UK Hospital Episode Statistics. A standardised UK cost model will be

applied for reported diagnostic and procedural codes. No attempt will be made to capture or determine the costs associated with primary care or other healthcare.

The primary analysis will describe the range of observed total costs and compare the mean total costs incurred in the three groups (or median, depending on the distribution of observations).

For the primary analyses we will not report societal costs (reflecting the actual sums paid by UK health-care purchasers over the duration of trial recruitment) or attempt to quantify other indirect costs - for example lost productivity, early retirement, social support costs etc. For academic purposes, this approach would be limited, reflecting more dynamic costing systems, subject to frequent change. Like many national purchasing models, UK health care tariffs involve an element of 'bundling' and simplification that would compromise the accuracy of presented results and limit application to other international systems. We will also not perform any medium or long term model projection of future costs, and will restrict the analysis to 'real' data reflecting true expenditure on all trial subjects in the first ninety days after surgery.

The case report form will be designed to capture key resource utilisation in hospital

We will also capture details of all subsequent hospitalisation events (involving at least one night in hospital). We will use Diagnostic Related Group and Procedure Codes from routine UK Hospital Episode Statistic data – which is readily available, cheap to collect and analyse and has good accuracy.

6.2 **Primary Quality of Life Outcome Measure**

This analysis will compare the mean (or median), patient reported quality of life scores using generic and disease-specific HRQoL measures will assess the profiles of Robotic, VATS and open lobectomy in the early and mid-postoperative phases. The extensively validated EQ-5D will assess generic aspects of health (http://www.euroqol.org/home.html),and will be used in the analysis of QALYs. The EORTC QLQ-C30 is one of the most widely used instruments for assessing HRQoL in patients with cancer. The questionnaire contains 30-items with five function scales (physical, role, cognition, emotional and social), nine symptom scales (fatigue, pain, nausea/vomiting, dyspnoea, insomnia, loss of appetite, constipation, diarrhoea, and financial problems), and a global health status/QoL scale.

The QLQ-LC13 is the lung cancer module with 13 items that assesses lung cancer–specific symptoms such as cough, haemoptysis, severity of shortness of breath, chest/ body pain, and chemotherapy/ radiotherapy side effects such as sore mouth, dysphagia, peripheral

neuropathy and hair loss. A higher scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, and a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale represents a high level of symptoms and problems.

Participants who agree to take part in the study will be asked to complete HRQoL questionnaires at baseline and post-operatively at 2 weeks (+/- 5days), 5 weeks (+/- 10 days) and 3 months (+/- 14 days) post-surgery.

Patients who die during the follow-up period will be allocated a score of zero.

6.3 Secondary Outcomes: Assessment of Efficacy

- Time from surgery to hospital discharge
- Adverse health events to 90 days
- In-hospital morbidity.
- Proportion and time to uptake of adjuvant treatment
- Proportion of patients who experience prolonged incision pain (defined as the need of analgesia > 5 weeks post-surgery)
- Generic and disease-specific HRQoL: EORTC QLQ-C30, QLQ-LC13 and EQ5D to 90 days (measured at baseline, 2 weeks, 5 weeks, and 3 months post surgery)

6.4 Secondary Outcome: Oncological outcome

- Proportion of patients who undergo complete resection during the procedure
- Proportion of patients upstaged to pN2 disease after the procedure

6.5 Expected Adverse Events

Data on adverse events will be collected from the time of consent until 90 days post surgery. As lung resection via open surgery, VATS or RATS is a significant surgical intervention, some adverse events are considered as ‘expected’. Adverse events experienced from the time of surgery until discharge from hospital (after surgery), and which are considered as expected, are listed below.

Procedural complications:
Pulmonary:
• Acute respiratory failure
• Atelectasis/ Pulmonary collapse
• Pneumonia / Chest Infection (defined by the administration of antibiotics)
• Empyema (defined as the requirement for antibiotics or drainage)
• Surgical emphysema (requiring intervention)
Bronchopleural fistula
• Prolonged Air leak (≥ 7 days)
• Post-drain pneumothorax requiring intervention
• Chylothorax
• ARDS (acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO2/FiO2 ratio ≤200 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic oedema).
• Acute Lung Injury (ALI), defined as above but by a 200 < PaO2/FiO2 ≤300 mmHg)
• Pleural effusion
Cardiovascular:
• Serious arrhythmia (defined by the requirement of intervention)
• Myocardial infarction (defined by elevated Troponin)
• Bleeding
• Blood clots
• Haematoma

Thromboembolic complications:
• Deep vein thrombosis
• Pulmonary embolus
• Venous thromboembolism (VTE)

GI complications, including:
• Peptic ulcer/GI bleed/perforation
• Pancreatitis (amylase >1500iu)
• Other (e.g. laparotomy, obstruction)

Renal complications:
• New haemofiltration/dialysis
• Acute Kidney injury (rise in serum creatinine >50% preoperative value to any rise above the reference range in previously normal values)

Infective complications:
• Sepsis (defined as antibiotic treatment for suspected infection)
• Wound infection
• Respiratory infection
• Other infection

Neurological complications:
• Transient ischaemic attack
• Stroke
• Acute psychosis

Other
• Re-operation (due to any reason, including bleeding, or other cause)
• Excess bleeding, (whether or not it requires reoperation)
• Wound dehiscence requiring treatment
• Insertion of a mini-tracheostomy tube
• Conversion from RATS or VATS to open surgery, for any reason
• Conversion of RATS to VATS for any reason
• Open & close thoracotomy in the event of inoperable lung cancer or extensive malignancy
• Laryngeal nerve damage
• Bronchoscopy for any cause

In hospital death due to any cause is considered a serious untoward event

Adverse events experienced from post-operative discharge until the end of study involvement (after the 90 days follow-up), and considered as expected, are listed below.

Disease specific complications:
• Disease recurrent; includes local, regional and distant recurrence
• New primary and secondary cancers
• Death due to disease progression (fatal event –Serious Adverse Event)

Procedural complications:
Pulmonary:
• Atelectasis/ Pulmonary collapse
• Pneumonia / Chest Infection (defined by the administration of antibiotics)
• Empyema (defined as the requirement for antibiotics or drainage)
• Bronchopleural fistula
• Pleural Effusion
• Prolonged air leak (defined as ≥ 7 days) or other post-drain pneumothorax requiring intervention
• Chylothorax
• ARDS (acute onset of respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia as defined by a PaO2/FiO2 ratio ≤200 mmHg, and no evidence of left atrial hypertension or a pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic oedema).
• Acute Lung Injury (ALI), defined as above but by a 200 < PaO2/FiO2 ≤300 mmHg)

Thromboembolic complications:
• Deep vein thrombosis
• Venous thromboembolism (VTE)
• Pulmonary embolus

Renal complications:
• New haemofiltration/dialysis

Infective complications:
epsis (defined as antibiotic treatment for suspected infection)
• Wound infection
• Respiratory infection
• Other infection

Neurological complications:
• Transient ischaemic attack
• Stroke

Cardiovascular:
• Bleeding
• Haematoma

Other:
• Re-operation for any reason (other than recurrence or progression)
• Wound dehiscence requiring treatment
• Bronchoscopy for any cause

It is also anticipated that a significant proportion of the patient population will go on to have adjuvant (post-operative) chemotherapy or radiotherapy after their resection. Such treatments are commonly associated with serious side effects and toxicities. To this end, a list of adverse events that are considered 'expected' for patients undergoing chemotherapy and radiotherapy are listed below.

Blood & lymphatic complications
- Anaemia
- Thrombocytopenia
- Neutropenia (Febrile Neutropenia)
- Myelosuppression

Gastrointestinal complications
- Nausea
- Vomiting
- Diarrhoea
- Constipation

Abnormal laboratory results
- Leukopenia
- Elevated AST / ALTs
- Elevated alkaline phosphatase

Nervous system complications
- Peripheral sensory neuropathy
- Peripheral motor neuropathy
- Headaches
- Insomnia

Immune system complications
- Anaphylaxis / Hypersensitivity reaction

Muscular complications
- Arthralgia
- Myalgia

Infective complications:
- Sepsis (defined as antibiotic treatment for suspected infection)
- Wound infection
- Respiratory infection
- Other infection

7 STATISTICAL CONSIDERATIONS

7.1 Primary Quality of Life Outcome Measure

Patient reported outcomes scores (HRQoL) and will be compared using a mixed regression model, adjusted for baseline measures where appropriate. Changes in treatment effect with time will be assessed by adding a treatment x time interaction to the model and comparing models using a likelihood ratio test. Deaths will be accounted for by modelling HRQoL and survival jointly. Model fit will be assessed and alternative models and / or transformations (e.g. to induce normality) will be explored where appropriate.

Reasons for non-completion of any assessment will be recorded and coded. Missing items or errors on questionnaire measures will be dealt with according to the scoring manuals or via imputation methods. Compliance rates will be reported in results, including the numbers of

patients who have withdrawn from the study, have been lost to follow up or died. Causes of death for trial participants will be recorded.

7.2 **Cost Outcome Measure**

The cost and quality of life data for each surgical technique and the difference between the techniques will be reported. The average cost and outcome on a per patient basis to produce incremental cost-effectiveness ratios for the three techniques, producing an incremental cost per QALY will be reported.

7.3 **Major Adverse Clinical Events**

Frequencies of adverse events will be described. Treatment differences will be reported with 95% confidence intervals.

7.4 **Sample Size**

We propose a sample size of 400-500 patients (1 year activity).

7.5 **Intention to Treat Analysis**

Patient data will be reported and analysed in the three groups on an intention to treat basis.

7.6 **Descriptive Statistics**

Descriptive statistics will be presented in terms of the numbers and proportions of patients or, for continuous variables, means or medians, range of observations, standard deviations.

7.7 **Comparative Statistics**

Tests of significance will be two sided. For the primary economic and QoL outcomes we will compare the means (or medians) of the scores recorded for the two randomised groups at 12

months. The absolute magnitude of the difference in adverse event rates will be presented, with 95% confidence limits.

7.8 Full Analysis Plan

A detailed analysis plan will be produced before the database is locked and before the performance of any study-related analyses (except for tasks performed by the independent statistician in support of the Data Monitoring and Safety Committee).

7.9 Data Monitoring and Safety

7.9.1 Interim Safety Analysis

A Data Monitoring and Safety Committee (DMSC) will be established under the chairmanship of an expert in trial conduct and reporting. This group will be tasked to create a plan for interim safety analysis. It is likely that one oanalyses will be appropriate in a study of this size and anticipated duration. After any safety review the DMSC will provide a report to the principal investigators with recommendations about the wisdom of study continuation.

The DMSC will be afforded access to all aspects of the trial management structure, clinical data and administrative documentation and will be asked to perform regular reviews of the progress and conduct of the venture.

8 TRIAL-RELATED ADVERSE EVENTS

Prospective monitoring of trial-related adverse events will start at date of procedure and continue for 90 days. The potential for trial-related adverse events will relate mainly to the surgery.

Subsequent clinical and adverse events will reflect the natural history and routine clinical management of the procedure and underlying disease.

8.1 Definitions of Adverse Events

8.1.1 Adverse Event (AE)

Any untoward medical occurrence

8.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity; consists of a congenital anomaly or birth defect; or
- is otherwise considered medically significant by the investigator.

8.2 Expected Serious Adverse Events/Clinical Outcomes

Some serious adverse events occurring in this trial will be expected as a consequence of the underlying disease and operation. Trial-related adverse events will be reviewed as described at paragraph 6.5. The results of the review will advise the sponsor about the 'expectedness' of adverse events. Case report forms will be designed to capture key clinical outcomes and adverse events during the trial period..

8.3 Trial-related SAE Reporting

Suspected Unexpected Serious Adverse Reactions/Events (SUSARs) along with all trial-related serious adverse events will be reported to the Research and Innovation manager at LHCH within 24 hours of becoming aware of the event. Upon receipt, these will be reviewed by the chief investigator and the trial unit staff for an immediate assessment of expectedness and causality. Events will be reported to the Research Ethics Committee (REC) within 7 days

for fatal or life-threatening SUSARs and within 15 days for SUSARs that are not fatal or life-threatening.

A summary of safety issues will be included in the annual progress report to the ethics committee.

9 TRIAL OBSERVATIONS AND FOLLOW UP

9.1 Case Report Forms (CRF)

A bespoke, web-based case report form (eCRF data guide) will be developed to capture the study specific data. Paper back-up copies will also be provided in case there is no immediate computer access in real time. Data will be entered by local trial personnel. Computer records will be held on a secure server and will be protected by password access. Checks for data consistency and validity will be performed at the point of data entry.

9.2 Follow-up Schedule

All patients will be followed up till 90 days

9.3 Time Windows for Follow up Contact

Follow-up contact should be completed within the following time windows from the date of the procedure

- 2 weeks follow-up ± 5 days from the date of the procedure
- 5 weeks follow-up ± 10 days from the date of the procedure
- 90 days follow-up ±14 days from the date of the procedure

9.4 Potential Threats to the Internal and External Validity of the Study

Internal threats to the potential validity of the study is that not all surgeons will perform all procedures. Some surgeons perform only open procedures, some VATS and open, some all three techniques. There may be a difference in outcomes between surgeons which manifests as a difference in a technique. Another possible threat is the number of procedures performed by one technique may change over the cause of the study.

An External threat to the validity of the study is whether Liverpool Heart and Chest Hospital has similar outcomes to other hospital. National lung cancer audit data suggests overall

outcomes are similar to other units in England and Wales. It does not however compare outcomes for each individual technique.

10 REGULATORY AND ETHICAL CONSIDERATIONS

10.1 Regulatory and Local Law /Guidelines Requirements

This trial will be conducted according to the principles of the ICH-GCP Good Clinical Practice, the Declaration of Helsinki (http://www.wma.net/) and NHS Research Governance Framework.

10.2 Institutional and Ethical Review and Approval

The Study Protocol, patient information sheet (PIS) and consent form will be approved by the National Research Ethics Service (NRES) before commencing the trial. Any amendments to this protocol, the PIS and / or consent form will require approval from the Steering Committee, NRES, HRA and local research governance prior to implementation.

10.3 Participation in Other Studies

Patients enrolled in COLT may also be enrolled in other observational or interventional studies so long as participation in each study does not compromise the conduct of the other. The guidance of the CI and CTU should be sought prior to enrolment.

11 STUDY ORGANISATION AND COMMITTEES

11.1 Sponsor

The Sponsor's role is clearly set out in the NHS Research Governance documents. The Research and Development Department at the ICE CAP Clinical Trials Unit of the Liverpool Heart and Chest Hospital NHS Foundation Trust will be responsible for ensuring the study is conducted to the standards set out in the NHS Research Governance Framework.

11.2 Trial Management Centre

The trial management will be conducted by the ICE CAP Clinical Trials Unit of the Liverpool Heart and Chest Hospital. The trials unit will be responsible for overall management of the trial including the following: protocol review, ethical submissions, development of the specification

for the data collection system, data management, meeting arrangements, quality assurance and preparation of trial documentation.

11.3 **Trial Steering Committee**

The conduct of the study will be overseen by a trial steering committee (TSC).. The TSC will delegate authority for operational or other pressing decisions to a smaller executive group.

11.4 **Data Monitoring and Safety Committee**

The role of the DMSC is described at section 7.10

11.5 **Monitoring Plan**

The proposed plan for trial monitoring is as follows:

- Weekly for the first 4 weeks then monthly audit of data completeness, internal consistency and quality

12 **INSURANCE AND INDEMNITY**

If the patient is harmed by taking part in this research project there are no specific indemnity or compensation arrangements. If a patient is harmed, due to someone's negligence, then the patient may have grounds for legal action, but they may have to pay for this. Regardless of this, if they wish to complain about any aspects of the way they have been treated or approached during the research project, the standard National Health Service complaint system will be available to them.

13 **DATA RECORDS AND ARCHIVING**

The Investigators will maintain the confidentiality of all study documentation and take measures to prevent accidental or premature destruction of these documents. We will retain study documents for at least 15 years after the results from the study have been reported.

13.1 **Data Protection**

The patients' personal data and Investigators' personal data, which may be included in the Sponsor and/or its representatives' database, shall be treated in compliance with all applicable laws and regulations; when archiving or processing personal data pertaining to the

Investigators and/or patients, the Sponsor or its representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

14 **END OF TRIAL**

14.1 **Planned Termination**

The trial will end when all patients have completed the observation period i.e. when the last patient recruited has completed the 90 day follow-up.

14.2 **Publication Policy**

The results of the trial will be submitted for publication in a peer review journal irrespective of the outcome. The study group will have sole responsibility for the content and approval of all manuscripts arising from the study prior to submission for publication.

15 ANNEX A: PROTOCOL AMENDMENT CHANGE LOG

Amendment Date	22nd April 2016	Version Pre	6	Version Post	7	Section / Para No	Pg 8 & 20
Original Text							
New Text							
Exclusion Criteria added: Pregnant women excluded							

Amendment Date		Version Pre		Version Post		Section / Para No	
Original Text							
New Text							

Amendment Date		Version Pre		Version Post		Section / Para No	
Original Text							
New Text							

16 REFERENCES

1. De Angelis, R., et al., Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE-5-a population-based study. Lancet Oncology, 2014. 15(1): p. 23-34.

2. National Lung Cancer Audit. Report for the audited period 2018: Care Quality Improvement Department, Royal College of Physicians (https://www.rcplondon.ac.uk/projects/outputs/nlca-annual-report-2018)

3. The Society for Cardiothoracic Surgery in Great Britain & Ireland. Third National Thoracic Surgery Activity & Outcomes Report (https://scts.org/wp-content/uploads/2019/06/Third-thoracic-blue-book-FINAL.pdf).

4. Get it right first time: Cardiothoracic Surgery GIRFT programme national speciality report 2018 (https://gettingitrightfirsttime.co.uk/wp-content/uploads/2018/04/GIRFT-Cardiothoracic-Report-1.pdf).

5. Cao, C., et al., A meta-analysis of unmatched and matched patients comparing video-assisted thoracoscopic lobectomy and conventional open lobectomy. Annals of cardiothoracic surgery, 2012. 1(1): p. 16-23.

6. Park BJ. Cost concerns for robotic thoracic surgery. Annals of Cardiothoracic Surgery; Vol 1, No 1 (May 2012): Minimally Invasive Pulmonary Resection 2012.

7. Park BJ, Flores RM. Cost Comparison of Robotic, Video-assisted Thoracic Surgery and Thoracotomy Approaches to Pulmonary Lobectomy. Thoracic Surgery Clinics18(3):297-300.

8. Kent M, Wang T, Whyte R, Curran T, Flores R, Gangadharan S. Open, Video-Assisted Thoracic Surgery, and Robotic Lobectomy: Review of a National Database. The Annals of Thoracic Surgery 2014 Jan;97(1):236-44.

9. Gray A, C.P., Wolstenholme J and Wordsworth S, Applied Methods of Cost-effectiveness Analysis in Healthcare. 2011, Oxford: Oxford University Press.

10. National Institute for Health and Care Excellence. Guides to the methods of technology appraisal 2013. http://www.nice.org.uk/article/PMG9/chapter/Foreword.

11. Dolan, P., Modeling valuations for EuroQol health states. Medical Care, 1997. 35(11): p. 1095-1108.

Bibliography

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86.
2. Cancer Research UK. Lung Cancer Incidence Statistics: Cancer Research UK; 2020 [cited 2020 8 March]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/incidence#heading-Zero.
3. Cancer Research UK. Lung cancer risk: Cancer Research UK; 2018 [cited 2020 26 May]. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung-cancer/risk-factors#ref1.
4. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, Rosso S, Coebergh JWW, Comber H, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. European Journal of Cancer. 2013;49(6):1374-403.
5. Arnold M, Rutherford MJ, Bardot A, Ferlay J, Andersson TM, Myklebust T, et al. Progress in cancer survival, mortality, and incidence in seven high-income countries 1995-2014 (ICBP SURVMARK-2): a population-based study. Lancet Oncol. 2019;20(11):1493-505.
6. Royal College of Physicians. National Lung Cancer Audit annual report 2016 (for audit period 2015). London: Healthcare Quality Improvement Partnership; 2017.
7. Office for National Statistics. Cancer diagnoses and age-standardised incidence rates for all types of cancer by age, sex and region including breast, prostate, lung and colorectal cancer. 2019 [Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017#the-three-most-common-cancers-vary-by-sex-and-age-group.
8. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol. 2016;11(1):39-51.
9. Royal College of Physicians. National Lung Cancer Audit annual report (for audit period 2018). 2020.
10. Office for National Statistics, Public Health England. Cancer survival in England: national estimates for patients followed up to 2017: Office for National Statistics; 2019 [cited 2020 8 March]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinengland/nationalestimatesforpatientsfollowedupto2017#acknowledgements.
11. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-13.
12. Veronesi G, Baldwin DR, Henschke CI, Ghislandi S, Iavicoli S, Oudkerk M, et al. Recommendations for Implementing Lung Cancer Screening with Low-Dose Computed Tomography in Europe. Cancers (Basel). 2020;12(6):1672.
13. Schag CA, Ganz PA, Wing DS, Sim MS, Lee JJ. Quality of life in adult survivors of lung, colon and prostate cancer. Quality Of Life Research: An International Journal Of Quality Of Life Aspects Of Treatment, Care And Rehabilitation. 1994;3(2):127-41.
14. Ko CY, Maggard M, Livingston EH. Evaluating health utility in patients with melanoma, breast cancer, colon cancer, and lung cancer: a nationwide, population-based assessment. J Surg Res. 2003;114(1):1-5.

15. Brown KF, Rumgay H, Dunlop C, Ryan M, Quartly F, Cox A, et al. The fraction of cancer attributable to modifiable risk factors in England, Wales, Scotland, Northern Ireland, and the United Kingdom in 2015. Br J Cancer. 2018;118(8):1130-41.
16. Doll R, Peto R, Boreham J, Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. BMJ. 2004;328(7455):1519.
17. Wao H, Mhaskar R, Kumar A, Miladinovic B, Djulbegovic B. Survival of patients with non-small cell lung cancer without treatment: a systematic review and meta-analysis. Systematic Reviews. 2013;2:10.
18. National Institute for Health and Care Excellence. Lung cancer:diagnosis and management: National Institute for Health and Care Excellence; 2019 [cited 2020 9 March]. Available from: https://www.nice.org.uk/guidance/ng122/chapter/Recommendations#treatment.
19. Royal College of Physicians. National Lung Cancer Audit, Annual report 2018 (for the audit period 2017). 2019.
20. Richens D. Cardiothoracic Surgery: GIRFT Programme National Specialty Report. Getting It Right First Time; 2018.
21. Royal College of Physicians, Society for Cardiothoracic Society in Great Britain and Ireland. National Lung Cancer Audit, Lung cancer clinical outcomes publication 2019 (for the 2017 audit period). London: Healthcare Quality Improvement Partnership; 2020.
22. Walcott-Sapp S, Sukumar M. The History of Pulmonary Lobectomy: Two Phases of Innovation: CTSNet; 2016 [cited 2020 9 March]. Available from: https://www.ctsnet.org/article/history-pulmonary-lobectomy-two-phases-innovation.
23. Abbas AE. Surgical Management of Lung Cancer: History, Evolution, and Modern Advances. Curr Oncol Rep. 2018;20(12):98.
24. Grismer JT, Read RC. Evolution of pulmonary resection techniques and review of the bronchus-first method. Ann Thorac Surg. 1995;60(4):1133-7.
25. Gale JW, Waters RM. Closed Endobronchial Anesthesia in Thoracic Surgery. Anesthesia & Analgesia. 1932;11(6):283-8.
26. ROBERTSHAW FL. Low resistance double-lumen endobronchial tubes. Br J Anaesth. 1962;34:576-9.
27. Pezzella AT, Adebonojo SA, Hooker SG, Mabogunje OA, Conlan AA. Complications of general thoracic surgery. Current problems in surgery. 2000;37(11):733-858.
28. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 412-8.
29. Faber LP. Individual ligation technique for lower lobe lobectomy. The Annals of Thoracic Surgery. 1990;49(6):1016-8.
30. Shimkin MB, Connelly RR, Marcus SC, Cutler SJ. Pneumonectomy and lobectomy in bronchogenic carcinoma. A comparison of end results of the Overholt and Ochsner clinics. The Journal of Thoracic and Cardiovascular Surgery,. 1962;44(4):503-19.
31. 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(Suppl 3).
32. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. The Annals Of Thoracic Surgery. 1995;60(3):615-22.
33. 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;40(3):271-4.
34. Altorki NK, Wang X, Wigle D, Gu L, Darling G, Ashrafi AS, et al. Perioperative mortality and morbidity after sublobar versus lobar resection for early-stage non-small-cell

lung cancer: post-hoc analysis of an international, randomised, phase 3 trial (CALGB/Alliance 140503). Lancet Respir Med. 2018;6(12):915-24.
35. Loddenkemper R, Mathur PN, Lee P, Noppen M. History and clinical use of thoracoscopy/pleuroscopy in respiratory medicine. Breathe. 2011;8(2):144-55.
36. Rogers ML, Duffy JP. Surgical aspects of chronic post-thoracotomy pain. European Journal of Cardio-Thoracic Surgery. 2000;18(6):711-6.
37. Silhoe ADL. The Evolution of VATS Lobectomy: IntechOpen; 2012 [cited 2020 30 August]. Available from: https://www.intechopen.com/books/topics-in-thoracic-surgery/the-evolution-of-vats-lobectomy.
38. Richards JMJ, Dunning J, Oparka J, Carnochan FM, Walker WS. Video-assisted thoracoscopic lobectomy: The Edinburgh posterior approach. Annals of Cardiothoracic Surgery. 2012;1(1):61-9.
39. McKenna Jr RJ, Benfield JR, Connolly JE, Cannon W. Lobectomy by video-assisted thoracic surgery with mediastinal node sampling for lung cancer. Journal of Thoracic and Cardiovascular Surgery. 1994;107(3):879-82.
40. McKenna Jr RJ, Wolf RK, Brenner M, Fischel RJ, Wurnig P. Is lobectomy by video-assisted thoracic surgery an adequate cancer operation? Annals of Thoracic Surgery. 1998;66(6):1903-7.
41. Yim APC, Ho JKS, Ko KM, Chau WS, Ma CC, Kyaw K. Video-assisted thoracoscopic anatomic lung resections: The initial Hong Kong experience. Chest. 1996;109(1):13-7.
42. Kirby TJ, Mack MJ, Landreneau RJ, Rice TW. Lobectomy-video-assisted thoracic surgery versus muscle-sparing thoracotomy: A randomized trial. The Journal of Thoracic and Cardiovascular Surgery. 1995;109(5):997-1002.
43. Shigemura N, Akashi A, Funaki S, Nakagiri T, Inoue M, Sawabata N, et al. Long-term outcomes after a variety of video-assisted thoracoscopic lobectomy approaches for clinical stage IA lung cancer: A multi-institutional study. Journal of Thoracic & Cardiovascular Surgery. 2006;132(3):507-12.
44. Swanson SJ, Herndon Ii JE, D'Amico TA, Demmy TL, McKenna Jr RJ, Green MR, et al. Video-assisted thoracic surgery lobectomy: Report of CALGB 39802 - A prospective, multi-institution feasibility study. Journal of Clinical Oncology. 2007;25(31):4993-7.
45. Society for Cardiothoracic Surgery in Great Britain & Ireland. Third National Thoracic Surgery Activity & Outcomes Report. Dendrite Clinical Systems Ltd; 2018.
46. Marino MV, Shabat G, Gulotta G, Komorowski AL. From Illusion to Reality: A Brief History of Robotic Surgery. Surgical Innovation. 2018;25(3):291-6.
47. Zirafa CC, Romano G, Key HT, Davini F, Melfi F. The evolution of robotic thoracic surgery. Annals of Cardiothoracic Surgery,. 2019;8(2):210-7.
48. Ashrafian H, Darzi A, Clancy O, Grover V. The evolution of robotic surgery: Surgical and anaesthetic aspects. British Journal of Anaesthesia. 2017;119:i72-i84.
49. Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, et al. Minimally Invasive versus Abdominal Radical Hysterectomy for Cervical Cancer. N Engl J Med. 2018;379(20):1895-904.
50. Jayne D, Pigazzi A, Marshall H, Croft J, Corrigan N, Copeland J, et al. Effect of Robotic-Assisted vs Conventional Laparoscopic Surgery on Risk of Conversion to Open Laparotomy Among Patients Undergoing Resection for Rectal Cancer: The ROLARR Randomized Clinical Trial. JAMA. 2017;318(16):1569-80.
51. Park DA, Lee MJ, Kim SH, Lee SH. Comparative safety and effectiveness of transoral robotic surgery versus open surgery for oropharyngeal cancer: A systematic review and meta-analysis. Eur J Surg Oncol. 2020;46(4 Pt A):644-9.
52. Coughlin GD, Yaxley JW, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic

prostatectomy: 24-month outcomes from a randomised controlled study. Lancet Oncol. 2018;19(8):1051-60.
53. Stolzenburg JU, Holze S, Neuhaus P, Kyriazis I, Do HM, Dietel A, et al. Robotic-assisted Versus Laparoscopic Surgery: Outcomes from the First Multicentre, Randomised, Patient-blinded Controlled Trial in Radical Prostatectomy (LAP-01). Eur Urol. 2021;79(6):750-9.
54. Parekh DJ, Reis IM, Castle EP, Gonzalgo ML, Woods ME, Svatek RS, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018;391(10139):2525-36.
55. Nyberg M, Hugosson J, Wiklund P, Sjoberg D, Wilderäng U, Carlsson SV, et al. Functional and Oncologic Outcomes Between Open and Robotic Radical Prostatectomy at 24-month Follow-up in the Swedish LAPPRO Trial. Eur Urol Oncol. 2018;1(5):353-60.
56. Wang Y, Gieschen H, Greenberger M, Yu X, Tian G, VanderWalde N, et al. Survival After Robotic-Assisted Prostatectomy for Localized Prostate Cancer: An Epidemiologic Study. Ann Surg. 2019.
57. Barocas DA, Salem S, Kordan Y, Herrell SD, Chang SS, Clark PE, et al. Robotic assisted laparoscopic prostatectomy versus radical retropubic prostatectomy for clinically localized prostate cancer: comparison of short-term biochemical recurrence-free survival. J Urol. 2010;183(3):990-6.
58. Mirkin KA, Kulaylat AS, Hollenbeak CS, Messaris E. Robotic versus laparoscopic colectomy for stage I-III colon cancer: oncologic and long-term survival outcomes. Surg Endosc. 2018;32(6):2894-901.
59. Sun Z, Kim J, Adam MA, Nussbaum DP, Speicher PJ, Mantyh CR, et al. Minimally Invasive Versus Open Low Anterior Resection: Equivalent Survival in a National Analysis of 14,033 Patients With Rectal Cancer. Ann Surg. 2016;263(6):1152-8.
60. The British Association of Urological Surgeons. Radical Prostatectomy Outcomes Data: Summary & Timescale of the Data: The British Association of Urological Surgeons Limited; 2021 [cited 2021 09 July]. Available from: https://www.baus.org.uk/patients/surgical_outcomes/radical_prostatectomy/timescales.aspx.
61. Barkun JS, Aronson JK, Feldman LS, Maddern GJ, Strasberg SM, Altman DG, et al. Evaluation and stages of surgical innovations. Lancet. 2009;374(9695):1089-96.
62. Yaxley JW, Coughlin GD, Chambers SK, Occhipinti S, Samaratunga H, Zajdlewicz L, et al. Robot-assisted laparoscopic prostatectomy versus open radical retropubic prostatectomy: early outcomes from a randomised controlled phase 3 study. Lancet. 2016;388(10049):1057-66.
63. McCulloch P, Altman DG, Campbell WB, Flum DR, Glasziou P, Marshall JC, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009;374(9695):1105-12.
64. National Institute for Health and Care Excellence. Colorectal cancer: NICE; 2020 [cited 2021 09 August]. Available from: https://www.nice.org.uk/guidance/ng151/chapter/Recommendations#management-of-local-disease.
65. Lim E, Batchelor T, Shackcloth M, Dunning J, McGonigle N, Brush T, et al. Study protocol for VIdeo assisted thoracoscopic lobectomy versus conventional Open LobEcTomy for lung cancer, a UK multicentre randomised controlled trial with an internal pilot (the VIOLET study). BMJ Open. 2019;9(10):e029507.
66. Lim E, Darlison L, Edwards J, Elliott D, Fennell DA, Popat S, et al. Mesothelioma and Radical Surgery 2 (MARS 2): protocol for a multicentre randomised trial comparing

(extended) pleurectomy decortication versus no (extended) pleurectomy decortication for patients with malignant pleural mesothelioma. BMJ Open. 2020;10(9):e038892.
67. Nyberg M, Sjoberg DD, Carlsson SV, Wilderäng U, Carlsson S, Stranne J, et al. Surgeon heterogeneity significantly affects functional and oncological outcomes after radical prostatectomy in the Swedish LAPPRO trial. BJU Int. 2021;127(3):361-8.
68. Corrigan N, Marshall H, Croft J, Copeland J, Jayne D, Brown J. Exploring and adjusting for potential learning effects in ROLARR: a randomised controlled trial comparing robotic-assisted vs. standard laparoscopic surgery for rectal cancer resection. Trials. 2018;19(1):339.
69. Nelson H, Sargent DJ, Wieand HS, Fleshman J, Anvari M, Stryker SJ, et al. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004;350(20):2050-9.
70. Porpiglia F, Morra I, Lucci Chiarissi M, Manfredi M, Mele F, Grande S, et al. Randomised controlled trial comparing laparoscopic and robot-assisted radical prostatectomy. Eur Urol. 2013;63(4):606-14.
71. Rajaram R, Mohanty S, Bentrem DJ, Pavey ES, Odell DD, Bharat A, et al. Nationwide Assessment of Robotic Lobectomy for Non-Small Cell Lung Cancer. The Annals of Thoracic Surgery. 2017;103(4):1092-100.
72. Oh DS, Reddy RM, Gorrepati ML, Mehendale S, Reed MF. Robotic-Assisted, Video-Assisted Thoracoscopic and Open Lobectomy: Propensity-Matched Analysis of Recent Premier Data. The Annals of Thoracic Surgery. 2017;104(5):1733-40.
73. Ng CSH, Macdonald JK, Gilbert S, Khan AZ, Kim YT, Louie BE, et al. Optimal Approach to Lobectomy for Non-Small Cell Lung Cancer: Systemic Review and Meta-Analysis. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery. 2019;14(2):90-116.
74. Farivar AS, Cerfolio RJ, Vallières E, Knight AW, Bryant A, Lingala V, et al. Comparing Robotic Lung Resection With Thoracotomy and Video-Assisted Thoracoscopic Surgery Cases Entered Into The Society of Thoracic Surgeons Database. Innovations. 2014;9(1):10-5.
75. Cerfolio RJ, Bryant AS, Skylizard L, Minnich DJ. Initial consecutive experience of completely portal robotic pulmonary resection with 4 arms. The Journal of Thoracic and Cardiovascular Surgery. 2011;142(4):740-6.
76. Fahim C, Hanna W, Waddell T, Shargall Y, Yasufuku K. Robotic-assisted thoracoscopic surgery for lung resection: the first Canadian series. Can J Surg. 2017;60(4):260-5.
77. Veronesi G, Agoglia BG, Bertolotti R, Borri A, Gasparri R, Spaggiari L, et al. Experience with robotic lobectomy for lung cancer. Innovations: Technology and Techniques in Cardiothoracic and Vascular Surgery. 2011;6(6):355-60.
78. Arnold BN, Thomas DC, Bhatnagar V, Blasberg JD, Boffa DJ, Detterbeck FC, et al. Defining the learning curve in robot-assisted thoracoscopic lobectomy. Surgery (United States). 2019;165(2):450-4.
79. McKenna RJ. Complications and learning curves for video-assisted thoracic surgery lobectomy. Thorac Surg Clin. 2008;18(3):275-80.
80. Louie BE, Wilson JL, Kim S, Cerfolio RJ, Park BJ, Farivar AS, et al. Comparison of Video-Assisted Thoracoscopic Surgery and Robotic Approaches for Clinical Stage I and Stage II Non-Small Cell Lung Cancer Using The Society of Thoracic Surgeons Database. Ann Thorac Surg. 2016;102(3):917-24.
81. Swanson SJ, Miller DL, McKenna RJ, Howington J, Marshall MB, Yoo AC, et al. Comparing robot-assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: results from a multihospital database (Premier). J Thorac Cardiovasc Surg. 2014;147(3):929-37.

82. Kent M, Wang T, Whyte R, Curran T, Flores R, Gangadharan S. Open, video-assisted thoracic surgery, and robotic lobectomy: review of a national database. Ann Thorac Surg. 2014;97(1):236-42; discussion 42-4.
83. Kneuertz PJ, D'Souza DM, Richardson M, Moffatt-Bruce SD, Merritt RE, Abdel-Rasoul M. Long-Term Oncologic Outcomes After Robotic Lobectomy for Early-stage Non–Small-cell Lung Cancer Versus Video-assisted Thoracoscopic and Open Thoracotomy Approach. Clinical Lung Cancer. 2020;21(3):214-24.e2.
84. Yang H-X, Woo KM, Sima CS, Bains MS, Adusumilli PS, Huang J, et al. Long-term Survival Based on the Surgical Approach to Lobectomy For Clinical Stage I Nonsmall Cell Lung Cancer: Comparison of Robotic, Video-assisted Thoracic Surgery, and Thoracotomy Lobectomy. Annals of surgery. 2017;265(2):431-7.
85. Lim E, Batchelor T, Dunning J, Shackcloth M, Anikin V, Naidu B. PL02.06 In Hospital Clinical Efficacy, Safety and Oncologic Outcomes from VIOLET: A UK Multi-Centre RCT of VATS Versus Open Lobectomy for Lung Cancer. Journal of Thoracic Oncology. 2019;14(10).
86. Mathisen DJ, Morse CR. Thoracic surgery- Lung resections, Bronchoplasty. Master techniques in surgery. 1st ed. ed: Lippincott Williams & Wilkins; 2014. p. 95-100.
87. National Institute for Health and Care Excellence. Lung and pleural cancers - recognition and referral. Scenario: Referral for suspected lung or pleural cancer: NICE; 2016 [cited 2020 10 March]. Available from: https://cks.nice.org.uk/lung-and-pleural-cancers-recognition-and-referral#!scenario.
88. Falcoz PE, Conti M, Brouchet L, Chocron S, Puyraveau M, Mercier M, et al. The Thoracic Surgery Scoring System (Thoracoscore): Risk model for in-hospital death in 15,183 patients requiring thoracic surgery. The Journal of Thoracic and Cardiovascular Surgery. 2007;133(2):325-32.
89. Brunelli A, Salati M, Rocco G, Varela G, Van Raemdonck D, Decaluwe H, et al. European risk models for morbidity (EuroLung1) and mortality (EuroLung2) to predict outcome following anatomic lung resections: an analysis from the European Society of Thoracic Surgeons database. 2017. p. 490-7.
90. Fleisher LA, Beckman JA, Brown KA, Calkins H, Chaikof E, Fleischmann KE, et al. ACC/AHA 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Circulation. 2007;116(17):1971-96.
91. British Thoracic Society, Society of Cardiothoracic Surgeons of Great Britain, Ireland Working Party. Guidelines on the selection of patients with lung cancer for surgery. Thorax. 2001;56(2):89-108.
92. Beckles MA, Spiro SG, Colice GL, Rudd RM. The Physiologic Evaluation of Patients With Lung Cancer Being Considered for Resectional Surgery. CHEST. 2003;123:105S.
93. Scott WJ, Allen MS, Decker PA, Darling G, Meyers B, Putnam JB, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: A secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial. Journal of Thoracic and Cardiovascular Surgery. 2010;139(4):976-83.
94. Licht PB, Jørgensen OD, Ladegaard L, Jakobsen E. A National Study of Nodal Upstaging After Thoracoscopic Versus Open Lobectomy for Clinical Stage I Lung Cancer. The Annals of Thoracic Surgery. 2013;96(3):943-50.
95. Whitson BA, Groth SS, Maddaus MA, Duval SJ, Swanson SJ. Surgery for Early-Stage Non-Small Cell Lung Cancer: A Systematic Review of the Video-Assisted Thoracoscopic Surgery Versus Thoracotomy Approaches to Lobectomy. Annals of Thoracic Surgery. 2008;86(6):2008-18.

96. Long H, Tan Q, Luo Q, Wang Z, Jiang G, Situ D, et al. Thoracoscopic Surgery Versus Thoracotomy for Lung Cancer: Short-Term Outcomes of a Randomized Trial. The Annals of Thoracic Surgery. 2018;105(2):386-92.
97. Rosen J, Salazar M, Dharmarajan K, Kim A. Length of Stay From the Hospital Perspective: Practice of Early Discharge Is Not Associated With Increased Readmission Risk after Lung Cancer Surgery. Annals of Surgery,. 2017;266(2):383-8.
98. Dziedzic R, Marjanski T, Binczyk F, Polanska J. Favourable outcomes in patients with early-stage non-small-cell lung cancer operated on by video-assisted thoracoscopic surgery: a propensity score-matched analysis. European Journal of Cardio-Thoracic Surgery,. 2018;54(3):547-53.
99. Yang CJ, Kumar A, Klapper JA, Hartwig MG, Tong BC, Harpole DH, et al. A National Analysis of Long-term Survival Following Thoracoscopic Versus Open Lobectomy for Stage I Non-small-cell Lung Cancer. Ann Surg. 2019;269(1):163-71.
100. Falcoz PE, Puyraveau M, Thomas PA, Decaluwe H, Hürtgen M, Petersen RH, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg. 2016;49(2):602-9.
101. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. The Lancet Oncology. 2016;17(6):836-44.
102. Rueth NM, Andrade RS. Is VATS Lobectomy Better: Perioperatively, Biologically and Oncologically? The Annals of Thoracic Surgery. 2010;89(6):S2107-S11.
103. Hanna WC, de Valence M, Atenafu EG, Cypel M, Waddell TK, Yasufuku K, et al. Is video-assisted lobectomy for non-small-cell lung cancer oncologically equivalent to open lobectomy? Eur J Cardiothorac Surg. 2013;43(6):1121-5.
104. Paul S, Isaacs Abby J, Treasure T, Altorki Nasser K, Sedrakyan A. Long term survival with thoracoscopic versus open lobectomy : propensity matched comparative analysis using SEER-Medicare database. BMJ: British Medical Journal. 2014;349:g5575.
105. Situ D, Long H, Tan Q, Luo Q. OA13.02 Video-Assisted Thoracoscopic Surgery vs. Thoracotomy for Non-Small Cell Lung Cancer: Survival Outcome of a Randomised Trial. Journal of Thoracic Oncology,. 2019;14(10):S240.
106. Denlinger CE, Fernandez F, Meyers BF, Pratt W, Zoole JB, Patterson GA, et al. Lymph Node Evaluation in Video-Assisted Thoracoscopic Lobectomy Versus Lobectomy by Thoracotomy. The Annals of Thoracic Surgery. 2010;89(6):1730-6.
107. Palade E, Passlick B, Osei-Agyemang T, Guenter J, Wiesemann S. Video-assisted vs open mediastinal lymphadenectomy for Stage I non-small-cell lung cancer: results of a prospective randomized trial. Eur J Cardiothorac Surg 2013;44(2):244-9.
108. Petersen RP, Pham D, Burfeind WR, Hanish SI, Toloza EM, Harpole JDH, et al. Thoracoscopic Lobectomy Facilitates the Delivery of Chemotherapy after Resection for Lung Cancer. The Annals of Thoracic Surgery. 2007;83(4):1245-50.
109. Medbery RL, Perez SD, Force SD, Gillespie TW, Pickens A, Miller DL, et al. Video-assisted thoracic surgery lobectomy cost variability: implications for a bundled payment era. Ann Thorac Surg. 2014;97(5):1686-92; discussion 92-3.
110. Farjah F, Backhus LM, Varghese TK, Mulligan MS, Cheng AM, Alfonso-Cristancho R, et al. Ninety-day costs of video-assisted thoracic surgery versus open lobectomy for lung cancer. Ann Thorac Surg. 2014;98(1):191-6.
111. Park BJ, Flores RM. Cost comparison of robotic, video-assisted thoracic surgery and thoracotomy approaches to pulmonary lobectomy. Thorac Surg Clin. 2008;18(3):297-300, vii.

112. Brunelli A, Crockatt A, Chaudhuri N, Kefaloyannis E. Ninety-day hospital costs for anatomic lung resections. European Journal of Cardio-Thoracic Surgery,. 2019;55(3):440-5.
113. Swanson SJ, Meyers BF, Gunnarsson CL, Moore M, Howington JA, Maddaus MA, et al. Video-assisted thoracoscopic lobectomy is less costly and morbid than open lobectomy: a retrospective multiinstitutional database analysis. Ann Thorac Surg. 2012;93(4):1027-32.
114. Kneuertz PJ, Singer E, D'Souza DM, Abdel-Rasoul M, Moffatt-Bruce SD, Merritt RE. Hospital cost and clinical effectiveness of robotic-assisted versus video-assisted thoracoscopic and open lobectomy: A propensity score-weighted comparison. J Thorac Cardiovasc Surg. 2019;157(5):2018-26.e2.
115. Veronesi G, Galetta D, Maisonneuve P, Melfi F, Schmid RA, Borri A, et al. Four-arm robotic lobectomy for the treatment of early-stage lung cancer. The Journal of Thoracic and Cardiovascular Surgery. 2010;140(1):19-25.
116. Oh DS, Cho I, Karamian B, DeMeester SR, Hagen JA. Early adoption of robotic pulmonary lobectomy: feasibility and initial outcomes. The American surgeon. 2013;79(10):1075-80.
117. Adams RD, Bolton WD, Stephenson JE, Henry G, Robbins ET, Sommers E. Initial Multicenter Community Robotic Lobectomy Experience: Comparisons to a National Database. The Annals of Thoracic Surgery. 2014;97(6):1893-900.
118. Kneuertz PJ, D'Souza D, Moffatt-Bruce SD, Merritt RE. Robotic lobectomy has the greatest benefit in patients with marginal pulmonary function. Journal of Cardiothoracic Surgery. 2018;13(1):1-7.
119. Cao C, Manganas C, Ang S, Yan TD. A SYSTEMATIC REVIEW AND META-ANALYSIS ON PULMONARY RESECTIONS BY ROBOTIC VIDEO-ASSISTED THORACIC SURGERY. Annals of Cardiothoracic Surgery. 2012;1(1):3-10.
120. O'Sullivan KE, Kreaden US, Hebert AE, Eaton D, Redmond KC. A systematic review and meta-analysis of robotic versus open and video-assisted thoracoscopic surgery approaches for lobectomy. Interactive CardioVascular and Thoracic Surgery. 2019;28(4):526-34.
121. Agzarian J, Fahim C, Shargall Y, Yasufuku K, Waddell TK, Hanna WC. The Use of Robotic-Assisted Thoracic Surgery for Lung Resection: A Comprehensive Systematic Review. Seminars in Thoracic and Cardiovascular Surgery. 2016;28(1):182-92.
122. Hu J, Chen Y, Dai J, Zhu X, Gonzalez-Rivas D, Jiang G, et al. Perioperative outcomes of robot-assisted vs video-assisted and traditional open thoracic surgery for lung cancer: A systematic review and network meta-analysis. International Journal of Medical Robotics and Computer Assisted Surgery. 2020:1-14.
123. Huang J, Li C, Li H, Lv F, Jiang L, Lin H, et al. Robot-assisted thoracoscopic surgery versus thoracotomy for c-N2 stage NSCLC: short-term outcomes of a randomized trial. Transl Lung Cancer Res. 2019;8(6):951-8.
124. Kwon ST, Zhao L, Reddy RM, Chang AC, Orringer MB, Brummett CM, et al. Evaluation of acute and chronic pain outcomes after robotic, video-assisted thoracoscopic surgery, or open anatomic pulmonary resection. The Journal of Thoracic and Cardiovascular Surgery. 2017;154(2):652-9.
125. Darr C, Cheufou D, Weinreich G, Hachenberg T, Aigner C, Kampe S. Robotic thoracic surgery results in shorter hospital stay and lower postoperative pain compared to open thoracotomy: a matched pairs analysis. Surgical endoscopy. 2017;31(10):4126-30.
126. Augustin F, Bodner J, Wykypiel H, Schwinghammer C, Schmid T. Initial experience with robotic lung lobectomy: report of two different approaches. Surgical Endoscopy: And Other Interventional TechniquesOfficial Journal of the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) and European Association for Endoscopic Surgery (EAES). 2011;25(1):108.

127. Giulianotti PC, Buchs NC, Bianco FM, Caravaglios G. Robot-assisted lung resection: Outcomes and technical details. Interactive Cardiovascular and Thoracic Surgery. 2010;11(4):388-92.
128. Park BJ, Melfi F, Mussi A, Maisonneuve P, Spaggiari L, Da Silva RKC, et al. Robotic lobectomy for non–small cell lung cancer (NSCLC): Long-term oncologic results. The Journal of Thoracic and Cardiovascular Surgery. 2012;143(2):383-9.
129. Cerfolio RJ, Ghanim AF, Dylewski M, Veronesi G, Spaggiari L, Park BJ. The long-term survival of robotic lobectomy for non–small cell lung cancer: A multi-institutional study. The Journal of Thoracic and Cardiovascular Surgery. 2018;155(2):778-86.
130. Melfi FM, Fanucchi O, Davini F, Romano G, Lucchi M, Dini P, et al. Robotic lobectomy for lung cancer: evolution in technique and technology. Eur J Cardiothorac Surg. 2014;46(4):626-30; discussion 30-1.
131. Wilson JL, Louie BE, Cerfolio RJ, Park BJ, Vallières E, Aye RW, et al. The Prevalence of Nodal Upstaging During Robotic Lung Resection in Early Stage Non-Small Cell Lung Cancer. The Annals of Thoracic Surgery. 2014;97(6):1901-7.
132. Alper T, Elena U, Erkan K, Kemal A, Mehmet Oğuzhan Ö, Özkan D. Lymph Node Dissection in Surgery for Lung Cancer: Comparison of Open vs. Video-Assisted vs. Robotic-Assisted Approaches. Annals of Thoracic and Cardiovascular Surgery. 2016;22(5):284.
133. Nelson DB, Mehran RJ, Mitchell KG, Rajaram R, Correa AM, Bassett RL, et al. Robotic-Assisted Lobectomy for Non-Small Cell Lung Cancer: A Comprehensive Institutional Experience. Annals of Thoracic Surgery. 2019;108(2):370-6.
134. Louie BE, Farivar AS, Aye RW, Vallières E. Early Experience With Robotic Lung Resection Results in Similar Operative Outcomes and Morbidity When Compared With Matched Video-Assisted Thoracoscopic Surgery Cases. The Annals of Thoracic Surgery. 2012;93(5):1598-605.
135. Singer E, Kneuertz PJ, D'Souza DM, Moffatt-Bruce SD, Merritt RE. Understanding the financial cost of robotic lobectomy: calculating the value of innovation? Ann Cardiothorac Surg. 2019;8(2):194-201.
136. Deen SA, Wilson JL, Wilshire CL, Vallières E, Farivar AS, Aye RW, et al. Defining the Cost of Care for Lobectomy and Segmentectomy: A Comparison of Open, Video-Assisted Thoracoscopic, and Robotic Approaches. Annals of Thoracic Surgery. 2014;97(3):1000-7.
137. Nasir BS, Bryant AS, Minnich DJ, Wei B, Cerfolio RJ. Performing robotic lobectomy and segmentectomy: cost, profitability, and outcomes. Ann Thorac Surg. 2014;98(1):203-8; discussion 8-9.
138. Kneuertz PJ, Singer E, D'Souza DM, Moffatt-Bruce SD, Merritt RE. Postoperative complications decrease the cost-effectiveness of robotic-assisted lobectomy. Surgery. 2019;165(2):455-60.
139. Toker A, Özyurtkan MO, Kaba E, Ayalp K, Demirhan Ö, Uyumaz E. Robotic anatomic lung resections: the initial experience and description of learning in 102 cases. Surg Endosc. 2016;30(2):676-83.
140. Melfi FM, Mussi A. Robotically assisted lobectomy: learning curve and complications. Thorac Surg Clin. 2008;18(3):289-95, vi-vii.
141. Park BJ. Cost concerns for robotic thoracic surgery. Ann Cardiothorac Surg. 2012;1(1):56-8.
142. Augustin F, Bodner J, Maier H, Schwinghammer C, Pichler B, Lucciarini P, et al. Robotic-assisted minimally invasive vs. thoracoscopic lung lobectomy: comparison of perioperative results in a learning curve setting. Langenbecks Arch Surg. 2013;398(6):895-901.
143. Liang H, Liang W, Zhao L, Chen D, Zhang J, Zhang Y, et al. Robotic Versus Video-assisted Lobectomy/Segmentectomy for Lung Cancer: A Meta-analysis. Ann Surg. 2018;268(2):254-9.

144. Ye X, Xie L, Chen G, Tang JM, Ben XS. Robotic thoracic surgery versus video-assisted thoracic surgery for lung cancer: a meta-analysis. Interact Cardiovasc Thorac Surg. 2015;21(4):409-14.
145. Wei S, Chen M, Chen N, Liu L. Feasibility and safety of robot-assisted thoracic surgery for lung lobectomy in patients with non-small cell lung cancer: a systematic review and meta-analysis. World J Surg Oncol. 2017;15(1):98.
146. Veronesi G, Novellis P, Difrancesco O, Dylewski M. Robotic assisted lobectomy for locally advanced lung cancer. J Vis Surg. 2017;3:78.
147. Veronesi G, Park B, Cerfolio R, Dylewski M, Toker A, Fontaine JP, et al. Robotic resection of Stage III lung cancer: an international retrospective study. Eur J Cardiothorac Surg. 2018;54(5):912-9.
148. Emmert A, Straube C, Buentzel J, Roever C. Robotic versus thoracoscopic lung resection, A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(35):e7633.
149. van der Ploeg APT, Ayez N, Akkersdijk GP, van Rossem CC, de Rooij PD. Postoperative pain after lobectomy: robot-assisted, video-assisted and open thoracic surgery. J Robot Surg. 2020;14(1):131-6.
150. Worrell SG, Dedhia P, Gilbert C, James C, Chang AC, Lin J, et al. The cost and quality of life outcomes in developing a robotic lobectomy program. J Robot Surg. 2019;13(2):239-43.
151. Haruki T, Kubouchi Y, Takagi Y, Kidokoro Y, Matsui S, Nakanishi A, et al. Comparison of medium-term survival outcomes between robot-assisted thoracoscopic surgery and video-assisted thoracoscopic surgery in treating primary lung cancer. Gen Thorac Cardiovasc Surg. 2020;68(9):984-92.
152. Huang L, Shen Y, Onaitis M. Comparative study of anatomic lung resection by robotic. J Thorac Dis. 2019;11(4):1243-50.
153. Lee BE, Shapiro M, Rutledge JR, Korst RJ. Nodal Upstaging in Robotic and Video Assisted Thoracic Surgery Lobectomy for Clinical N0 Lung Cancer. Ann Thorac Surg. 2015;100(1):229-33; discussion 33-4.
154. Yang CF, Sun Z, Speicher PJ, Saud SM, Gulack BC, Hartwig MG, et al. Use and Outcomes of Minimally Invasive Lobectomy for Stage I Non-Small Cell Lung Cancer in the National Cancer Data Base. Ann Thorac Surg. 2016;101(3):1037-42.
155. Sesti J, Langan RC, Bell J, Nguyen A, Turner AL, Hilden P, et al., editors. A Comparative Analysis of Long-Term Survival of Robotic Versus Thoracoscopic Lobectomy. Fifty-sixth Annual Meeting of The Society of Thoracic Surgeons; 2020 25-28 Jan; New Orleans, LA: The Annals of Thoracic Surgery.
156. Toosi K, Velez-Cubian FO, Glover J, Ng EP, Moodie CC, Garrett JR, et al. Upstaging and survival after robotic-assisted thoracoscopic lobectomy for non-small cell lung cancer. Surgery. 2016;160(5):1211-8.
157. Park SY, Suh JW, Narm KS, Lee CY, Lee JG, Paik HC, et al. Feasibility of four-arm robotic lobectomy as solo surgery in patients with clinical stage I lung cancer. J Thorac Dis. 2017;9(6):1607-14.
158. Kneuertz PJ, Cheufou DH, D'Souza DM, Mardanzai K, Abdel-Rasoul M, Theegarten D, et al. Propensity-score adjusted comparison of pathologic nodal upstaging by robotic, video-assisted thoracoscopic, and open lobectomy for non-small cell lung cancer. J Thorac Cardiovasc Surg. 2019;158(5):1457-66.e2.
159. Paul S, Jalbert J, Isaacs AJ, Altorki NK, Isom OW, Sedrakyan A. Comparative effectiveness of robotic-assisted vs thoracoscopic lobectomy. Chest. 2014;146(6):1505-12.
160. Subramanian MP, Liu J, Chapman WC, Olsen MA, Yan Y, Liu Y, et al. Utilization Trends, Outcomes, and Cost in Minimally Invasive Lobectomy. Ann Thorac Surg. 2019;108(6):1648-55.

161. Novellis P, Bottoni E, Voulaz E, Cariboni U, Testori A, Bertolaccini L, et al. Robotic surgery, video-assisted thoracic surgery, and open surgery for early stage lung cancer: comparison of costs and outcomes at a single institute. J Thorac Dis. 2018;10(2):790-8.
162. Stamenkovic S, Slight RD. Resource implications of robotic thoracic surgery: what are the wider issues? Ann Cardiothorac Surg. 2019;8(2):250-4.
163. Park BJ, Flores RM, Rusch VW. Robotic assistance for video-assisted thoracic surgical lobectomy: technique and initial results. J Thorac Cardiovasc Surg. 2006;131(1):54-9.
164. Augustin F, Bodner J, Wykypiel H, Schwinghammer C, Schmid T. Perioperative results of robotic lung lobectomy: summary of literature. Surg Endosc. 2012;26(4):1190-1.
165. International Association for the Study of Lung Cancer. Staging Manual in Thoracic Oncology, Second Edition. North Fort Myers, FL: Editorial Rx Press; 2016.
166. Office for National Statistics. Health state life expectancies, UK: 2016 to 2018: Office for National Statistics; 2019 [cited 2020 16 August]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/healthstatelifeexpectanciesuk/2016to2018#life-expectancy-at-a-local-level-in-the-uk.
167. De Angelis R, Sant M, Coleman MP, Francisci S, Baili P, Pierannunzio D, et al. Cancer survival in Europe 1999-2007 by country and age: results of EUROCARE--5-a population-based study. Lancet Oncol. 2014;15(1):23-34.
168. Cao C, Manganas C, Ang SC, Yan TD. A meta-analysis of unmatched and matched patients comparing video-assisted thoracoscopic lobectomy and conventional open lobectomy. Ann Cardiothorac Surg. 2012;1(1):16-23.
169. U.S. Department of Health and Human Sciences. Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0: National Institutes of Health; 2017 [cited 2020 16 August]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
170. Lim E, Begum S, Batchelor T, Krishnadas R, Shackcloth M, Dunning J, et al. S23 Optimum diagnostic pathway and pathologic confirmation rate of early stage lung cancer: results from VIOLET. Thorax. 2019;74 (Suppl 2)(A15).
171. Davini F, Ricciardi S, Zirafa CC, Cavaliere I, Romano G, Melfi F. Treatment of pulmonary nodule: from VATS to RATS. J Vis Surg. 2018;4:36.
172. Kim MP, Nguyen DT, Meisenbach LM, Graviss EA, Chan EY. Da Vinci Xi robot decreases the number of thoracotomy cases in pulmonary resection. Journal of Thoracic Disease. 2019;11(1):145-53.
173. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 1900-7.
174. Kalhor NMC. MEDIASTINAL PATHOLOGY. Online access with purchase: Springer: SPRINGER INTERNATIONAL PU; 2018. p. 13-27.
175. Engels EA, Pfeiffer RM. Malignant thymoma in the United States: demographic patterns in incidence and associations with subsequent malignancies. International journal of cancer. 2003;105(4):546-51.
176. DeVita, Hellman, and Rosenberg's cancer : principles & practice of oncology / editors Vincent T. DeVita, Jr., Theodore S. Lawrence, Steven A. Rosenberg ; with 384 Contributing Authors. Philadelphia [i pozostałe]: Wolters Kluwer; 2019. p. 700-12.
177. Girard N, Ruffini E, Marx A, Faivre-Finn C, Peters S. Thymic epithelial tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2015;26(Supplement 5):v40-v55.

178. Marx A, Chan JKC, Coindre J-M, Detterbeck F, Girard N, Harris NL, et al. The 2015 World Health Organization Classification of Tumors of the Thymus: Continuity and Changes. Journal of Thoracic Oncology. 2015;10(10):1383-95.
179. Masaoka A, Monden Y, Nakahara K, Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer. 1981;48(11):2485-92.
180. Carter BW, Benveniste MF, Madan R, Godoy MC, Groot PMd, Truong MT, et al. IASLC/ITMIG Staging System and Lymph Node Map for Thymic Epithelial Neoplasms. RadioGraphics. 2017;37(3):758-76.
181. Falkson CB, Bezjak A, Darling G, Gregg R, Malthaner R, Maziak DE, et al. The Management of Thymoma: A Systematic Review and Practice Guideline. Journal of Thoracic Oncology. 2009;4(7):911-9.
182. Detterbeck F, Parsons A. Thymic tumors: a review of current diagnosis, classification, and treatment. In: Patterson G, Cooper J, Deslauriers J, Lerut A, Luketich J, Rice TW, et al., editors. Thoracic and Esophageal Surgery. 3rd ed. Philadelphia: Elsevier; 2008. p. 1589-614.
183. Attaran S, Pilling J, Harrison-Phipps K, McCormack D. Which stages of thymoma benefit from adjuvant chemotherapy post-thymectomy? Interactive Cardiovascular and Thoracic Surgery. 2012;15(2):273-5.
184. Patel S, Macdonald OK, Nagda S, Bittner N, Suntharalingam M. Evaluation of the Role of Radiation Therapy in the Management of Malignant Thymoma. International Journal of Radiation Oncology, Biology, Physics. 2012;82(5):1797-801.
185. Forquer JA, Rong N, Fakiris AJ, Loehrer PJ, Sr., Johnstone PAS. Postoperative radiotherapy after surgical resection of thymoma: differing roles in localized and regional disease. International journal of radiation oncology, biology, physics. 2010;76(2):440-5.
186. Korst RJ, Kansler AL, Christos PJ, Mandal S. Adjuvant radiotherapy for thymic epithelial tumors: a systematic review and meta-analysis. The Annals of thoracic surgery. 2009;87(5):1641-7.
187. Weksler B, Shende M, Nason KS, Gallagher A, Ferson PF, Pennathur A. The role of adjuvant radiation therapy for resected stage III thymoma: a population-based study. The Annals of thoracic surgery. 2012;93(6):1822-8.
188. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 2179-93.
189. Kalhor NMC. MEDIASTINAL PATHOLOGY. Online access with purchase: Springer: SPRINGER INTERNATIONAL PU; 2018. p. 341-98.
190. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 2194-225.
191. Kalhor NMC. MEDIASTINAL PATHOLOGY. Online access with purchase: Springer: SPRINGER INTERNATIONAL PU; 2018. p. 399-454.
192. Wang T, Yin H, Han S, Yang X, Wang J, Huang Q, et al. Malignant peripheral nerve sheath tumor (MPNST) in the spine: a retrospective analysis of clinical and molecular prognostic factors. J Neurooncol. 2015;122(2):349-55.
193. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 2144-59.
194. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 1974-98.

195. Park BJ, Flores R, Downey RJ, Bains MS, Rusch VW. Management of major hemorrhage during mediastinoscopy. Journal of Thoracic and Cardiovascular Surgery. 2003;126(3):726-31.
196. Rice D. Endobronchial Ultrasound (EBUS) Biopsy of Mediastinal Lymph Nodes: CTSNet; 2013 [cited 2020 9 June]. Available from: https://www.ctsnet.org/article/endobronchial-ultrasound-ebus-biopsy-mediastinal-lymph-nodes.
197. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 2000-5.
198. Blumberg D, Port JL, Weksler B, Delgado R, Rosai J, Bains MS, et al. Thymoma: a multivariate analysis of factors predicting survival. Ann Thorac Surg. 1995;60(4):908-13; discussion 14.
199. Regnard JF, Magdeleinat P, Dromer C, Dulmet E, de Montpreville V, Levi JF, et al. Prognostic factors and long-term results after thymoma resection: a series of 307 patients. J Thorac Cardiovasc Surg. 1996;112(2):376-84.
200. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 2033-8.
201. Erickson C, Tieu B. Surgical Treatment for Early Stage Thymomas: Approach and Technique: CTSNet; 2015 [cited 2020 10 June]. Available from: https://www.ctsnet.org/article/surgical-treatment-early-stage-thymomas-approach-and-technique.
202. Bhora FY, Chen DJ, Detterbeck FC, Asamura H, Watanabe H, Falkson C, et al. The ITMIG/IASLC thymic epithelial tumors staging project: A proposed lymph node map for thymic epithelial tumors in the forthcoming 8th edition of the TNM classification of malignant tumors. Journal of Thoracic Oncology. 2014;9(9):S88-S96.
203. Jurado J, Javidfar J, Newmark A, Lavelle M, Bacchetta M, Gorenstein L, et al. Minimally Invasive Thymectomy and Open Thymectomy: Outcome Analysis of 263 Patients. The Annals of Thoracic Surgery. 2012;94(3):974-82.
204. Liu HP, Yim APC, Wan J, Chen H, Wu YC, Liu YH, et al. Thoracoscopic removal of intrathoracic neurogenic tumors: A combined Chinese experience. Annals of Surgery. 2000;232(2):187-90.
205. Takeda S-i, Miyoshi S, Minami M, Matsuda H. Intrathoracic neurogenic tumors—50 years': experience in a Japanese institution. European Journal of Cardio-Thoracic Surgery. 2004;26(4):807-12.
206. LoCicero J, III, Feins RH, Colson YL, Rocco GMD. Shields' general thoracic surgery. Online access with purchase: Lippincott, Williams & Wilkins Doody Collection. 8th ed. ed: Wolters Kluwer; 2019. p. 2006-31.
207. Pennathur A, Qureshi I, Schuchert MJ, Dhupar R, Ferson PF, Gooding WE, et al. Comparison of surgical techniques for early-stage thymoma: Feasibility of minimally invasive thymectomy and comparison with open resection. The Journal of Thoracic and Cardiovascular Surgery. 2011;141(3):694-701.
208. Liu TJ, Lin MW, Kao MW, Chen KC, Chang CC, Kuo SW, et al. Video-assisted thoracoscopic surgical thymectomy to treat early thymoma: A comparison with the conventional transsternal approach. Annals of Surgical Oncology. 2014;21(1):322-8.
209. Ye B, Tantai J-C, Ge X-X, Li W, Feng J, Cheng M, et al. Surgical techniques for early-stage thymoma: Video-assisted thoracoscopic thymectomy versus transsternal thymectomy. The Journal of Thoracic and Cardiovascular Surgery. 2014;147(5):1599-603.

210. Friedant AJ, Handorf EA, Su S, Scott WJ. Minimally Invasive versus Open Thymectomy for Thymic Malignancies: Systematic Review and Meta-Analysis. Journal of Thoracic Oncology. 2016;11(1):30-8.
211. Hess NR, Sarkaria IS, Pennathur A, Levy RM, Christie NA, Luketich JD. Minimally invasive versus open thymectomy: a systematic review of surgical techniques, patient demographics, and perioperative outcomes. Ann Cardiothorac Surg. 2016;5(1):1-9.
212. Landreneau RJ, Dowling RD, Ferson PF. Thoracoscopic resection of a posterior mediastinal neurogenic tumor. CHEST. 1992;102(4):1288-90.
213. Riquet M, Mouroux J, Pons F, Debrosse D, Dujon A, Dahan M, et al. Videothoracoscopic excision of thoracic neurogenic tumors. The Annals of Thoracic Surgery. 1995;60(4):943-6.
214. Cardillo G, Carleo F, Khalil MW, Carbone L, Treggiari S, Salvadori L, et al. Surgical treatment of benign neurogenic tumours of the mediastinum: a single institution report. European Journal of Cardio-thoracic Surgery. 2008;34(6):1210-4.
215. Seong YW, Kang CH, Choi J-W, Kim H-S, Jeon JH, Park IK, et al. Early clinical outcomes of robot-assisted surgery for anterior mediastinal mass: its superiority over a conventional sternotomy approach evaluated by propensity score matching. European Journal of Cardio-Thoracic Surgery. 2014;45(3):E68-E73.
216. Weksler B, Tavares J, Newhook TE, Greenleaf CE, Diehl JT. Robot-assisted thymectomy is superior to transsternal thymectomy. Surgical Endoscopy. 2012;26(1):261-6.
217. O'Sullivan K, Higgins P, Kreaden U, Hebert A, Eaton D, Redmond K. A Systematic Review of Robotic Versus Open and Video Assisted Thoracoscopic Surgery (Vats) Approaches For Thymectomy. Ann Cardiothorac Surg 2019;8(2):174-93.
218. Cerfolio RJ, Bryant AS, Minnich DJ. Starting a Robotic Program in General Thoracic Surgery: Why, How, and Lessons Learned. Annals of Thoracic Surgery. 2011;91(6):1729.
219. Fok M, Bashir M, Harky A, Sladden D, DiMartino M, Elsyed H, et al. Video-Assisted Thoracoscopic Versus Robotic-Assisted Thoracoscopic Thymectomy: Systematic Review and Meta-analysis. Innovations (Philadelphia, Pa). 2017;12(4):259-64.
220. Kamel MK, Rahouma M, Stiles BM, Nasar A, Altorki NK, Port JL. Robotic Thymectomy: Learning Curve and Associated Perioperative Outcomes. J Laparoendosc Adv Surg Tech A. 2017;27(7):685-90.
221. Buentzel J, Heinz J, Hinterthaner M, SchAaAaAeA ndube F, Straube C, Roever C, et al. Robotic versus thoracoscopic thymectomy: The current evidence. The International Journal of Medical Robotics and Computer Assisted Surgery. 2017;13(4):e1847.
222. Bo Y, Ji-Cheng T, Wang L, Xiao-Xiao G, Jian F, Ming C, et al. Video-assisted thoracoscopic surgery versus robotic-assisted thoracoscopic surgery in the surgical treatment of Masaoka stage I thymoma. World Journal of Surgical Oncology. 2013;11(1):1-5.
223. Radkani P, Joshi D, Barot T, Williams R. Robotic video-assisted thoracoscopy: minimally invasive approach for management of mediastinal tumors. Journal of Robotic Surgery. 2018;12(1):75-9.
224. Li H, Li J, Huang J, Yang Y, Luo Q. Robotic-assisted mediastinal surgery: the first Chinese series of 167 consecutive cases. J Thorac Dis. 2018;10(5):2876-80.
225. Augustin F, Schmid T, Bodner J. The robotic approach for mediastinal lesions. International Journal of Medical Robotics and Computer Assisted Surgery. 2006;2(3):262-70.
226. Melfi F, Fanucchi O, Davini F, Viti A, Lucchi M, Ambrogi MC, et al. Ten-year experience of mediastinal robotic surgery in a single referral centre. European Journal of Cardio-thoracic Surgery. 2012;41(4):847-51.
227. Broussard BL, Wei B, Cerfolio RJ. Robotic surgery for posterior mediastinal pathology. Ann Cardiothorac Surg. 2016;5(1):62-4.

228. Zirafa CC, Melfi F. Robot-assisted surgery for posterior mediastinal mass. J Thorac Dis. 2017;9(12):4929-31.
229. World Health Organisation. Chronic respiratory diseases. COPD: Definition: World Health Organisation,; 2020 [cited 2020 11 March]. Available from: https://www.who.int/respiratory/copd/definition/en/.
230. Ralston S, Penman I, Strachan M, Hobson R, Britton R, Davidson SS. Davidson's principles and practice of medicine. 2018. Elsevier. 23rd. [545-628]. Available from: https://search-ebscohost-com.liverpool.idm.oclc.org/login.aspx?direct=true&db=cat00003a&AN=lvp.b5560543&site=eds-live&scope=site.
231. World health organisation. The top 10 causes of death: World health organisation; 2018 [cited 2020 11 March]. Available from: https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.
232. National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease in over 16s: diagnosis and management NICE2019 [cited 2020 11 March]. Available from: https://www.nice.org.uk/guidance/ng115/chapter/Recommendations.
233. O'Donnell D, Laveneziana P. Physiology and consequences of lung hyperinflation in COPD. European Respiratory review. 2006;15(100):61-7.
234. Cooper JD. The History of Surgical Procedures for Emphysema. The Annals of Thoracic Surgery. 1997;63(2):312-9.
235. Naef AP. History of emphysema surgery. The Annals Of Thoracic Surgery. 1997;64(5):1506-8.
236. Cooper JD, Trulock EP, Triantafillou AN, Patterson GA, Pohl MS, Deloney PA, et al. Bilateral pneumectomy (volume reduction) for chronic obstructive pulmonary disease. J Thorac Cardiovasc. 1995;109(1):106-16.
237. Utz JP, Hubmayr RD, Deschamps C. Lung Volume Reduction Surgery for Emphysema: Out on a Limb Without a NETT. Mayo Clinic Proceedings. 1998;73(6):552-66.
238. Weinmann G, Chiang Y, Sheingold S. The National Emphysema Treatment Trial (NETT). A Study in Agency Collaboration. Proceedings of the American Thoracic Society,. 2008;5(4):381-4.
239. National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. The New England Journal of Medicine. 2003;348:2059-73.
240. Fishman A, Fessler H, Martinez F, McKenna RJ, Jr., Naunheim K, Piantadosi S, et al. Patients at high risk of death after lung-volume-reduction surgery. New England Journal of Medicine. 2001;345(15):1075-83.
241. DeCamp MM, Blackstone EH, Naunheim KS, Krasna MJ, Wood DE, Meli YM, et al. Patient and Surgical Factors Influencing Air Leak After Lung Volume Reduction Surgery: Lessons Learned From the National Emphysema Treatment Trial. Annals of Thoracic Surgery. 2006;82(1):197.
242. Ramsey SD, Shroyer AL, Sullivan SD, Wood DE. Updated evaluation of the cost-effectiveness of lung volume reduction surgery. Chest. 2007;131(3):823-32.
243. Global Initiative for Chronic Obstructive Lung Disease. Pocket Guide to COPD Diagnosis, Management and Prevention. A Guide for Health Care Professionals 2019 report. Global Initiative for Chronic Obstructive Lung Disease,; 2019.
244. Safety and efficacy of median sternotomy versus video-assisted thoracic surgery for lung volume reduction surgery. The Journal of Thoracic and Cardiovascular Surgery. 2004;127(5):1350-60.
245. NHS England. LVR stocktake April 2020. 2020.

246. Ginsburg ME, Thomashow BM, Yip CK, DiMango AM, Maxfield RA, Bartels MN, et al. Lung volume reduction surgery using the NETT selection criteria. Ann Thorac Surg. 2011;91(5):1556-60; discussion 61.
247. Clark SJ, Zoumot Z, Bamsey O, Polkey MI, Dusmet M, Lim E, et al. Surgical approaches for lung volume reduction in emphysema. Clin Med (Lond). 2014;14(2):122-7.
248. Herth FJ, Noppen M, Valipour A, Leroy S, Vergnon JM, Ficker JH, et al. Efficacy predictors of lung volume reduction with Zephyr valves in a European cohort. Eur Respir J. 2012;39(6):1334-42.
249. Davey C, Zoumot Z, Jordan S, McNulty W, Carr D, Hind M, et al. Bronchoscopic lung volume reduction with endobronchial valves for patients with heterogeneous emphysema and intact interlobar fissures (the BeLieVeR-HIFi study): a randomised controlled trial. The Lancet. 2015;386(9998):1066-73.
250. Klooster K, ten Hacken NH, Hartman JE, Kerstjens HA, van Rikxoort EM, Slebos DJ. Endobronchial Valves for Emphysema without Interlobar Collateral Ventilation. N Engl J Med. 2015;373(24):2325-35.
251. Kemp SV, Slebos DJ, Kirk A, Kornaszewska M, Carron K, Ek L, et al. A Multicenter Randomized Controlled Trial of Zephyr Endobronchial Valve Treatment in Heterogeneous Emphysema (TRANSFORM). Am J Respir Crit Care Med. 2017;196(12):1535-43.
252. Sciurba F, Ernst A, Herth J, Strange C, Criner G, Marquette C, et al. A randomised study of endobronchial valves for advanced emphysema. The New England Journal of Medicine. 2010;363(13):1233-44.
253. Gompelmann D, Herth FJ, Slebos DJ, Valipour A, Ernst A, Criner GJ, et al. Pneumothorax following endobronchial valve therapy and its impact on clinical outcomes in severe emphysema. Respiration. 2014;87(6):485-91.
254. National Institute for Health and Care Excellence. Endobronchial valve insertion to reduce lung volume in emphysema: NICE; 2017 [cited 2020 14 May]. Available from: https://www.nice.org.uk/guidance/ipg600/chapter/2-Indications-and-current-treatments.
255. Hazelrigg SR, Boley TM, Naunheim KS, Magee MJ, Lawyer C, Henkle JQ, et al. Effect of bovine pericardial strips on air leak after stapled pulmonary resection. Ann Thorac Surg. 1997;63(6):1573-5.
256. Stammberger U, Klepetko W, Stamatis G, Hamacher J, Schmid R, Wisser W, et al. Buttressing the staple line in lung volume reduction surgery: a randomised three-center study. The Annals of Thoracic Surgery,. 2000;70(6):1820-5.
257. Shanahan B, Redmond K. Robot-Assisted Left Upper Lobe Lung Volume Reduction Surgery With Intraoperative Firefly Perfusion Assessment: CTSNet; 2019 [cited 2020 16 July]. Available from: https://www.ctsnet.org/article/robot-assisted-left-upper-lobe-lung-volume-reduction-surgery-intraoperative-firefly.
258. Intuitive Surgical. Da Vinci by Intuitive 2020 [cited 2020 27 July]. Available from: https://www.intuitive.com/en-us/products-and-services/da-vinci.
259. GraphPad Software. Introducing Prism 8 2018 [cited 2020 27 July]. Available from: https://www.graphpad.com/scientific-software/prism/.
260. Geiser T, Schwizer B, Krueger T, Gugger M, Hof VI, Dusmet M, et al. Outcome after unilateral lung volume reduction surgery in patients with severe emphysema. European Journal of Cardio-Thoracic Surgery. 2001;20(4):674-8.
261. Mineo TC, Pompeo E, Mineo D, Rogliani P, Leonardis C, Nofroni I. Results of unilateral lung volume reduction surgery in patients with distinct heterogeneity of emphysema between lungs. The Journal of Thoracic and Cardiovascular Surgery. 2005;129(1):73-9.
262. Oey IF, Waller DA, Bal S, Singh SJ, Spyt TJ, Morgan MD. Lung volume reduction surgery - a comparison of the long term outcome of unilateral vs. bilateral approaches. European Journal of Cardio-Thoracic Surgery. 2002;22(4):610-14.

263. 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;55(1):91-115.
264. Breivik EK, Björnsson GA, Skovlund E. A comparison of pain rating scales by sampling from clinical trial data. Clin J Pain. 2000;16(1):22-8.