Thesis

IMPACT OF NEOADJUVANT THERAPY ON ADVERSE EVENTS FOLLOWING SLEEVE RESECTION OF THE LUNG

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CERTIFICA: Que la presente Tesis Doctoral, titulada "IMPACT OF NEOADJUVANT THERAPY ON ADVERSE EVENTS FOLLOWING SLEEVE RESECTION OF THE LUNG" que para optar al grado de Doctor presenta **Dª. MARÍA RODRÍGUEZ PÉREZ**, ha sido realizada en el Departamento de Cirugía de la Universidad de Salamanca, cumpliendo todos los requisitos necesarios para su presentación y defensa ante el Tribunal Calificador.

Y para que así conste, a los efectos oportunos, firmo la presente en Salamanca a 17 de Octubre de 2018

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María Rodríguez was at the Brigham and Women´s Hospital from 07/31/2016 until 07/15/2018. During that time, she started working on her thesis, titled: IMPACT OF NEOADJUVANT THERAPY ON ADVERSE EVENTS AFTER SLEEVE RESECTION OF THE LUNG. María dedicated to it a lot of her time in our Institution, finishing the main manuscript before she left.

The manuscript presents one of the largest series of sleeve resections and it addresses an important topic for both, thoracic surgeons and Non Small Cell Lung Cancer patient´s. Up to date, the administration of neoadjuvant therapy in sleeve resection candidates remains a controversial topic in thoracic surgery.

Also, despite the advance in surgical techniques and evidence-based treatments, sleeve resections remain a challenging operation, making it difficult to obtain large series that could help clarify these treatment controversies.

In her thesis, María enlightens some of these aspects and what is more important, she shows the administration of neoadjuvant therapy before sleeve resection can negatively affect the outcomes of those patients.

María´s thesis is well written, is scientifically rigorous and clinically relevant and we are very proud of her work at the Brigham and Women´s Hospital. I consider the thesis ready to be presented and to be published.

Please, don´t hesitate to contact us with any further questions or concerns,

Sincerely,

Michael Jaklitsch

Professor of Surgery

Harvard Medical School

To Francisco, half of my merits are his.

To my family, they are the definition of unconditional support. I would have never been here without their love, their values and their hard work.

To my friends, they know who they are. They have been a continuous inspiration and they have taught me distances can mean nothing at all.

To Michael, for giving me the opportunity to do research in the daily craziness I used to live in and for becoming our second family there. We are going to miss spending Christmas with them.

To Carlos and Sam, for their help in all our projects.

To both, Salamanca and Brigham´s colleagues. In order to grow, you need to let go!

TABLE OF CONTENTS

1. PREFACE

PREFACE:

Despite advances in chemotherapy and radiation, surgery offers the highest disease-free and overall survival rates for stage I and stage II lung cancer.

Pulmonary resections can differ considerably in the amount of airway and parenchyma removed. Central tumors may require a pneumonectomy, or removal of the entire ipsilateral lung. Tumors that involve the airway known as the distal bronchus intermedius may require the removal of the lower and middle lobes of the right lung, a procedure known as a bilobectomy. Most early stage tumors are resected with a lobectomy, removing one of the natural divisions of the lung and the lymphatics that drain the lobe. Smaller tumors confined to a single segment can be resected with a segmentectomy.

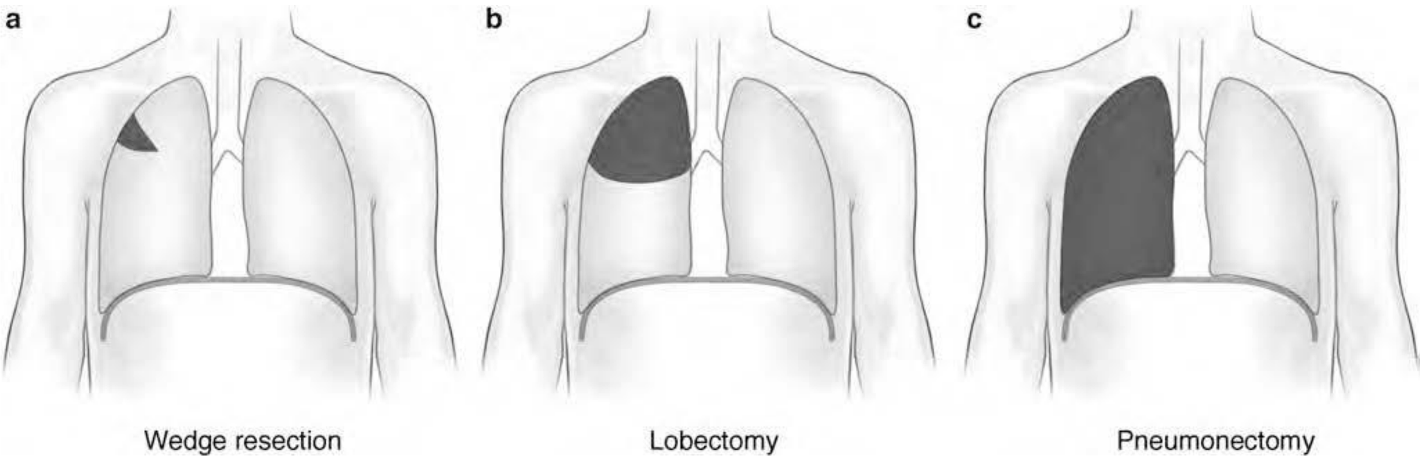

Figure 1: Types of pulmonary resections (Billmeier and Jaklitsch, 2011).

Sleeve resections are a type of surgical procedure characterized by the resection of a circumferential portion (sleeve) of the bronchus with or without parenchyma. To reconstruct the airway anatomy, they require a subsequent circumferential bronchial or trachea-bronchial anastomosis. For instance, an intraluminal carcinoid of the bronchus intermedius may be resected with the airway alone, while an endobronchial squamous cell cancer of the right upper lobe may require a lobectomy with a sleeve reconstruction of the right main bronchus to the bronchus intermedius. Tumors that also involve the adjacent pulmonary artery may also require a vascular sleeve resection to preserve lung tissue.

Vascular sleeve resections are a topic unto themselves and will not be specifically addressed in this thesis.

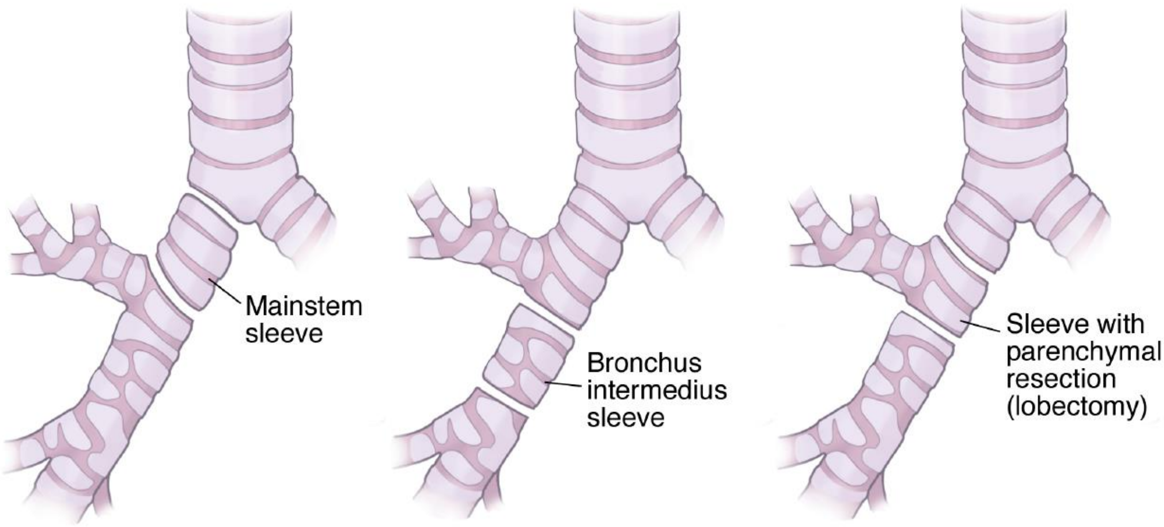

Figure 2: Types of sleeve resection (Artwork by Marcia Williams).

The choice as to what type of lung resection is chosen for a given patient is based on different variables. Some are related to the patient (comorbidities, pulmonary function tests, etc.) and others related to the tumor itself. Tumor-related variables influencing the magnitude of surgery include: size, central versus peripheral location, relationship with surrounding structures, airway involvement, lymphatic drainage, or challenging anatomy. For those tumors located peripherally, with no direct airway involvement, the preferred surgery continues to be lobectomy. Lobectomy is offered if the measurements of the patient's cardiopulmonary reserve predict that this can safely be done. For smaller peripheral tumors, and especially for those patients with moderate to severe pulmonary dysfunction, segmental resection is gaining in popularity. This is consistent with the Clinical Statement of The Society of Thoracic Surgeons Task Force on CT Screening, "the Task Force recommends the least parenchymal resection compatible with current diagnostic and oncologic principles performed through the least invasive surgical approach for the diagnosis and treatment of screen-detected nodules (Rocco *et al.*, 2013)".

When the tumor invades the airway, after careful bronchoscopic planning, a more extended resection to achieve negative bronchial margins is usually required. For example, for tumors invading the right upper lobe orifice, extending to the right main stem bronchus, a pneumonectomy would be the standard option. For tumors invading the bronchus intermedius, a bilobectomy would be the procedure most commonly performed. Likewise, if the tumor is invading the left main stem bronchus, proximal to the left upper lobe, a left sided pneumonectomy would be the traditional surgery performed (Fuentes, 2003).

Proceeding with these surgeries for airway invading tumors would, unfortunately, require the resection of a great amount of lung parenchyma, with the short and long term consequences related to the loss of functional alveoli (Alexiou *et al.*, 2003). Some patients who would require a pneumonectomy for tumor control would be considered unfit for surgery and thus prevented to have any type of resection because of the increased risk of perioperative mortality (D'amato *et al.*, 2009) and long term complications (Rodríguez *et al.*, 2013). Sleeve resections and bronchoplasties preserve the uninvolved lung parenchyma.

To avoid resection of an unproportioned amount of lung parenchyma to resect airway tumors and to mitigate the functional limitations of the patient after more extended procedures, bronchoplastic techniques arose as a valid alternative for tumor control and parenchyma preservation.

Bronchoplastic procedures involve resections of the airway distal to the tracheal carina. Surrounding lung parenchyma may or may not be involved. The most common bronchoplastic resections are sleeve resections, which are circumferential airway resections that require remaining airways to be joined by end-to-end anastomosis with or without a vascular anastomosis. Consequently, lung parenchyma can be preserved for gas exchange.

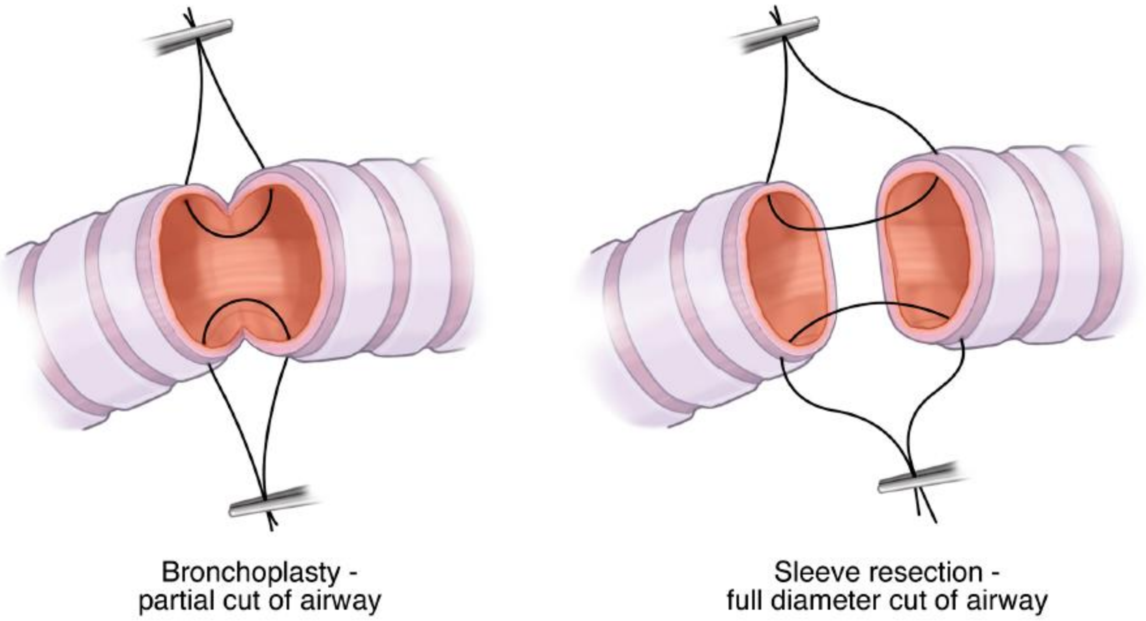

Figure 3: Bronchoplasty versus sleeve resections (Artwork by Marcia Williams).

Sleeve resections were first described in 1947 (Thomas, 1956), but there were two milestones leading to their acceptance by the Thoracic Surgery community: the tracheal resection techniques developed by Hermes Grillo (Grillo, 1965) and the advances in lung transplant techniques (Perelman and Rabinowitsch, 1970; 1976).

Sleeve resections, although technically more challenging, have been shown to be equivalent to extended resections in terms of local control and long term outcomes (Bagan *et al.*, 2005). What remains controversial is whether the rate of complications after sleeve resection, especially in the setting of neoadjuvant treatment, is higher when compared to other types of anatomic resections. Some studies have already shown the negative impact of chemotherapy and radiation treatments on the bronchial blood supply and in the bronchial anastomotic healing (Yamamoto *et al.*, 2000; Stamatis, 2008), while others, most of them with a limited number of patients included, have not confirmed a higher risk of airway complications in sleeve resection after neoadjuvant treatment (Milman *et al.*, 2009).

2. INTRODUCTION

INTRODUCTION

The development of bronchoplastic procedures could not be understood without the knowledge of the evolution of the surgical approaches to the lung, as well as tracheal resections and transplantation techniques. Also, it is the anatomy of the bronchial tree that makes it possible to perform this type of operation, taking always into consideration the relationship of the airway with the surrounding structures.

a) Development of surgical approaches to the lung

Although Thoracic Surgery was not recognized as an independent surgical specialty until World War II (Lindskog, 1957; Kittle, 2000), the development of approaches to the lung since the Thirteenth Century was related to treatment of trauma induced injuries (Lindskog, 1957; Kittle, 2000). Rolandus (also known as Roland of Parma, Italy) was the first who described the treatment of a lung herniation in 1499, something thought to be impossible until that date (Lindskog, 1957; Kittle, 2000; Walcott-Sapp and Sukumar, 2016). With the evolution of the anatomical and technological knowledge, different approaches to the pleural cavity were subsequently described intermittently and rarely (American Medical and American Association for Thoracic, 1920; Walcott-Sapp and Sukumar, 2016). Some authors would just let the lung necrose and adhere to the chest wall before removing it, while others would ligate and excise the protruding lung (American Medical and American Association for Thoracic, 1920; Brunn, 1929; Lindskog, 1957; Kittle, 2000; Walcott-Sapp and Sukumar, 2016). In the era of tuberculosis (1400-1900s in Europe and America), the need to come up with newer and more effective therapies encouraged surgeons to try new approaches to the pleural cavity (Lilienthal, 1922; Kittle, 2000).

It was Milton Anthony, founder of the Medical Academy of Georgia (USA), who in 1821 is credited with performing the first resection of the chest wall to evacuate a lung abscess (Antony, 1824). This promptly moved other colleagues to explore the idea of thoracoplasties to collapse tuberculosed lungs. Carlo Forlanini, from Pavia, was one of the biggest advocates for induced pneumothorax and collapse therapy in the treatment of tuberculosis (American Medical and American Association for Thoracic, 1920).

Similar thoracic surgery techniques used successfully in traumatic injuries and tuberculosis were used in the nineteenth century by Jules Emile Pean, a French surgeon. Pean performed the first lung resection for a tumor in Paris, France. He sutured the pleura to the lung and then removed a portion of the lung with galvanic current cautery. Afterwards, he applied carbolic acid dressings until the resection area was healed (Samson, 1940).

Comparative anatomy studies revealed knowledge of the lung anatomy and physiology and the best techniques for ligation of the hilar structures (American Medical and American Association for Thoracic, 1920; Brunn, 1929; Lindskog, 1957; Kittle, 2000). Although mortality and the rate of complications were elevated, lung resection started to be accepted for the treatment of tuberculosis, as advocated by Theodore Tuffier and Eugène-Louis Doyen in France (Tuffier, 1891; American Medical and American Association for Thoracic, 1920; Doyen, 1985).

Tuberculosis was the indication for the first reported pneumonectomy. It was in 1895 when William Macewen performed it successfully in Glasgow, removing the entire left lung of a tuberculosis patient (Macewen, 1906; Kittle, 2000; Walcott-Sapp and Sukumar, 2016).

Macewen was a Scottish surgeon. He was a pioneer in modern endotracheal anesthesia with orotracheal intubation and the performance of pneumonectomies. He was credited with brain surgery, the development of bone graft surgery, and the surgical treatment of hernia. He was also noted for his early and creative use of photographs for documenting patients' cases and for teaching surgery. He led the way for the development of other anatomical lung resections without pneumonectomy.

With the aspiration of contrast media into the bronchial tree, bronchiectasis could be diagnosed and lung resection became the operation of choice for treatment. Several lobectomies were reported by Thermisokles Gluck in Germany and by William Wayne Babcock in Philadelphia (1908) (Babcock, 1908). The 20^{th} century brought not only advances in instrumentation and anesthesia, but also important changes in antisepsis. Encouraged by the new possibilities and outcomes, Evarts Ambrose Graham, in 1925, in Saint Louis, performed the first multiple-staged pneumonectomy for bronchiectasis (Graham, 1923; Graham and Singer, 1933).

Surgery for bronchiectasis continued to develop. Famous surgeons such as Rudolf Nissen, Robert Janes, Norman Shenstone and Edward Churchill as prominent names (Churchill, 1930; Shenstone and Janes, 1932; Roberts and Nelson, 1933; Nissen, 1949; Lindskog, 1957) debated the best approach to the hilum and the ligation of the hilar structures (Brunn, 1929; Samson, 1940; Lindskog, 1957; Kittle, 2000; Walcott-Sapp and Sukumar, 2016).

Graham performed the first one stage pneumonectomy for lung cancer in 1933 (Graham and Singer, 1933). The patient was Dr. James Gilmore, a 48-year-old obstetrician-gynecologist from Pittsburgh, PA. The diagnosis had been made with liliodol bronchogram and pathology confirmed with a biopsy specimen obtained from a rigid bronchoscopy (Walcott-Sapp and Sukumar, 2016). Graham thought the treatment of lung cancer with radical pneumonectomy would be more effective than with limited resections, as had been shown in tumors of other organs (Graham and Singer, 1933; Kittle, 2000; Walcott-Sapp and Sukumar, 2016).

By 1940, most of the technical difficulties of lobectomy and pulmonary resection were solved and the principle of lung tissue conservation was developed. Streptomycin was introduced in 1945, sparking the improvement of medical treatment of tuberculosis, and a subsequent decrease in surgery for tuberculosis (Sihoe, 2014). Further animal research and wartime surgical experience with traumatic bronchial transections facilitated the development of techniques for sleeve lobectomy and bronchoplastic procedures (Kittle, 2000; Walcott-Sapp and Sukumar, 2016).

History of Bronchoplastic Resections

It was 1956 when Sir Clement Price Thomas, surgeon at the Westminster and Brompton hospitals in London, reported a patient in whom he had performed a circumferential resection of the right main bronchus for an adenoma projecting out of the origin of the right upper lobe bronchus (Thomas, 1956). The airway was closed by sewing the bronchus intermedius to the remnant of the right main bronchus. The operation was a success, and the patient was soon able to resume his work as a Royal Air Force pilot in active flying duties (Walcott-Sapp and Sukumar, 2016).

In 1952, Price Thomas, while taking care of a patient with bronchial stricture secondary to tuberculosis, performed a left upper lobe sleeve resection, managing to salvage the left lower lobe of his patient. He afterwards concluded 'that when two ends of a bronchus are sewn together they can unite in the same way as two pieces of intestine' (Johnston and Jones, 1959).

With the good results of these operations and the fast postoperative return of the patients to their duties, sleeve resection also became a suitable operation for the treatment of carcinoma of the bronchus (Johnston and Jones, 1959). After Price Thomas' reports, Phillip Allison in Oxford performed the first sleeve resection for a lung cancer (1952) (Johnston and Jones, 1959). The first published report of the use of bronchoplasty, however, is owned by Donald Paulson and Robert Shaw in Dallas, in 1955 (Paulson and Shaw, 1955). In their report, they present 18 patients who underwent sleeve resection for both benign and malignant conditions. In this article, they were the first to advocate the idea that sleeve resection had the benefit of preservation of lung parenchyma over pneumonectomy, especially in those patients with low pulmonary reserve. Following this report, they presented follow up articles (Paulson and Shaw, 1960; Deslauriers *et al.*, 2009) demonstrating that in lung cancer patients bronchoplasties could be done electively, even with compromised pulmonary function (Deslauriers *et al.*, 2009).

In 1959, James Johnston and Peter Jones (Johnston and Jones, 1959) reported a cohort of 98 lung cancer patients previously treated by sleeve resection. In that article, after reviewing the results of sleeve resections done by others and those done by them, they concluded that bronchoplasties were a safe option and that their long-term results were comparable to those obtained by other types of resection such as pneumonectomy and lobectomy.

As the trend to lung parenchymal preservation continued in the 1950s and 1960s, some technical advances were made. Grillo (Grillo, 1965), with his extensive and meticulous work in tracheal resection and reconstruction, led the way to better bronchial anastomoses. In addition, the experience with bronchial anastomoses in the development of lung transplantation (Perelman and Rabinowitsch, 1970; 1976) made sleeve resection and reconstruction part of the inventory of almost every thoracic surgeon.

In 1983, Richard Firmin presented the experience of the Brompton Hospital, in London, with a series of 90 patients who underwent sleeve resections between 1964 and 1974. The operative mortality of the series was 1 %. The most common complications were bronchial stenosis, which occurred in 6 % of patients. It was secondary to tumor recurrence in 4 % of the patients and to cicatrization in 2 %. The indication for the surgery was squamous cell carcinomas of the upper lobe (76/90) in most of the patients. Among patients diagnosed with malignancies, the 5-year survival was 71 % when the hilar lymph nodes were not affected by tumor and 17 % when they were involved. Their sleeve resection results were very similar to those results they were obtaining with pneumonectomies. They subsequently concluded that sleeve resections were a more conservative approach to treat lung cancer with similar long-term survival results to those obtained with pneumonectomies (Firmin *et al.*, 1983).

In 1984 and updated in 1986, Penfield Faber from Chicago, published one of the most extensive series of sleeve lobectomies that has been published to date. This series included 101 patients who underwent sleeve resections for lung cancer. This group described bronchial dehiscence (treated with completion pneumonectomy), empyema and bronchial stenosis among the main complications encountered. Also, they concluded sleeve resections were suitable operations for both pulmonary compromised and non-compromised patients (Faber *et al.*, 1984). In a follow up article, they increased the series to 115 sleeve resections and they described a 1.7 % operative mortality rate and a 5 % rate of technical failure, understood as anastomotic dehiscence requiring completion pneumonectomy (Jensik *et al.*, 1986). They concluded that sleeve resections, when technically feasible and when complete resection could be achieved, should be considered as the procedure of choice in patients with resectable lung cancer.

The last significant series of sleeve resections was reported by Ingolf Vogt-Moykopff from Heidelberg, Germany (Vogt-Moykopf *et al.*, 1986). In this report, published in 1986, the authors included 248 sleeve procedures, both bronchoplastic and angioplastic resections in lung cancer patients. When the resection was complete, the five-year survival rate of early stage lung cancer patients was 35 % and the perioperative (30-day mortality) rate was 9 % in bronchial sleeve resection and 5 % in combined bronchial and vascular sleeve resections. With these results, the authors concluded sleeve resections should be done more liberally, especially in lung cancer patients.

As the history of lung resections shows, since the initial days of pneumonectomy, the field of thoracic surgery has advanced considerably. In the current days, the performance of pneumonectomies has been significantly reduced in favor of other types of lung sparing resections, but it remains a suitable operation for centrally located or locally advanced tumors in carefully selected surgical candidates.

Pneumonectomy remains associated with high complication rates, especially for patients with limited pulmonary function. With these considerations in mind, bronchoplastic procedures were introduced as alternatives to pneumonectomy for patients with disease involving proximal bronchi (Paulson and Shaw, 1960).

Although initial indications for sleeve resections were for lung parenchyma-sparing purposes and for limited respiratory function candidates (Wain, 1998; Ma *et al.*, 2007), the truth is that sleeve lobectomy has become accepted for anatomically suitable tumors, regardless of pulmonary function.

Differences between bronchoplasty and sleeve resection

Bronchoplasty refers to any procedure that involves bronchial reconstruction or anastomosis to restore the bronchial lumen anatomy. The most commonly performed bronchoplasty is sleeve resection, but it can be performed after wedge resection of the airway (Narendra and Schmidt, 2018). They don't necessarily involve circumferential reconstruction or anastomosis of the airway as sleeve resections do.

Bronchoplasties have had an important role in the management of both benign and malignant conditions of the airway, allowing for maximum preservation of lung parenchyma (Bueno *et al.*, 1996; Jalal and Jeyasingham, 2000). The most commonly used bronchoplastic technique; however, is the sleeve resection (End *et al.*, 2000; Nagayasu *et al.*, 2015).

b) <u>Indications for sleeve lobectomy</u>

Sleeve lobectomy is most commonly indicated for lesions involving main or lobar bronchi (Tronc F, 2008). These lesions typically are benign to low-grade malignant neoplasms and stenosis (Wain, 1998). Carcinoid tumors are the most common low-grade neoplasm treated with sleeve resection. They account for more than 80 % of reported sleeves, followed by mucoepidermoid tumors, fibrous histiocytomas, hamartomas and adenoid cystic carcinomas (Wain, 1998). Most strictures involve traumatic or post-infectious etiologies. Sleeve lobectomy for bronchogenic carcinomas is less common, and is performed in less than 10 % of operable cases of lung cancers. In addition to the anatomic location, a sleeve lobectomy has a role when the bronchial resection margin is at risk of being affected by the tumor or in the case of peri-bronchial lymph node involvement (Wain, 1998). Sleeve lobectomy is also indicated for patients with impaired cardiopulmonary function (Suzuki *et al.*, 2000).

General indications for sleeve resection as a lung parenchyma sparing procedure include FEV1 < 50 % predicted value and DLCO < 50 % predicted value (Wain, 1998).

Any lobe can be resected with a sleeve resection; however, the most commonly performed operation is the right upper lobe sleeve resection (Suzuki *et al.*, 2000; Wright, 2006). The explanation lies in the anatomy of the right mainstem bronchus and its anatomic relation to the long bronchus intermedius (Wain, 1998; Tronc F, 2008). The left upper lobe is the second most common site for sleeve lobectomy. A left upper lobe sleeve resection is technically more challenging due to presence of the aorta and left recurrent nerve (Wain, 1998; Tronc F, 2008).

c) Contraindications of sleeve lobectomy

Patients with advanced lung cancer, specifically T4 disease, are typically poor candidates for sleeve lobectomy. Involvement of the pleura, superior vena cava, atria, or transverse aortic arch are also considered contraindications (Faber, 1995). Relative contraindications include invasion of the pericardium, phrenic nerve, vagus nerve, and diaphragm (Faber, 1995). The presence of N1 or N2 nodal disease does not contraindicate sleeve lobectomy, but N2 significantly impairs long-term outcomes due to its association with systemic recurrences (Mehran *et al.*, 1994; Terzi *et al.*, 2002; Kim *et al.*, 2005; Yildizeli *et al.*, 2007; Schirren *et al.*, 2011; Berry *et al.*, 2014). Sleeves are generally performed in this setting when, in order to achieve an appropriate oncologic resection, the alternative is a pneumonectomy. If the patient is diagnosed with N2 nodal disease and it is not clear if he/she would tolerate a more extended resection than a bronchoplasty, definitive medical treatment should be carefully considered.

d) Patient selection for sleeve resection

Flexible bronchoscopy is the most important diagnostic step in identifying potential candidates for sleeve lobectomy (Wain, 1998). The key finding is endobronchial tumor extension from segmental bronchi to the lobar or main bronchial orifice (Tronc F, 2008). Bronchoscopy also allows for tissue biopsy, which is particularly important if a malignancy is suspected (Faber, 1995). Mucosal biopsy both proximal and distal to the lesion should be attempted to assess tumor extension when feasible (Faber, 1995). Detection of decreased bronchial wall motion during respiration may be a sign of peri-bronchial tumor infiltration, and this requires further radiographic evaluation to assess for tumor extent and its relationship to the airway (Rendina *et al.*, 2002). Radiographic studies play a supplemental role to bronchoscopy in identifying potential surgical candidates. Computed tomography (CT) allows for better appreciation of disease size, extent, and location relative to mediastinal and thoracic structures (Tronc F, 2008). Magnetic resonance imaging (MRI) can help interpretation of ambiguous CT findings. If suspicious mediastinal lymph nodes are identified, further investigation via PET, EBUS or mediastinoscopy is warranted as N2 disease may indicate the need for pneumonectomy or neoadjuvant treatment (Faber, 1995; Yildizeli *et al.*, 2007; Deslauriers *et al.*, 2009). General pre-operative considerations for other pulmonary resections should also be considered for sleeve lobectomy candidates.

e) Anatomy of the airway

The lung is a complex anatomic structure, isolated by the visceral pleura from the surrounding structures but intimately related to them. An organizational outline of the anatomy of the lung can be helpful:

- Anatomy of the airway is sub-divided into:
    - The proximal airway, including the supraglottic, glottis and infraglottic areas. This portion of the airway is outside the focus of this thesis.

- The distal airway, which includes the trachea, the mainstem bronchi and multiple bronchial divisions (Tsuchiya, 2008).

  - Trachea: The trachea is a cartilaginous and fibromuscular structure extending from the cricoid cartilage (located approximately at the level of the sixth cervical vertebra) to the carina (located at the level of the fifth thoracic vertebra). Its length varies depending on the age of the patients. It ranges from 3 cm at birth to up to 10-12 cm in adults (one third is extra thoracic in the throat, and two thirds are intrathoracic). The tracheal diameter is also variable, and it goes from 13 to 25 mm in males to 10 to 21 mm in females (Grillo, 1965).The trachea consists of 4 different layers: the mucosa, the submucosa, the cartilage in the front or smooth muscle in the posterior wall, and the adventitia.
  - Bronchi: The bronchi can be divided into two types: extrapulmonary (outside the pleural envelope) and intrapulmonary (inside the pleural envelope) (Tsuchiya, 2008). Both mainstem bronchi and the bronchus intermedius are extrapulmonary, with important dissection implications. They are structurally similar to the trachea, with horse-shoe shaped cartilaginous rings and a posterior membranous portion. The intrapulmonary bronchi have a less clear structure than the extrapulmonary ones. They consist of irregularly shaped cartilage plates distributed around the bronchus in a paving stone configuration (Tsuchiya, 2008).These differences should be considered when reconstructing the airway, as failure to do so would have important consequences in the creation of the anastomosis. Shape mismatch is another important factor to consider when suturing the two bronchial edges together (Hollaus *et al.*, 2001).

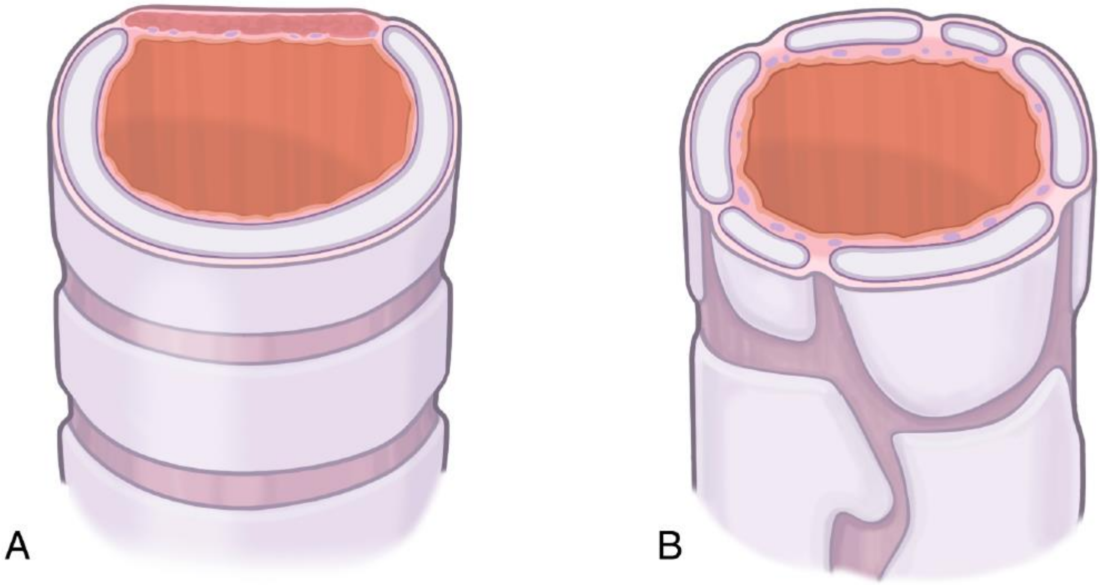

Figure 4: Differences between extrapulmonary airway (A) and intrapulmonary airway (B). (Artwork by Marcia Williams).

- The vascular supply to the trachea and bronchi is characterized by a wide variability (Tsuchiya, 2008). It is important to know these variations as every effort to preserve this vasculature should be made, especially in sleeve resections. The bronchial blood supply depends on branches arising from the inferior thyroid arteries, the intercostal arteries, and the bronchial arteries. These arteries, except for the branches of the thyroid artery, tend to form a very rich vascular anastomosis in the subcarinal area. This peri-bronchial plexus follows the bronchi into the lung parenchyma and supplies blood to the visceral pleura and the walls of the pulmonary arteries and veins (vasa vasorum).

  Bronchial arteries originate from the thoracic aorta, at the level of T5 and T6 (Walker *et al.*, 2015). The left bronchial arteries normally arise directly from the aorta. Right bronchial arteries can originate from the aorta, but most of the time, they share a common origin with another artery, normally an intercostal artery (Morita *et al.*, 2010). The most frequent pattern is a shared origin of the right bronchial artery and an intercostal artery (52 % of cases at CT angiography), a finding known as a common intercostal-bronchial artery trunk. This trunk tends to originate from the anteromedial or posteromedial thoracic aortic wall and runs superiorly, giving one or more intercostal arteries before continuing inferiorly as the bronchial artery (Cauldwell and Siekert, 1948; Pump, 1963; Morita *et al.*, 2010; Ziyawudong *et al.*, 2012).Less frequently, the left and right bronchial arteries share a common origin (32 % of right and 36 % of left bronchial arteries at CT angiography), a finding known as the common trunk of both bronchial arteries. The common trunk of both bronchial arteries normally originates from the anterior-lateral thoracic aortic wall (Morita *et al.*, 2010).

A study performed in 150 cadavers described up to nine types of variations in bronchial artery anatomy (Cauldwell and Siekert, 1948). The most common variation, type 1 (40.6 % of cases), consisted of one right bronchial artery arising from a common intercostal-bronchial artery trunk and two left bronchial arteries. Type 2 was the second most common pattern (21.3 %), consisting of a single bronchial artery on each side, with the right bronchial artery originating from a common intercostal-bronchial artery trunk. Type 3 was the third most common pattern (20.6 %), consisting of two bronchial arteries on each side, with one of the right bronchial arteries originating from a common intercostal-bronchial artery trunk. Types 4–9 were other variations of bronchial arteries, with up to four arteries on each side. Although type 1 was the most common anatomic pattern in the original study (Cauldwell and Siekert, 1948), other authors have reported type 3 to be the most common variant (Liebow, 1965; Kasai and Chiba, 1979).

- Lung parenchyma: It is composed of five lobes divided into 19 segments and its main function is the gas exchange at the alveolar level.

Both lungs are divided into lobes. Each lobe is also divided into segments. The segments are an important unit of the lung for the close relationship they have with the segmental bronchi. The right lung consists of 10 segments: 3 located in the right upper lobe (apical, anterior and posterior), 2 forming the right middle lobe (medial and lateral), and 5 in the right lower lobe (superior, basilar medial, basilar anterior, basilar lateral, and basilar posterior). The left lung is formed by 9 segments: 4 located in the left upper lobe (apical, posterior, anterior, and lingula) and 5 in the left lower lobe (superior, basilar anterior, basilar medial, basilar lateral, and basilar posterior).

The lungs are surrounded by the intimately attached visceral pleura. In the absence of effusion or pneumothorax, the visceral pleura is in contact with the parietal pleura and the lateral surface of the mediastinum. The visceral pleura invaginates into the lungs to form the intra-lobar fissures. There is one minor and one major fissure in the right lung and one major fissure in the left lung. The pleura also forms the inferior pulmonary ligament, which extends inferiorly along the mediastinum from the inferior pulmonary vein to the diaphragm.

- Pulmonary vasculature: There is a close relationship with the bronchus and the pulmonary vessels. These consist of the pulmonary arteries and veins. The pulmonary artery arises from the right ventricle and divides into 2 branches. The right pulmonary artery runs posterior to the aorta and the superior vena cava. It lies anterior to the right tracheobronchial angle, lateral to the atria and anterior and inferior to the right mainstem bronchus. It gives branches that supply the upper lobe and runs anterior to the bronchus intermedius. The left pulmonary artery originates anterior to the left mainstem bronchus and the secondary carina. These are important spatial relationships when planning the surgical approach and the extent of the resection (Tsuchiya, 2008).

f) Surgical technique

The standard approach for sleeve lobectomy is through a posterolateral thoracotomy or a muscle-sparing anterolateral incision (Faber, 1995; Nagayasu *et al.*, 2015). Once the chest has been opened, pre-operative assessment should be conducted by visualization and palpation of the hilum, lung parenchyma, pleural surfaces, lymph nodes, and other surrounding structures. Specifically, M1a disease with pleural carcinomatosis or bulky disease at the hilum requiring pneumonectomy would preclude sleeve resection. If no contraindications are encountered, mobilization of the lobe should be started.

The surgery begins at the hilum with a circumferential cut of the visceral pleural reflection onto the mediastinal pleura. This includes mobilization of the inferior pulmonary ligament. This is followed by careful dissection of the superior and inferior pulmonary veins to isolate them from surrounding structures. Furthermore, the superior pulmonary vein is dissected more distally to clearly identify the upper lobe venous branches from the right middle lobe vein. Prior to division of the venous branches, the pulmonary artery trunk and distal lobar and segmental branches are comfortably dissected from the nodal tissue and identified. Dissection should be carried out carefully preserving the bronchial vessels that will supply the remaining distal lung parenchyma. Once lobar arterial supply has been adequately identified and transected, the corresponding pulmonary veins should similarly be divided. Incomplete fissures should be divided at this time as well.

Once the hilar structures have been mobilized, and the final decision has been made in favor of a sleeve resection, then the vascular structures are divided. Generally, we prefer to divide the venous drainage of the lobe first, which then further exposes the slightly more posterior arterial branches. The arterial branches are then divided, fully exposing the bronchial structures.

Airway dissection and transection should be completed only after the rest of the hilar structures have been divided. Most anastomotic complications result from disruption of mucosal blood flow to the bronchi; therefore, careful consideration should be given to the bronchial blood supply which is located within the peri-bronchial tissue. Unnecessary lymph node dissection should be avoided when possible, as this may also compromise bronchial blood supply. The presence of a single right bronchial artery makes these considerations particularly important when performing right sided sleeve lobectomies. To preserve the bronchial artery blood supply, the proximal bronchi should be circumferentially divided with a sharp knife close to the origin of the main bronchus.

Although the anatomy of the bronchial arteries varies considerably, at this point it is possible to identify and try to preserve those arteries.

Most commonly, bronchial arteries on the right run both posteriorly and anteriorly in the tracheobronchial angle. On the left, they run posterior to the membranous part of the mainstem bronchus. They tend to bifurcate and to form a plexus that connects to both the pulmonary arterial tree and branches of the other bronchial arteries. Thus, the bronchial arteries connect to both the pulmonary vasculature system and the systemic system. It is this phenomenon that allows lung transplantation without re-implantation of the bronchial arteries. The transplanted lung allograft obtains perfusion of the donor airway through reverse flow from the pulmonary vasculature to the donor bronchial arteries.

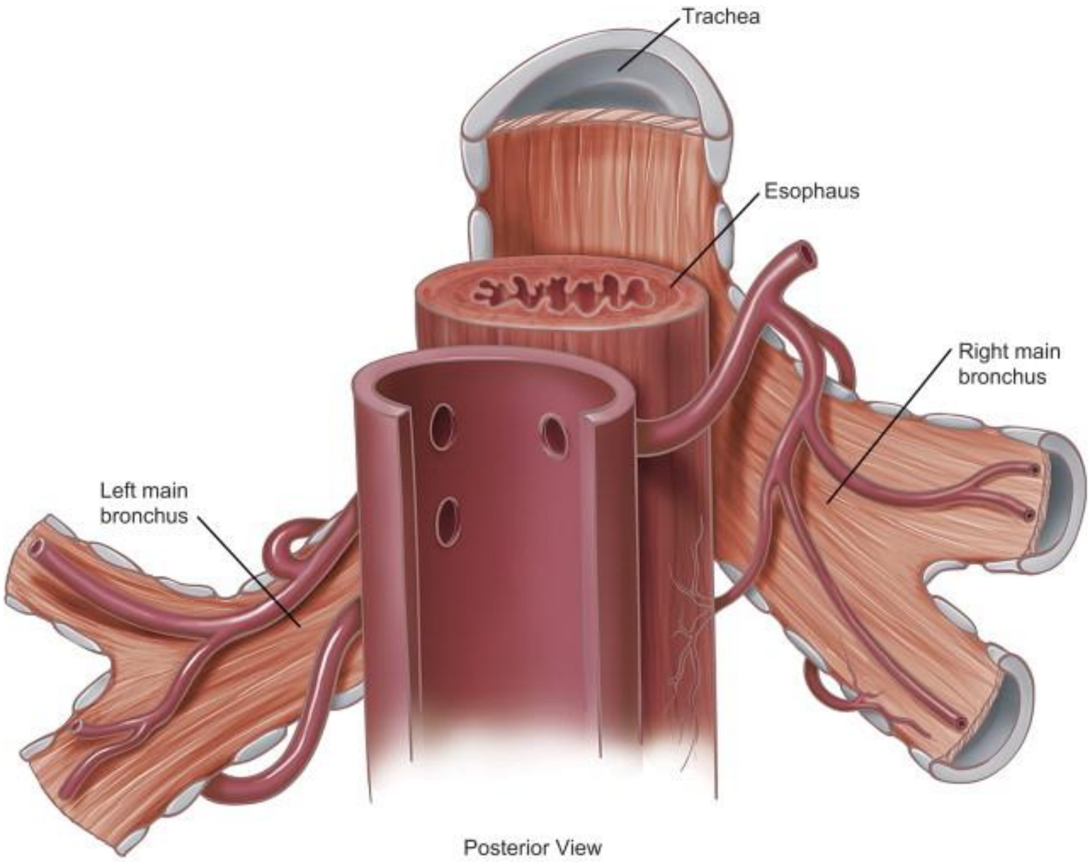

Figure 5: Bronchial arteries anatomy (Riquet, 2007).

Distal bronchotomy should be made in a similar fashion at the level of the segmental bronchi, which is the location of a rich pulmonary and systemic arteriolar anastomoses. Frozen histological evaluation of bronchial resection margins is recommended before performing the final anastomosis. Tumor-free margins of at least 5 mm for high-grade carcinomas and 3 mm for low-grade lesions are considered minimal requirements. If these margins cannot be obtained, a more extended pulmonary resection should be performed (Wain, 1998). Carcinoma in situ and less severe forms of dysplasia at the margins, however, do not require additional resection, as these findings have not been associated with higher recurrence rates (Wain, 1998).

The proximal and distal airways should be anastomosed in an end-to-end fashion. The anastomosis should be completed under minimal tension and with minimal luminal size mismatch. If these goals are achieved, there is no limit in regard to the maximum distance that can be anastomosed. The maximal distance of a sleeve resection is a right lower lobe to the proximal right main bronchus (about 5 cm) or the left lower lobe back to the left main bronchus (5 to 7 cm). Tension can be typically minimized releasing the inferior pulmonary ligament. When further mobilization is necessary, an infrahilar pericardial release may be performed by dividing the pericardium below the inferior border of the inferior pulmonary vein in a U-shaped cut (Figure 6)(Wright, 2006; Wadell and Uy, 2015).

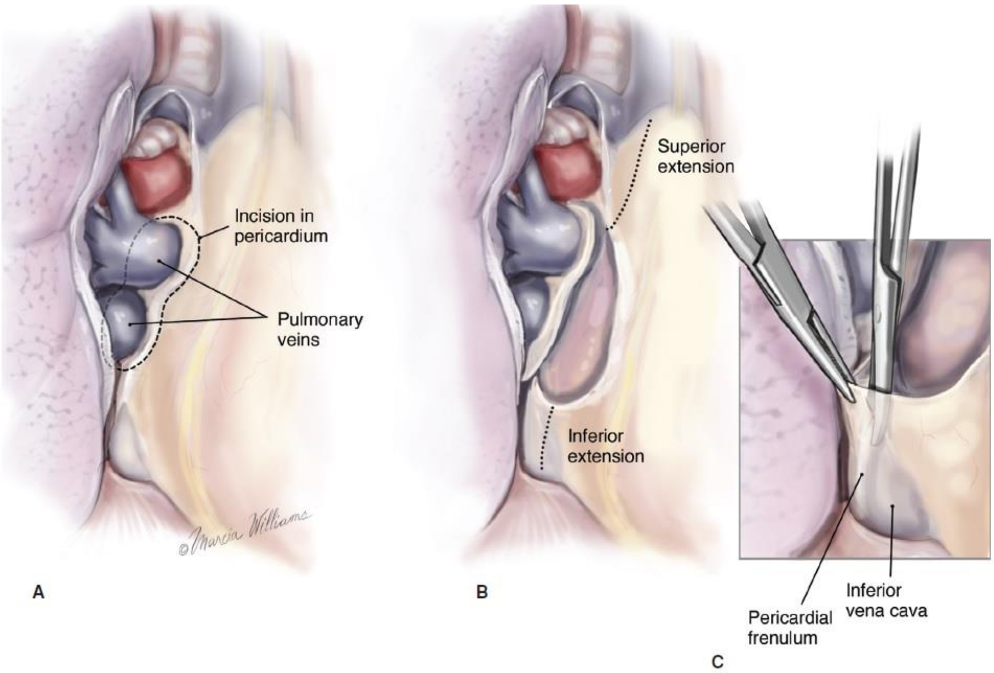

Figure 6: Pericardial release (Wadell and Uy, 2015).

Most surgeons perform the bronchial anastomosis in an interrupted fashion, however, an uninterrupted technique is also acceptable (Bayram *et al.*, 2007; Palade *et al.*, 2015). Short and long-term results are comparable in both human series (Kutlu and Goldstraw, 1999; Bayram *et al.*, 2007) and canine models (Lowson, 1893). If possible, the use of a layer-to layer orientation, sewing membranous portion to membranous portion and cartilaginous portion to cartilaginous portion, should be utilized as it minimizes potential inconsistencies in luminal architecture (Hollaus *et al.*, 2001). Furthermore, it prevents kinking of the distal airway with subsequent retained secretions in the postoperative period.

Ideally, the anastomosis should be begun in the region most difficult to visualize. Most authors use sutures at both ends of the airway where the posterior membrane meets the bronchus to align the rings. These traction sutures should be placed both in the proximal and distal transected airway not only to prevent torsion and mal-positioning but also to release further tension in the remaining suture line. Absorbable 3-0 or 4–0 sutures (polyglactin or Vicryl^{TM}) are traditionally used since the recommendation by Dr. Hermes Grillo (Grillo, 1965). The knots are placed outside the bronchial lumen. This suture is chosen to decrease the rate of stricture and granuloma formation (Wright, 2006). On the other hand, if a continuous suture is preferred, polydioxanone (PDS^{TM}) or polypropylene (Prolene^{TM}) monofilament sutures are also broadly used (Kutlu and Goldstraw, 1999; Palade *et al.*, 2015).

To account for discrepancies in bronchial lumen diameter, there are several techniques that can be utilized. One relatively simple approach is the application of space-suturing to stretch the smaller lumen to better approximate the larger (Wright, 2006). Other methods include the excision of a small wedge of tissue and plication of the larger bronchus (Bayram *et al.*, 2007) or telescoping techniques. Telescoping techniques should be reserved for scenarios in which significant mismatch exists among diameters between proximal and distal bronchi (Hollaus *et al.*, 2001). The primary limitation in telescoping methods is the remaining shelf of bronchial tissue, which tends to protrude into the bronchial lumen. This tissue may necrose or serve as a focus for secretion retention or infection.

When possible, the anastomosis should be covered with pedicled tissue to prevent bronchopleural and bronchovascular fistula formation. The use of pedicled tissue is also thought to aide in the formation of systemic blood flow to the anastomosis (Klepetko *et al.*, 1999). Easily mobilized pedicled tissues include intercostal muscle flaps or pericardial fat pads.

Special care in preparing and handling the flaps should be focused on preserving their blood supply. The pedicle is the intercostal artery and vein for intercostal muscle flaps. The pedicle is the superior or middle branch of the pericardial-phrenic artery for upper pericardial fat pads or the musculophrenic branches of the internal mammary artery in the case of an inferior pericardial fat pad (Anderson and Miller, 1995). Alternate options include the thymus (whose arterial blood supply arises from the internal thoracic artery and the inferior thyroid arteries and the venous drainage is by the thymic vein to the innominate vein) (Raj and Pillay, 2015), omentum (vascularized by the gastroepiploic artery that is on the same side as the lung resection) (Mathisen *et al.*, 1988; Khaghani *et al.*, 1994; Boulton and Force, 2010), and pleura (Wright, 2006).

Before closing the chest, it is recommended to perform surveillance flexible bronchoscopy to evaluate for luminal continuity at the anastomosis. Even the slightest mucosal inconsistencies predispose for stricture formation (Tronc F, 2008). All residual secretions and blood should also be removed from the airway at the time of final bronchoscopy (Tronc F, 2008).

Although sleeve lobectomy and bronchoplastic procedures have traditionally been performed through a posterolateral thoracotomy, some authors have described its feasibility by minimally invasive approaches or VATS (Video-Assisted Thoracic Surgery) (Mahtabifard *et al.*, 2008; Gonzalez-Rivas *et al.*, 2013; Zhou *et al.*, 2015; Ma and Liu, 2016) and RATS (Robot-Assisted Thoracic Surgery) (Cerfolio, 2016; Lin *et al.*, 2016; Pan *et al.*, 2016; Gu *et al.*, 2017).

The number of reports of minimally invasive sleeve resection in the literature is growing. The largest series was published by Zhou et al (Zhou *et al.*, 2015) in 2015. In that study, including 10 sleeve resection patients, the authors concluded that sleeve resection could be performed safely by VATS with similar short and long-term results when compared to thoracotomy.

In 2016, Robert Cerfolio (Cerfolio, 2016) reported the early results of 8 patients who underwent RATS sleeve resection, with no 30 or 90-day mortality and without bronchial anastomosis complications at 6 months. He concluded it was a feasible and safe alternative to thoracotomy in experienced hands.

In that year, too, Pan et al (Pan *et al.*, 2016) reported 21 cases of robotic sleeve resections, both bronchial and vascular. Although it was an initial experience, they concluded it was feasible and with acceptable long-term results.

g) Types of sleeve resections and specific considerations

1. Right upper lobe sleeve resection (Mentzer et al., 1993; Mentzer, 1998; Ibrahim et al., 2013):

This sleeve resection can be performed either through a lateral (4^{th} rib interspace) or through a posterolateral thoracotomy (5^{th} rib interspace), given the anatomy of the right upper lobe bronchus. The dissection in these cases must be carefully planned and completed. Once in the chest, a detailed and complete exploration should be made, including the chest wall and the entire lung surface. In case any signs of metastatic disease are encountered, there would be no indication for proceeding with the sleeve resection. Next, the hilum is addressed, and the pulmonary artery is dissected out and isolated. A right-angle clamp or other type of dissector should be easily placed behind the artery, and a vascular loop or cord tape is passed around it.

The pulmonary artery dissection is an important step. If careful and complete dissection is not achieved, the next steps will become more difficult and unsafe. If any concern exists regarding the ability to obtain good proximal control of the artery, we recommend opening the pericardium and obtain control of the proximal right pulmonary artery just lateral to the superior vena cava.

Afterwards, the main-stem bronchus and the right upper lobe bronchus should be dissected free from the surrounding structures. Where the right upper lobe bronchus and the bronchus intermedius bifurcate lays the sump node. This node drains all three lobes of the right lung. Removing this node will open the field for subsequent dissection of the bronchus intermedius. Running medial and inferior to this node is the superior segmental branch of the pulmonary artery.

The right upper lobe vein is ligated. The ascending truncus branch of the pulmonary artery is ligated. The fissure can be completed at this point with sequential firings of the stapler. The remaining posterior recurrent segmental branch of the pulmonary artery can be transected.

Now, the mainstem bronchus is sharply divided proximal to the takeoff of the right upper lobe bronchus. It is of crucial importance that division of the airway is perpendicular to its long axis. Failure to do so will result in a more difficult anastomosis later. In a similar way, the bronchus intermedius is divided just distally to the right upper lobe takeoff.

Different techniques and tricks have been used to achieve the best possible perpendicular cut, from placing the knife blade in a right-angle clamp, to starting the cut with the knife and finishing it with Metzembaum scissors, to assure the desired angle is achieved.

Frozen-section margins are mandatory, as they will determine if there is a need for further airway resection, including a possible conversion to a pneumonectomy. If the distal margin is positive for tumor, expanding the resection to include the middle lobe, or middle lobe and superior segmental bronchus while preserving at least the basilar branches to the right lower lobe bronchus may allow the surgeon to perform a bilobectomy instead of a pneumonectomy. If it is the proximal margin that is positive for tumor on frozen section, a resection of the carina with anastomosis of the right middle and lower lobes can be considered.

After assuring appropriate negative margins, the anastomosis of the two edges of the bronchus is performed. The remaining right mainstem bronchus is reunited with the bronchus intermedius. It is essential that the anastomosis is performed under no tension, and careful attention should be paid to avoid torsion or kinking of the reconstructed bronchus. To assure no tension of the anastomosis, several maneuvers have been described. These include, systematically releasing the inferior pulmonary ligament. When tension is still present, dissection of the subcarinal and paratracheal area will gain some proximal relaxation to perform the anastomosis. In case tension is still observed, an infrahilar pericardial release (previously described) can be performed to try to bring the edges together without force.

Because of the different calibers of the mainstem bronchus and the bronchus intermedius, the size discrepancy between them should be corrected with careful suture placement. Both interrupted and running techniques offer good results, and the choice of one or the other depends mostly on the surgeon's preferences. The distance of the sutures in one bronchial side should be the same as that in the other if the airways are approximately the same size. A good rule to follow is to place the sutures 2 to 3 mm apart and 2 to 3 mm back from the cut edge of the bronchus. If the airways do not match in size, placement of the sutures closer on the smaller bronchus and slightly further apart on the larger bronchus can correct the size discrepancies and assure an air-tight anastomosis.

After the anastomosis is completed, it is checked under water or saline (as this allows visibility of an air leak) and a Valsalva maneuver is performed by the anesthesiologist. If no air leak is detected, the authors proceed with placement of a buttress to the airway anastomosis.

Reinforcement of the anastomosis with a flap to provide a source of new vasculature to facilitate healing is controversial, though some surgeons do it routinely. This flap is not intended to produce a tight anastomosis, but to provide a source of vasculature to facilitate healing of the partly devascularized bronchus and prevent its breakdown and separate the nearby pulmonary artery from the bronchus. Pleural, mediastinal or azygous vein flaps can be used, based on the surgeon's choice. Finally, the chest tube is left in place and the incision is closed. I highly recommend postoperative bronchoscopy at the end of the procedure to clear retained secretions distal to the anastomosis. Most patients can be extubated in the operating room.

2. *Right middle lobe sleeve resection (Mentzer et al., 1993; Isbell and Jones, 2011):*

As noted, the right upper lobe sleeve resection is the classically described procedure. A right-middle-lobe sleeve resection is uncommon for the technical challenges it carries. The technique is similar to that described for the right upper lobe sleeve resection but with the attention centered in the middle lobe vasculature and airway structures. However, it should be noted that in all the described resections, proximal control of the arterial blood supply is essential. Accordingly, isolation of the pulmonary artery descending truncus is performed in almost all cases.

The challenges of the right middle lobe sleeve resection are secondary to the anatomical relationships of its airway and its blood supply. In the middle lobe, the vein is anterior to the airway, and the pulmonary artery branches are located behind the bronchus. This makes the vasculature less accessible. Also, division of the distal airway is a critical step because the superior segment bronchus arises just opposite to the middle lobe bronchus. It may be difficult to preserve the superior segmental bronchus if the appropriate angle of division of the airway is not achieved. The transection of the proximal bronchus intermedius needs to be angled too, because failure to do so will prevent a well size-matched anastomosis. Due to this airway caliber mismatch, the right middle lobe sleeve resection has been considered technically more challenging than other resections, leading in multiple occasions to a right lower bilobectomy with preservation of the right upper lobe.

3. Left upper lobe sleeve resection (Mentzer et al., 1993; Sundaresan, 1998; Isbell and Jones, 2011):

As with the right-sided resection, proximal control of the pulmonary artery is obtained first. The anatomic characteristics of the pulmonary artery on the left side, being shorter, with an early takeoff of the anterior segmental branch and running around the left mainstem bronchus may make proximal control more challenging.

Most of the steps are similar to the right upper lobe sleeve resection. First, the posterior aspect of the fissure is completed with a stapler and all the anatomic structures are identified. It is critical at this point to avoid injuring the superior segmental branch of the pulmonary artery, which runs in this area. The vein and the artery branches are divided. The bronchus is divided proximally and distally to the takeoff of the left upper lobe bronchus.

Special care is needed in the distal airway division, because the superior segmental bronchus takeoff occurs a short distance from the left upper lobe bronchus takeoff. A tape around the bronchus helps to delineate these relationships. The rest of the steps are performed as previously described.

4. Left lower lobe sleeve resection (Gonzalez-Rivas et al., 2013; Galetta and Spaggiari, 2017):

This is one of the most technically challenging sleeve resections given the particular relationship of the left mainstem bronchus and the pulmonary artery.

The first step is to divide the inferior pulmonary ligament and the posterior mediastinal pleura to gain access to the posterior hilum. Circumferential divisions of the visceral pleural to mediastinal pleural reflection is helpful to free up all of the hilum. The pulmonary artery is identified, dissected and controlled at the fissure. The superior segmental and basilar segmental branches of the pulmonary artery can be stapled at this point. Lymph node dissection of the subcarinal space will greatly help in order to gain proximal control of the airway. The airway needs to be transected proximally and distally following the principles stated above. Special attention should be given to the retraction of the pulmonary artery to the upper lobe when performing the anastomosis, as the artery and the pericardium can obstruct the field.

5. *Proximal airway resection (carina and distal trachea) (Grillo, 1965):*

Performing a resection of the proximal airway (carina and distal trachea), always requires a sleeve resection. To begin resection of the distal trachea or carina, a bronchoscopy is routinely performed to help surgical planning.

The incisions described have been multiple, from sternotomy to left and right sided posterolateral thoracotomies, but all of them aim to provide the best possible surgical field to obtain a tension free anastomosis.

Again, achieving good exposure and careful dissection of all the anatomic structures becomes mandatory for a successful resection. On the left side, this begins with mobilization of the left pulmonary artery and aortic arch. The ligamentum arteriosum can be divided and this greatly improves the visualization of the carina and distal trachea. Special attention is required to identify and preserve the recurrent laryngeal nerve. On the right side, the surgical approach begins with the dissection of the carina and mobilization of the right pulmonary artery and bronchus.

Because of the delicate vascular supply to the distal trachea, careful mobilization must be done while preserving the small vessels in the trachea-esophageal groove. Just the necessary portion of the airway should be dissected. Normally, this is 3 to 4 mm around the pretracheal space, where division of the trachea takes place.

Of note, traditional single-lung ventilation is challenging once the airway has been transected. To facilitate continued ventilation, a sterile circuit, with an armored endotracheal tube, is passed onto the field. Operative planning is crucial at this time, as communication with the anesthesia team should be close and clear. The JET ventilator can be used, too, but there are several disadvantages to its use. First of all, as the airway is open, it is not possible to stablish positive end expiratory pressure (PEEP), making difficult to ventilate obese patients or patients with reduced pulmonary compliance (Biro, 2010). Likewise, it is not possible to measure appropriately the peak inspiratory pressure and end-tidal carbon dioxide, leading to hypercapnia, dynamic hyperinflation, barotrauma and hypothermia (Young, 1989; Myles *et al.*, 1997; Fernandez-Bustamante *et al.*, 2006).

There is a growing experience of using Extra-Corporeal Membrane Oxygenation (ECMO) support during this portion of the operation with an open airway.

The most commonly performed proximal airway procedure is the resection of the left main bronchus without lung tissue removal, and anastomosis of the distal trachea to the left main bronchus in an end-to-end fashion. The same anastomotic principles that we have previously described under the right upper lobe sleeve resection apply to this operation, as well. The right lung is included in the airway again with an end-to-side anastomosis. This anastomosis can be performed to the distal trachea or to the left mainstem bronchus (depending on available length), in a tension-free manner.

This anastomosis is performed in a similar interrupted suture fashion, generally with 3-0 Vicryl^{tm}. Of note, the distal tracheal transection and the proximal bronchial transection should be performed at the level of the cartilaginous rings to provide enough strength for the anastomosis. As described previously, the anastomoses are traditionally wrapped with a pedicled flap before closure of the chest (Figure 7).

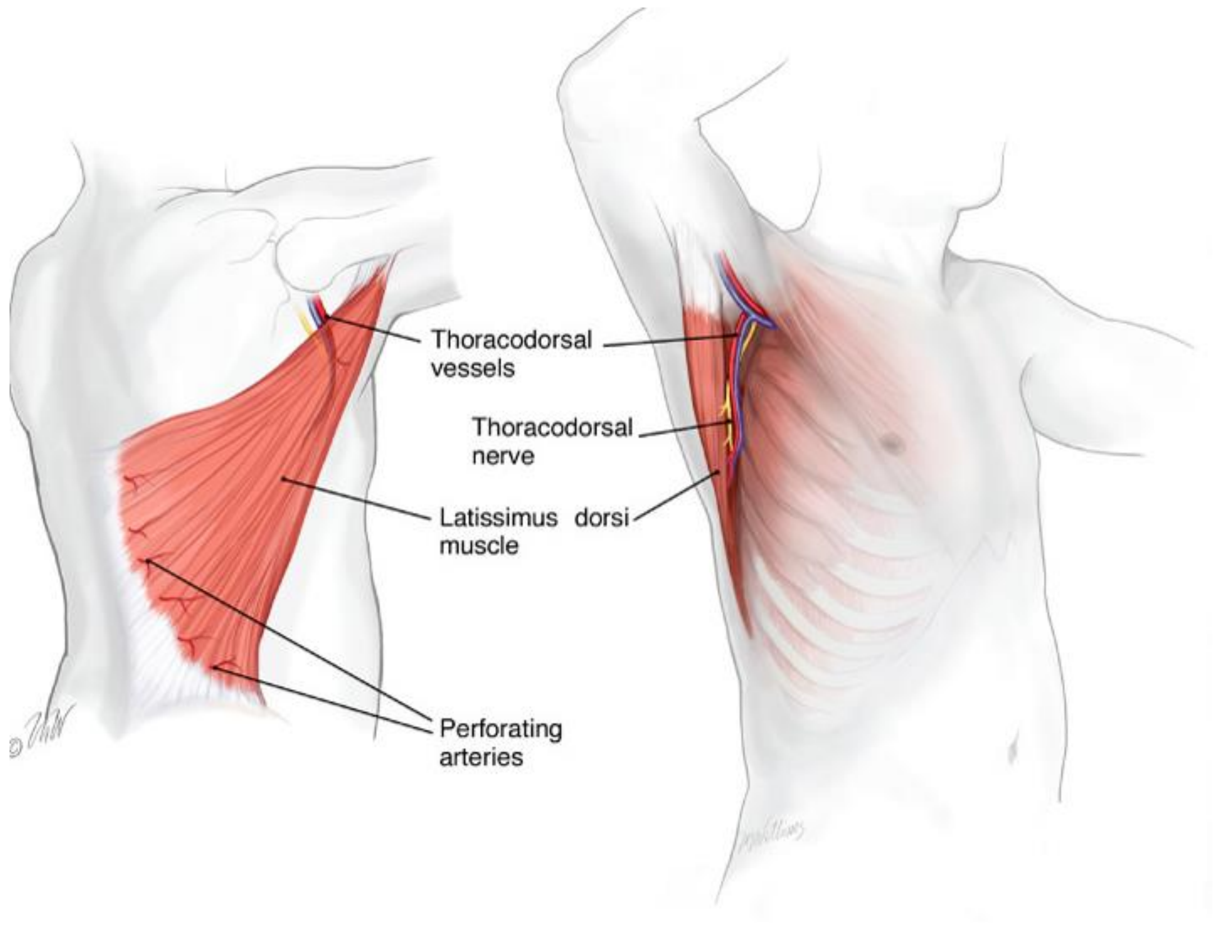

Figure 7: Latissimus dorsi pedicled muscle flap (Orgill *et al.*, 2015).

Role of ECMO in airway resection

ECMO is being used with more frequency in complicated airway resections and reconstructions. It allows the anesthesia team to maintain an appropriate gas exchange at the same time that ensures an unobstructed operative field (eliminating the need for cross field ventilation) and facilitates precise surgical dissection. It is currently used for both ventilator and hemodynamic support in lung transplantation, airway resection and reconstruction and extended tumor resections (Hoetzenecker *et al.*, 2017).

Some authors (Hoetzenecker *et al.*, 2017) consider ECMO pre-emptively in all surgical candidates with critical airway problems or resections. They use it routinely when complete airway occlusion or prolonged cross-field ventilation is anticipated. The most important part of these complex airway reconstructions is an optimal surgical exposure with adequate control of the patient's ventilation, and ECMO can facilitate both.

There are different available configurations:

1) Veno-venous (V-V) ECMO: It is the preferred modality for airway resections. It offers complete pulmonary function support with appropriate CO_2 exchange and oxygenation. Its main advantage when compared to veno-arterial support (V-A) is the decreased risk of complications related to arterial cannulation, such as bleeding, pseudoaneurysms, ischemia of the limbs and embolic episodes (Jacobs *et al.*, 1997; Lorusso *et al.*, 2016). The most common configuration is femoral-jugular with two cannulas (Hoetzenecker *et al.*, 2017).
2) Single-cannula V-V ECMO: One of the most remarkable advances in the ECMO field has been the development of double-lumen cannulas that allow single vessel access instead of femoro-femoral or femoro-jugular configurations. Increased experience with these cannulas after lung transplantation has allowed their introduction in airway surgery too (Reeb *et al.*, 2011; Gothner *et al.*, 2015). Its main disadvantage is that the placement of the cannula in the right atrium requires either fluoroscopy or a transesophageal echocardiogram to avoid complications such as perforations (Johnson *et al.*, 2014).
3) Veno-arterial ECMO: In contrast with V-V ECMO, it also provides hemodynamic support. This can become of crucial importance in

emergencies, for example, when an airway occlusion has led to hemodynamic compromise. It also facilitates heart retraction and mobilization in complex cases of airway reconstruction. Its disadvantage is that it is more invasive than the V-V approach and it has been associated with an increased number of complications like neurological events (embolic episodes, infarction, and hemorrhage) and vascular complications (dissections, limb ischemia, aneurysms and pseudoaneurysms). Another important consideration is that femoro-femoral A-V ECMO sometimes is unable to provide adequate central oxygenation in patients with high cardiac output.

V-V ECMO is, thus, the configuration of choice for airway resections, as it can fully support the patient's ventilatory function with either one or two cannulas (Ko *et al.*, 2015). For complex carinal reconstructions, a central V-A ECMO approach is preferred if extensive manipulation of the heart and the great vessels is required to assure adequate visualization (Lang *et al.*, 2014).

The main disadvantages that were previously reported with ECMO, such as bleeding and distal tumor cell spread, have been overcome by recent technological advances. In the new ECMO circuits, the risk of bleeding can be minimized using only partial heparinization (with goal activated clotting times of 160-180 seconds) and the risk of tumor cell spread has become negligible, as ECMO is a closed circuit and the suctioned products can be left unused (Hasegawa *et al.*, 2002).

Since 2015, when the first report of the use of ECMO in airway reconstruction at the Toronto General Hospital was published (Ko *et al.*, 2015), several authors have assessed the utility of ECMO in complex oncologic and benign airway resections (Horita *et al.*, 1996; Keeyapaj and Alfirevic, 2012; Lang *et al.*, 2014; Wang *et al.*, 2014).

6. *Lymph node dissection in sleeve resection*

Although most authors (Wain, 1998; Wright, 2006) recommend to avoid excessive lymph node dissection to avoid bronchial devascularization, it has been extensively established that there is a relationship between advance nodal status (N2 disease) and decreased long term survival after sleeve resection (Rea *et al.*, 1997; Tronc *et al.*, 2000;

Fadel *et al.*, 2002; Yildizeli *et al.*, 2007; Rea *et al.*, 2008; Deslauriers *et al.*, 2009). For this reason, if invasive nodal staging has not been performed preoperatively, it becomes mandatory to do so before proceeding with the sleeve resection (Faber, 1995; Yildizeli *et al.*, 2007; Deslauriers *et al.*, 2009). In case residual N2 disease is found at this stage, consideration for pneumonectomy or medical treatment instead of sleeve resection is prudent.

h) <u>Outcomes of sleeve resections</u>

Overall survival following sleeve lobectomy for patients with Non-Small Cell Lung Cancer (NSCLC) ranges from 39 %–53 % at 5 years and 28 %–34 % at 10 years (Tronc *et al.*, 2000; Fadel *et al.*, 2002; Mezzetti *et al.*, 2002; Kim *et al.*, 2005; Ludwig *et al.*, 2005; Ma *et al.*, 2007; Yildizeli *et al.*, 2007; Deslauriers *et al.*, 2009).

In a series of 217 patients reported by Bagan et al in 2005, 5-year survival rates were recorded as high as 72 % (Table 1). The report was limited to patients who underwent right upper lobe sleeve lobectomy, however, which has been suggested to be a less challenging operation when compared to other lobes (Bagan *et al.*, 2005). Sleeve lobectomy for pulmonary carcinoid has excellent results with 5 and 10 year survivals ranging from 100 % to 92 %, respectively (Fadel *et al.*, 2002; Terzi *et al.*, 2002). Documented factors decreasing long-term survival following a sleeve lobectomy include incomplete resection and nodal involvement (Table 1) (Rea *et al.*, 1997; Tronc *et al.*, 2000; Fadel *et al.*, 2002; Yildizeli *et al.*, 2007; Rea *et al.*, 2008; Deslauriers *et al.*, 2009). The influence on long-term survival of sleeve lobectomy from the squamous cell carcinoma type, age at resection, and induction radiotherapy remains unclear (Terzi *et al.*, 2002; Yildizeli *et al.*, 2007).

Complications following sleeve lobectomy range between 15 % and 51 % of patients, as Predina et al described (Tables 1 and 2) (Predina *et al.*, 2010). Common complications include sputum retention and secondary atelectasis. Life-threatening complications include bronchovascular or bronchopleural fistula, and anastomotic failure (stricture and breakdown) (Tronc F, 2008). Bronchovascular fistula, bronchopleural fistula, and anastomotic failure can result from disruption of the bronchial blood flow during airway dissection or excessive tension at the anastomotic site. Bronchovascular fistula occurs in less than 2 % of cases of sleeve lobectomy but is one of the most feared complications (Tronc F, 2008). Bronchopleural fistula is slightly more common, occurring in 5 % of sleeve lobectomies (Tronc *et al.*, 2000; Fadel *et al.*, 2002; Mezzetti *et al.*, 2002; Terzi *et al.*, 2002; Yildizeli *et al.*, 2007; Rea *et al.*, 2008; Konstantinou *et al.*, 2009). Death from bronchopleural fistula follows in approximately 40 % of the patients (Yildizeli *et al.*, 2007; Rea *et al.*, 2008). Anastomotic stricture or breakdown occurs in 1 %–4 % of patients undergoing sleeve lobectomy (Table 2 and 3) (Tronc *et al.*, 2000; Fadel *et al.*, 2002; Yildizeli *et al.*, 2007; Rea *et al.*, 2008). Post-operative or 30-day mortality for sleeve lobectomy is approximately 5 % in recent reports. Commonly documented causes of early mortality include bronchopleural fistula, bronchovascular fistula, cardiac complications, pneumonia or empyema, and pulmonary embolism. Less frequent causes include renal failure, acute respiratory distress syndrome, hemothorax, and respiratory failure.

Author (Year)	Number of Patients	5-Year Survival (%)			10-Year Survival (%)		
		N_0	N_1	N_2	N_0	N_1	N_2
Rea et al (1997) (Rea *et al.*, 1997)	179	72	36	22	59	27	14
Icard et al (1999) (Icard *et al.*, 1999)	110	57	29	33	26	18	33
Van Schil et al (2000) (Van Schil *et al.*, 2000)	145	62	29	31	53	21	6

Table 1: Survival rates according to lymph node status after sleeve resection for NSCLC (Deslauriers *et al.*, 2009).

Author (Year)	Number of Patients	5-Year Survival (%)	Complications (%)	30-Day Mortality (%)
Konstantinou et al (2009) (Konstantinou *et al.*, 2009)	45	57*	15	2
Rea et al (2007) (Rea *et al.*, 2008)	93	39.7	Within 30 Days-17.9 After 30 Days-16.3	4.5
Yildizeli et al (2007) (Yildizeli *et al.*, 2007)	218	53	22.9	4.1
Mezzetti et al (2006) (Mezzetti *et al.*, 2002)	38	43	10.8	3.6
Terzi et al (2002) (Terzi *et al.*, 2002)	48**	38.8***	-	6**
Fadel et al (2002) (Fadel *et al.*, 2002)****	139	52	12.9	2.9
Tronc et al (2000) (Tronc *et al.*, 2000)	184	52	Within 30 Days-14 % After 30 Days-2 %	1.6

* Survival at 4 years

** Results from "contemporary phase" which was described by authors as era after routine of CT, use of mediastinoscopy, and advanced bronchoscopic techniques

*** Survival excludes stage IV patients

**** Data includes both NSCLC patients and pulmonary carcinoid patients

Table 2: 5-year survival, postoperative complications, and 30-day mortality results after sleeve lobectomy for NSCLC (Rea *et al.*, 2008; Predina *et al.*, 2010).

Author (Year)	Number of Patients	Sleeve Lobectomy			Pneumonectomy		
		5-Year Survival (%)	30-Day Mortality (%)	Complications (%)	5-Year Survival (%)	30-Day Mortality (%)	Complications (%)
Melloul et al (2008)* (Melloul *et al.*, 2008)	115	-	0	26	-	3	44
Ma et al (2007) (Ma *et al.*, 2007)	2984**	50.3	3.5	31.3	30.6	5.7	31.6
Jiménez et al (2006) (Jiménez *et al.*, 2006)	255	56	2.8	36.1	32	9.1	36.3
Bagan et al (2005) ***(Bagan *et al.*, 2005)	217	72.5	4.5	28.8	51.2	12.6	29.9
Ludwig et al (2005) (Ludwig *et al.*, 2005)	310	39	4.3	38	27	4.9	26
Kim et al (2005) (Kim *et al.*, 2005)	249	53.7	6.1	51****	59.5	4.1	35****
Deslauriers et al (2004) (Deslauriers *et al.*, 2004)	1230	52	1.6	-	31	5.3	-

* Includes only data of patients under 70 years age

** Report is a meta-analysis

*** Includes only data involving right upper lobe sleeve lobectomies and right pneumonectomies with limited nodal involvement (N0, intra-lobar N1 and skip metastasis)

**** Complications only include those which took place during the early postoperative period

Table 3: 5-year survival, 30-day mortality, and postoperative complications among NSCLC patients undergoing sleeve lobectomy or pneumonectomy (Rea *et al.*, 2008; Predina *et al.*, 2010).

3. RATIONALE

RATIONALE

a) <u>Eligibility for major anatomic resection</u>

There are multiple factors that have been related to eligibility for major anatomic resection and to perioperative risk. Among them, patient characteristics (comorbidities, age), structural aspects related to the surgical center (volume, specialization), and process factors directly related with the management of complications and surgical access (open, minimally invasive) (Brunelli *et al.*, 2013). Each of these play an important role. These factors should be carefully considered when planning a pneumonectomy or sleeve resection.

A meticulous cardiopulmonary evaluation is recommended in those patients who are sleeve resection candidates and it includes spirometry with predicted postoperative (ppo) FEV1 % values and diffusing capacity (DLCO %), a cardiac evaluation, and a cardiopulmonary exercise test when indicated. If any coronary stenosis is found, this should be treated prior to the lung resection (Figure 8) (Brunelli *et al.*, 2010; Brunelli *et al.*, 2013).

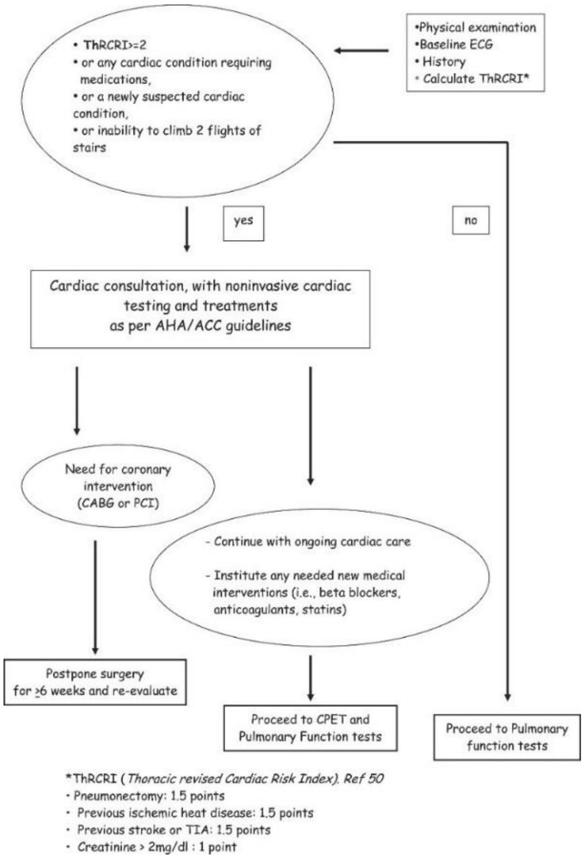

Figure 8: Physiologic evaluation cardiac algorithm.*ThRCRI (Brunelli *et al.*, 2010).

In patients deemed high risk for lobectomy or greater operations, pneumonectomy should be avoided and thus, a sleeve resection, when possible, performed. This group of patients includes those with ppoFEV1 % and or ppoDLCO % < 30 %, high risk cardiac evaluation, cardiopulmonary exercise test with a VO2max < 10 ml/kg/min or <35 % (Figure 9) and those patients considered too frail to survive the operation (patients with significant weight loss, exhaustion, weakness, slow gate and in generally low activity) (Fried *et al.*, 2001; Beckert *et al.*, 2017).

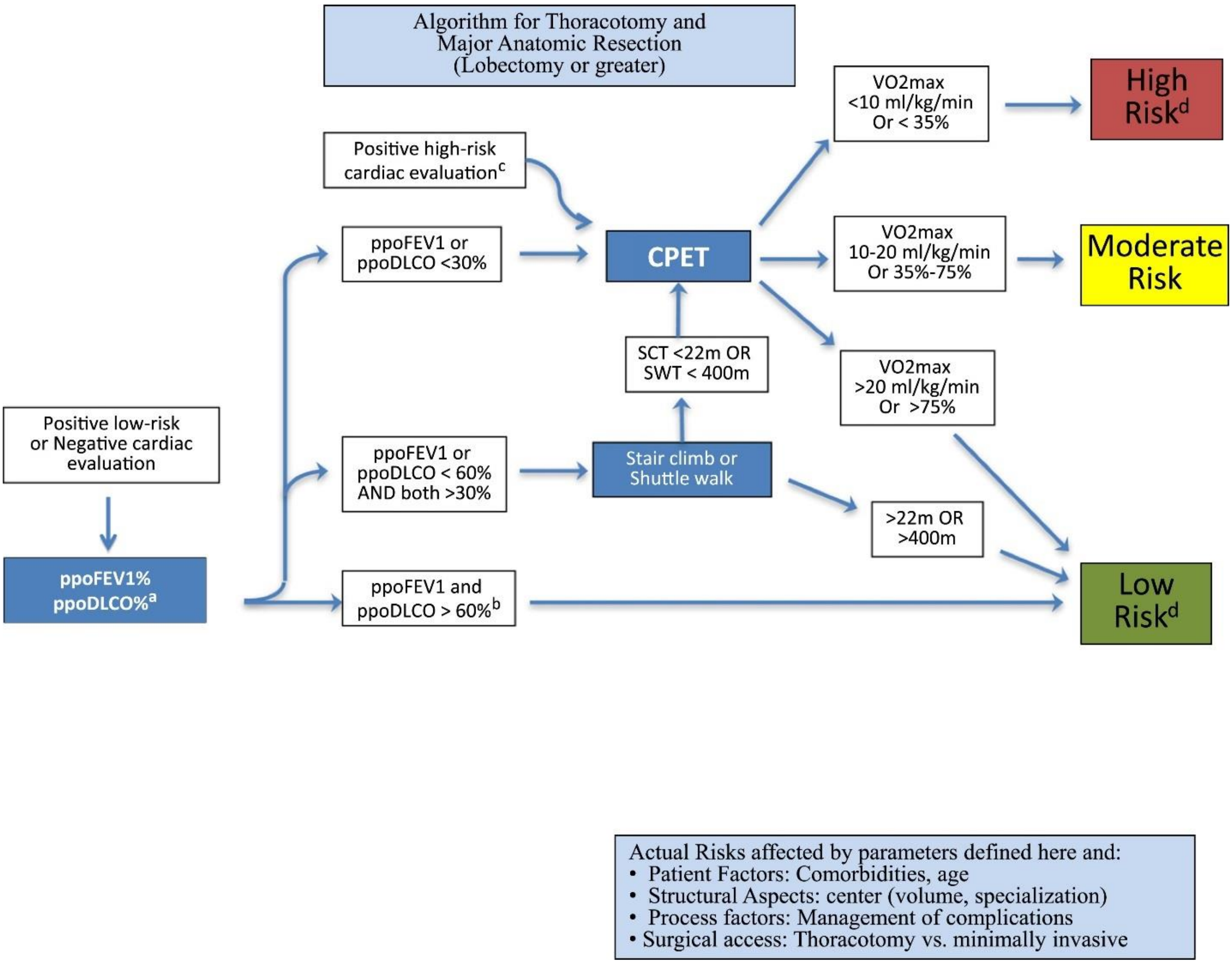

Figure 9: Physiologic evaluation resection algorithm (Brunelli *et al.*, 2013).

In those cases where pneumonectomy is the only suitable operation, it is important to remember that it has proven its oncologic value in fit surgical candidates, but it is associated with significantly decreased survival at 6 months (Rodríguez *et al.*, 2013) and in early stage lung cancer patients (Jiménez *et al.*, 2006; Rodríguez *et al.*, 2015), mainly related to cardiopulmonary complications (Rodríguez *et al.*, 2013) (Figure 10).

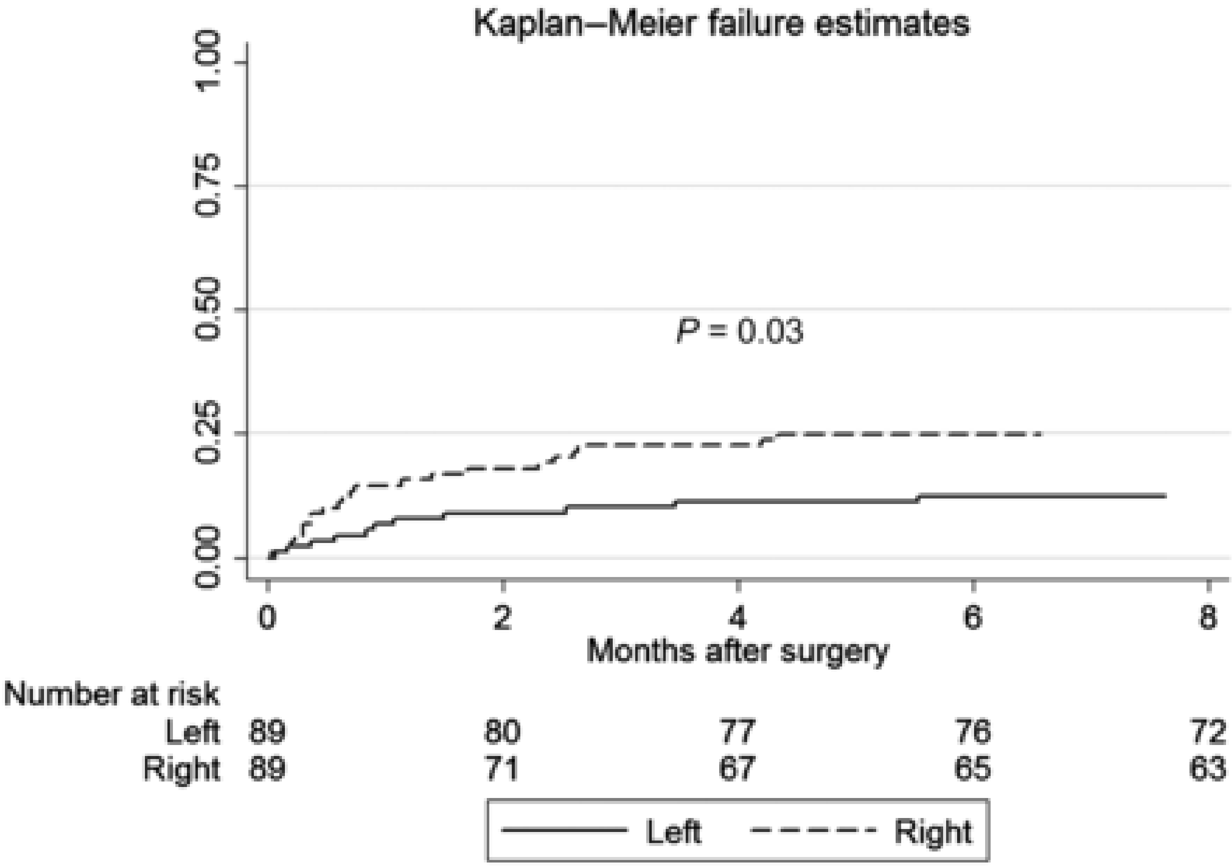

Figure 10: Six-month death hazard of the pneumonectomy patients (matched cases) (Rodríguez *et al.*, 2013).

Although sleeve resections are technically described as a more challenging operation and were initially reserved for those patients with limited pulmonary function tests (Deslauriers *et al.*, 2009), they have proven to offer similar short and long term results to those of pneumonectomy in the right candidates (Bagan *et al.*, 2005; Kim *et al.*, 2005; Ludwig *et al.*, 2005; Ma *et al.*, 2007; Melloul *et al.*, 2008; Deslauriers *et al.*, 2009).

b) Landmark series

The series reporting sleeve resections are not as common as those analyzing other types of procedures and the number of patients included is limited, too.

The first significant series of bronchoplastic procedures was reported by Donald Paulson and Robert Shaw in 1959 (Paulson and Shaw, 1960) at the Southern Surgical Association meeting.

In their article, they reported a series of 462 patients who underwent anatomic resection for bronchogenic carcinoma between January 1945 and December 1958. Among those patients, 230 underwent a lobectomy (27 of them included a bronchoplastic procedure) and 232 patients underwent a pneumonectomy. Of all patients undergoing surgery, 22 % survived 5 years. This overall 5-year survival was further subdivided into 14 % of those having pneumonectomies and 30 % of those having lobectomies (Paulson and Shaw, 1960), (Table 4 and Figure 11).

Type of operation	Number	Deaths, n (%)
Pneumonectomy	232	20 (8.6)
Lobectomy	230	9 (3.9)
Total	462	29 (6.2)

Table 4: Operative mortality of Paulson and Shaw’s series (Paulson and Shaw, 1960).

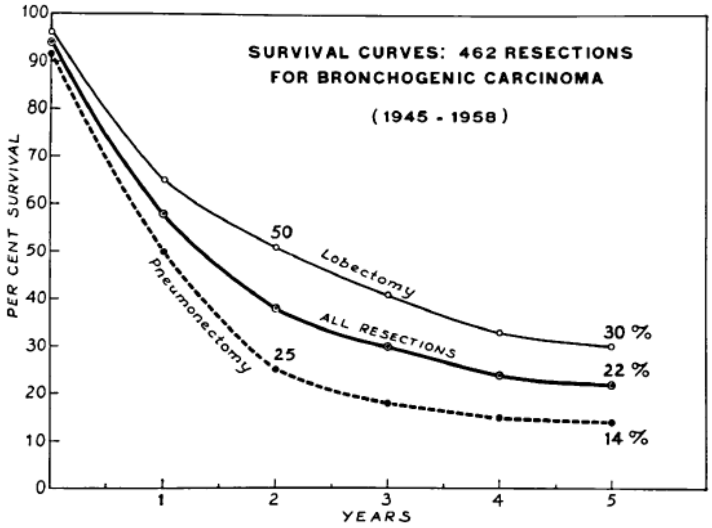

Figure 11: Survival curves of the series (Paulson and Shaw, 1960).

In their series, 50 % of the patients undergoing a lobectomy survived at least two years, whereas only 25 % of the patients who underwent a pneumonectomy achieved that benchmark. The authors observed that, 'bronchogenic carcinomas occur frequently in association with pulmonary emphysema and reduced pulmonary function, preservation of lung tissue where possible is of utmost importance'. These authors advocated bronchoplastic operations to avoid pneumonectomy.

In accordance with their philosophy of preserving as much parenchyma as possible, the authors performed bronchoplastic procedures for 3 main indications:

1. As a curative procedure for low grade hilar lesions, preferably without nodal involvement,
2. As a 'compromise procedure' for poor cardiac or pulmonary function,
3. To 'extend resectability' of the extensive lesions involving the lower trachea, carina and contralateral main bronchus.

In 8 years, from 1951 to 1959, they performed 27 bronchoplastic or sleeve procedures (2 tracheobronchial reconstructions and bronchoplastic procedures with lobectomy). The first nine were reported separately (Paulson and Shaw, 1955). All the patients underwent surgery for bronchogenic carcinoma and all of the airway reconstructions were for hilar lesions.

The 27 patients included in this initial series were men and their ages ranged from 47 to 68 years. Two of the patients underwent the bronchoplastic procedure to extend resectability due to carinal and contralateral bronchus involvement. The remaining 25 patients underwent the surgery as a curative procedure, 12 for small hilar lesions (eight without nodal involvement) and the other 13 patients were functionally compromised (nine with hilar involvement). The procedures performed are described in Figure 12.

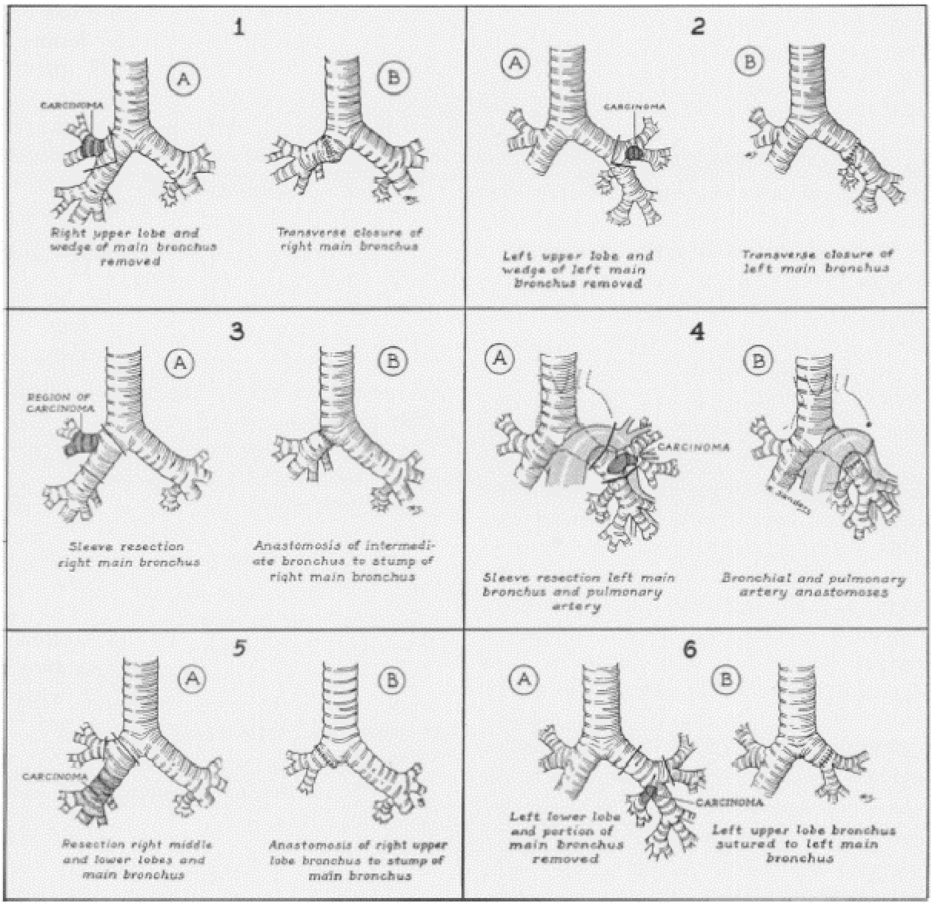

Figure 12: Types of bronchoplastic procedures done in 25 patients for bronchogenic carcinoma. Panel 1 is right upper lobe resected with bronchoplasty, panel 2 is left upper lobectomy with bronchoplasty, panel 3 is right upper lobe sleeve resection, panel 4 is left upper lobe sleeve resection, panel 5 is right lower and middle lobes resected and right upper lobe preserved by sleeve, and panel 6 is left lower lobe sleeve resection (Paulson and Shaw, 1960).

All of these bronchoplastic procedures were performed in combination with lobectomies. Wedge resection of the right main bronchus combined with a right upper lobectomy was performed once. Wedge resections of the left main bronchus combined with left upper lobectomy were done twice. In three patients, the right middle and lower lobes and varying portions of the main bronchus were resected with anastomosis of the right upper lobe to the bronchial stump or trachea.

Resection of the left lower lobe and a portion of the left mainstem bronchus with anastomosis of the left upper lobe to the main bronchus was done in 4 patients. Sleeve resection of the left main bronchus and pulmonary artery together, with a left upper lobectomy was done in one case.

Based on their experience, the authors concluded that the greatest usefulness of sleeve resections was for lesions involving the right upper lobe bronchus, where a right upper lobectomy with anastomosis of the right main bronchus and the bronchus intermedius and a good nodal dissection achieved the same oncologic results as pneumonectomy but preserved the middle and lower lobes. They did this resection fourteen times in their series.

The authors included a careful description of their technique, including placing the patients in prone position to facilitate anatomical exposure of the airway, and performance of the anastomosis with interrupted cotton sutures (Paulson and Shaw, 1960). They also explained the importance of the postoperative care, when the clearance of secretions becomes of utmost importance. They recommended naso-tracheal catheter aspiration systematically in all the patients and they placed up to four tracheostomies to prevent postoperative mucous plugging.

Among the complications described in this series, the most common are bronchopleural fistula and empyema, with two patients dying in the first 30 days after the surgery and another two developing post anastomotic bronchial stenosis. Four of 27 patients also experienced local recurrence of their tumor (Table 5).

Complications of sleeve resection	n (%)
Operative mortality	1 (3.7)
Bronchial fistula	1 (3.7)
Empyema	4 (14.8)
Granulation tissue obstruction	3 (11.1)
Obstructive bronchial stenosis	2 (7.4)
Sutures removed bronchoscopically	5 (18.5)
Recurrence carcinoma in the lumen	4 (14.8)

Table 5: Complications in Paulson and Shaw's series, including 27 sleeve resections (Paulson and Shaw, 1960).

The patients who underwent a bronchoplastic procedure in this study had an 86 % survival at 2 years, 71 % survival at 3 years and 43 % survival at 5 years, which compared favorably to those who had undergone lobectomy (Figure 13).

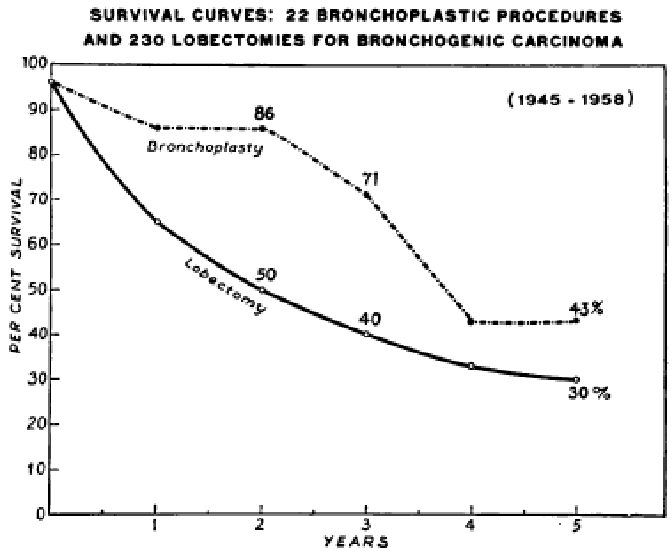

Figure 13: Survival curves of 22 patients having bronchoplastic procedures combined with lobectomies compared to 230 patients having lobectomies for bronchogenic carcinoma calculated by the life table method (Paulson and Shaw, 1960).

Remarkably, all the patients who did not have nodal involvement were alive at 3 years and 70 % survived 5 years. With these results, the authors concluded that bronchoplastic procedures, when no nodal involvement can be observed, are an excellent alternative to more extended procedures and they should be widely used when technically feasible.

From 1959, also, is the series of James Johnston and Peter Jones (Johnston and Jones, 1959), who reported on 98 patients who had undergone any type of sleeve resection for bronchial carcinoma since 1953. The patients were operated on in two hospitals: The Royal Brompton Hospital in London and the Baguley Hospital in Manchester.

The ages of the patients included ranged from 30 to 79 years and among them were 17 women. Similar to the series of Paulson and Shaw, most of their patients underwent a bronchoplastic or sleeve resection because their cardiorespiratory function did not allow a more extended resection. Also, two of the patients underwent the operation in the setting of isolated chest wall metastasis with palliative intent.

The operations performed are shown in Table 6 (Johnston and Jones, 1959) and again, great emphasis is given to a careful bronchoscopic planning and chest cavity inspection to choose the adequate procedure and to rule out the incidence of metastasis.

Type of operation	Number (%)
Right upper lobe sleeve resection	47 (48)
Right upper bilobectomy sleeve resection	12 (12.2)
Right upper bilobectomy + apical lower sleeve resection	2 (2)
Right lower bilobectomy sleeve resection	2 (2)
Left upper lobectomy sleeve resection	30 (30.6)
Left upper lobectomy + apical lower lobectomy sleeve resection	4 (4)
Right upper lobectomy with sleeve resection of right and left main bronchus	1 (1)
• With chest wall	3 (3)
• With sleeve pulmonary artery	5 (5.1)
• With segmental pulmonary artery	3 (3)

Table 6: Type of operation in 98 patients in Johnston and Jones (Johnston and Jones, 1959).

The authors' techniques were very similar to that described by Paulson and Shaw and they advocated for apical and basilar chest tubes and daily or twice daily chest X-rays to facilitate the early detection and aggressive treatment of atelectasis.

The main complications observed in this series were atelectasis, pneumothorax, atrial fibrillation and sutures coughed up (Tables 7 and 8).

Early complications	Number (%)
Atelectasis requiring bronchoscopy	9 (9.18)
Temporary pneumothorax	6 (6.12)
Persistent air space	1 (1)
Small infected pleural pocket	1 (1)
Contralateral staphylococcal lung abscesses	1 (1)
Pneumonia in anastomosed lobe	2 (2)
Superficial wound infection	2 (2)
Thrombophlebitis	2 (2)
Pulmonary embolus	1 (1)
Auricular fibrillation	9 (9.18)

Table 7: Early complications in the series from Johnston and Jones (Johnston and Jones, 1959).

Late complications	Number (%)
Sutures coughed up or removed	7 (7.14)
Granulation tissue polyp at suture line	2 (6.12)
Hemoptysis due to granulation tissue	1 (1)
Temporary stenosis due to granulation tissue	1 (1)
Other strictures early or late	0 (1)

Table 8: Late complications in the series from Johnston and Jones (Johnston and Jones, 1959).

In this series, the authors reported eight deaths directly related to the operation, accounting for 8 % of operative mortality. Among the eight deaths, two were attributed to coronary thrombosis, two to postoperative pneumonia and atelectasis, one secondary to a pulmonary artery thrombosis, one to bronchopleural fistula, one because of an intestinal obstruction, and the last patient died 6 weeks after the operation when receiving radiotherapy after a profuse episode of hemoptysis.

Despite these deaths, the authors' operative mortality rate of 8 % was comparable to the mortality rate observed after lobectomy at the Brompton Hospital during the same period in history. Furthermore, the overall survival was better in the sleeve and bronchoplasty group than the one observed after lobectomies (Table 9). Consequently, they concluded sleeve resections were a safe operation to offer in the setting of bronchial carcinoma. They also advocated for increased surgical indications, allowing those patients who were not good lobectomy candidates to undergo the sleeve operation with similar results to those achieved by lobectomies and better than those of the pneumonectomies (Table 10).

Survival after 1 year compared with lobectomy	Number	Alive, n (%)
Sleeve resection	65	52 (80)
Lobectomy (Price Thomas)	114	84 (74)

Table 9: 1-year survival of sleeve resections compared to lobectomies (Johnston and Jones, 1959).

Mortality rate according to age after pneumonectomy	Number	Dead, n (%)
60 +	105	23 (22)
50-59	163	33 (20)
49 -	83	6 (7)

Table 10: Mortality rate of pneumonectomy according to age (Johnston and Jones, 1959).

The conservation of lung tissue seemed to benefit both compromised and uncompromised patients, and with this background the next significant series of sleeve resections was published.

It was in 1984 when Faber et al (Faber *et al.*, 1984) presented their series of 101 patients who underwent sleeve resection at Rush-Presbyterian-St. Luke's Hospital in Chicago, and for the first time, patients who underwent preoperative irradiation were included in the study.

The operations were performed between January 1962 and July 1982. The series consisted of 87 men and 14 women. The age ranged from 40 to 79 years. In the series 55 patients had received preoperative irradiation (4000 rads given over 4 weeks). The radiation decision was made in the setting of a clinical trial for bronchial carcinoma treatment until 1971 and electively afterwards. Most of the procedures performed were right upper lobe sleeve resections (Table 11). All of them were considered curative and systematic nodal dissection was completed.

Type of operation	Number (%)
Right bronchial sleeve resection	58 (57.4)
• Right upper lobe sleeve resection	50 (49.5)
• Right upper bilobectomy	2 (1.9)
• Right upper bilobectomy + arterial sleeve resection	1 (0.9)
• Right lower bilobectomy	1 (0.9)
• Sleeve bronchus intermedius middle lobe	1 (0.9)
• Sleeve bronchus intermedius lower lobe	1 (0.9)
Left Bronchial sleeve resection	43 (42.57)
• Left upper lobe sleeve resection	30 (29.7)
• Left lower lobe sleeve resection	13 (12.8)

Table 11: Sites of carcinoma in patients undergoing sleeve resection (Faber *et al.*, 1984).

The authors also carefully described their techniques, especially the suture material used to perform the anastomosis. At the beginning of the series they used silk, but were dissatisfied with the high incidence of granulomas. They switched to Tevdek^{tm}, yet that suture also produced granulation tissue at the anastomosis site. Finally, 3-0 coated polyglycolic suture (similar to Vicryl^{tm}) became the suture of choice. They also emphasized the importance of cartilage to cartilage anastomosis, blood supply preservation by avoiding unnecessary bronchial dissection, and the placement of two or three sutures in the corners of the anastomosis to mitigate the tension in the remaining surfaces. They performed a systematic bronchoscopy in the operating room after finishing the anastomosis and if this was not found satisfactory, the airway anastomosis was redone immediately.

Of the 101 patients, 7 patients underwent completion pneumonectomy for anastomotic problems and they were not included in further analysis. The remaining 94 showed a 5-year survival of 30 % and a 10-year survival of 22 %. The sleeve lobectomy group that did not undergo irradiation (43 patients) had a 5-year survival of 34 % and a 10-year survival of 25 %. The 51 patients that had preoperative radiation had a 5-year survival of 25 % and a 10-year survival of 16 % (Figure 14). These differences were not statistically significant (p= 0.102).

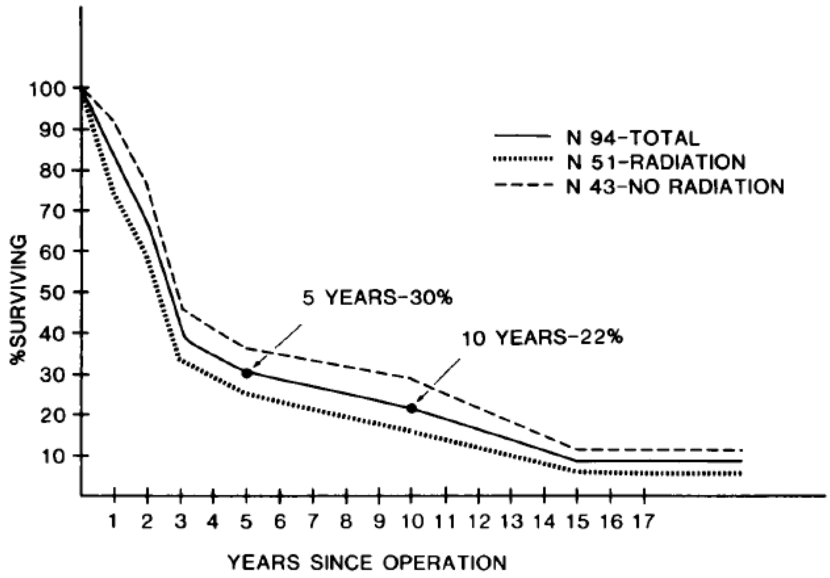

Figure 14: Life-table analysis of 94 patients undergoing sleeve lobectomy for bronchogenic carcinoma in the series by Faber et al (Faber *et al.*, 1984)

The TNM staging was not applied until 1972, but these authors analyzed their data accordingly. The pathologic characteristics of the patients analyzed are shown in Table 12 (Faber *et al.*, 1984).

Stage	Radiation therapy	
	Yes, n (%)	No, n (%)
T1 N0 M0	7 (6.9)	16 (15.8)
T1 N1 M0	3 (2.9)	7 (6.9)
T2 N0 M0	16 (15.84)	10 (9.9)
T2 N1 M0	9 (8.91)	12 (11.88)
T3 N0 M0	2 (1.9)	1 (0.9)
T1 N2 M0	1 (0.9)	1 (0.9)
T2 N2 M0	4 (3.9)	3 (2.9)
T3 N2 M0	1 (0.9)	1 (0.9)

Table 12: Staging of sleeve lobectomies (Faber *et al.*, 1984).

Please note that in this early manifestation of the system of stage grouping, stage I included T1N1 (currently stage IIa). Stage II only included T2N1 tumors (currently stage IIb). Finally, stage III included T3 tumors with direct invasion of the chest wall or mediastinum (possible to be stage IIa, currently) or with N2 disease (currently stage IIIa).

Most of the patients with stage I who did not receive irradiation therapy had T2 N0 M0 lesions. It is interesting to see that, among the patients treated with preoperative irradiation, almost half of them (16/33) had T1N0M0 lesions, probably secondary to the tumor downsizing produced by the irradiation.

Patients with stage II lesions had positive hilar nodes and patients with stage III lesions had positive mediastinal lymph nodes.

The 5-year survival rate of patients with stage I lesions was 36 % and the 10- year survival rate was 25 %. 5 year-survival for stage II patients was 18 % and 15 % for stage III (Figure 15).

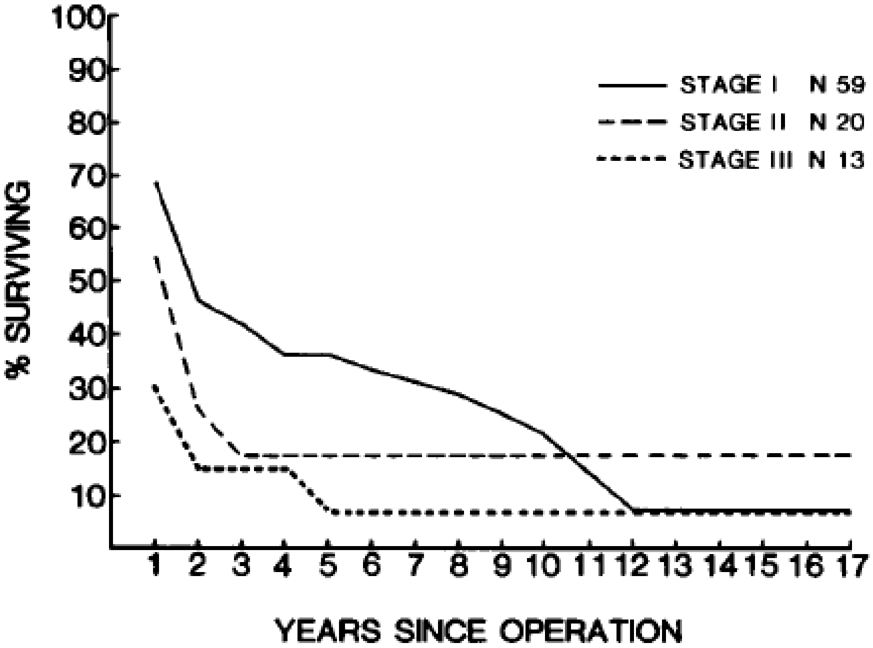

Figure 15: Life-table analysis of patients undergoing sleeve lobectomy for bronchogenic carcinoma by stage in Faber et al (Faber *et al.*, 1984).

The operative mortality of this series was 2 % (2 patients); one from inadequate ventilation during the procedure and the other secondary to adult respiratory distress syndrome. During the follow-up, 3 more deaths were observed; one due to myocardial infarction, one secondary to pneumonia and the last one after a fistula developed between the pulmonary artery and the bronchial anastomosis.

Among the patients who required completion pneumonectomy for anastomotic dehiscence, 4 out of seven had received preoperative irradiation.

There were 9 recurrences at the anastomotic site, most of them treated with radiation and chemotherapy.

The authors, encouraged by their results despite the high recurrence rate observed in their series (10 %), recommended sleeve resection as the operation of choice when technically feasible and when the extent of the tumor permits it. They even recommended sleeve resection when the patient could tolerate a pneumonectomy (Faber *et al.*, 1984).

This report is of significant value not only because of the number of sleeve resections included, but also, because it is the first to include neoadjuvant treatment in the setting of sleeve resections. Although the indications for neoadjuvant irradiation in the series were based in a clinical trial and in surgeons' preferences, the modern truth is that the current indications for neoadjuvant treatment in sleeve resection candidates remain unclear and controversial.

The last remarkable report of sleeve resections is the one published by Hong et al in 2018 (Hong *et al.*, 2018). Although the foci of their report were extended sleeve lobectomies (63 patients), they compared this extended group with their previous 20 years' experience of 477 sleeve lobectomies. The study included both patients with and without neoadjuvant chemoradiation therapy although the survival outcomes are not separately studied. Among the patients included in this report, 10.1 % in the sleeve lobectomy group received neoadjuvant chemoradiation.

This paper focused on the influence of anastomotic complications on the outcomes of: length of stay, in-hospital mortality, recurrence rate, overall and disease-free survival, and postoperative complications. They also included in the analysis those patients who required a completion pneumonectomy for anastomotic problems (6 % in the extended sleeve resection group versus 2 % in the sleeve lobectomy group). This is the largest series of sleeve resections and bronchoplasties published to date. The authors concluded that both sleeve resection and extended sleeve resection are feasible and safe operations for patients with centrally located NSCLC.

c) <u>Role of neoadjuvant therapy in sleeve resection candidates</u>

Most of the patients requiring sleeve resection are staged, by the 7^{th} TNM classification (Goldstraw *et al.*, 2007), as T2 (tumor involving the main bronchus but more than 2 cm away from the carina) or T3 (tumor < 2cm from carina or with involvement of the carina). Regarding nodal stage, they are also frequently N1 (hilar nodes making airway dissection more challenging or affecting hilar structures) or N2 (Mediastinal lymph nodes affected, prompting neoadjuvant treatment and subsequent restaging).

These classifiers make surgical candidates for sleeve resection at least stage IB (T2a N0 M0) according to both 7th and 8th edition (Detterbeck *et al.*, 2017) of the TNM staging system. Although, multimodality treatment is accepted worldwide as part of the management of locoregionally advanced NSCLC (at least stage IIIA), its benefits remain controversial in earlier stages of the disease.

1. Neoadjuvant chemotherapy in surgical candidates

The role of neoadjuvant therapy in early stage lung cancer was initially studied with the hope of decreasing distant micro metastasis and local tumor burden, with the possibility of increasing resectability and improving overall survival.

In the early 1990s, two randomized trials of neoadjuvant chemotherapy in patients with resectable NSCLC demonstrated increased survival when adding preoperative platinum based chemotherapy to surgery than with surgery alone (Roth *et al.*, 1994; Rosell *et al.*, 1999). Critics of these studies pointed out the small number of patients included, the unexpected poor outcomes in the control arm and the great heterogeneity of the populations studied.

In 2006, seven neoadjuvant therapy randomized trials were included in a meta-analysis. It consisted of 988 patients and was able to demonstrate an overall survival improvement of 20 % in the treatment group compared with only 14 % (p= 0.02) in the control group (Burdett *et al.*, 2006). Among the studies included in this meta-analysis, three of the largest ones were primarily responsible for the differences observed.

Among them, the study from Depierre et al (Depierre *et al.*, 2002) randomized 355 patients staged from IB to IIIA to two cycles of neoadjuvant cisplatin, ifosfamide and mitomycin followed by surgery versus surgery alone. Those patients who had a good preoperative response (64 %) received two additional adjuvant cycles after surgery. Patients diagnosed with pT3 or N2 disease received neoadjuvant radiation (40 Gy delivered in 2 Gy daily fractions 5 days per week). It is important to remember that in this study, mediastinal staging and lymph node dissection or sampling were left to the discretion of the surgeon and no lesser operation was allowed even if the disease had shrunk enough to consider it. In total, 355 patients were randomized. Response to preoperative chemotherapy was 64 %, with two deaths related to the neoadjuvant treatment. Postoperative mortality was 6.7 % in the neoadjuvant group and 4.5 % in the surgical group (p= 0.38). Median survival was 37 months in the preoperative chemotherapy group and 26 months in the surgical group (p=0.15). Overall survival of the patients included in the neoadjuvant therapy group increased from 3.8 % the first year to 8.6 % at 4 years with significant benefit observed among N0 and N1 patients (p=0.027). After a non-significant excess of deaths during the treatment period, the effect of neoadjuvant chemotherapy was deemed beneficial on survival (p= 0.044). In addition, disease free survival was significantly increased among those patients who received neoadjuvant chemotherapy (p= 0.033). As the authors did not find increased deaths or morbidity in the neoadjuvant group compared with the control group (6.7 % deaths versus 4.5 % deaths, p=0.38) they concluded neoadjuvant therapy was a safe practice for those patients with resectable lung cancer.

On counter balance, a multicenter randomized controlled trial designed by Gilligan et al (Gilligan *et al.*, 2007) failed to show any differences between cisplatin-based chemotherapy versus surgery alone. The study included 588 patients from 4 different centers diagnosed with stage I to stage III NSCLC. The overall survival observed in the experimental group was 44 % versus 45 % in the control group (Hazard Ratio: 1.02). Interestingly, up to 33 % of the patients included in the chemotherapy arm were downstaged, but this did not affect the planned surgery. No increased surgical mortality and morbidity were observed in the chemotherapy group. The main limitations of this study, (limitations that could have contributed to its negative results) were the different chemotherapy regimens (up to 6 different regimens were allowed) and the large number of stage I patients included (61 %), making it more difficult to reach statistical significance.

In 2007, the results of the Southwest Oncology Group (SWOG) 9900 trial were updated and presented. 388 patients diagnosed with resectable lung cancer were randomized to surgery alone versus three cycles of neoadjuvant carboplatin and paclitaxel. Although it was not statistically significant, a trend towards increased 5-year overall survival was observed in the experimental arm (43 % versus 50 %, Hazard Ratio = 0.81) (Pisters *et al.*, 2007).

Several other Phase II studies including cisplatin/vindesine/ifosfamide (Lorent *et al.*, 2004), cisplatin/vinblastine (Sugarbaker *et al.*, 1995), cisplatin/docetaxel (Betticher *et al.*,

2003) and cisplatin/gemcitabine (Migliorino *et al.*, 2002) combinations have been able to demonstrate the role of other new generation agents as neoadjuvant treatment.

All these studies present several limitations as to the inability to properly stage patients preoperatively (Staging was mostly radiologic, with few insisting on pre-resectional pathologic staging such as CALGB study 8935 (Sugarbaker *et al.*, 1995)), the great variability of the chemotherapy regimens and the different stages of lung cancer included in each randomized trial. Even with the limitations stated above and the subsequent difficulties interpreting the data, all of them suggested a role for induction chemotherapy for patients with stage II or IIIA NSCLC who were operable candidates.

2. Postoperative complication risk after neoadjuvant chemotherapy

There have been controversial reports regarding the risk of postoperative complications in those patients who have undergone neoadjuvant therapy.

In 2001 Roberts compared 34 patients who underwent neoadjuvant chemotherapy with 67 that did not. The patients were matched by age, comorbidity and pulmonary function. In the group of patients that received neoadjuvant chemotherapy, an increased rate of life threatening complications such as postoperative pneumonia, emergency surgery, ICU admission or reintubation was found (6.0 % versus 26.5 %, P = .0036). Major complications, including prolonged hospital stay (19.4 % versus 47.1 %, P = .0037), reintubation (3.0 % versus 17.6 %, P = .0093), and tracheostomy (0 % versus 11.8 %, P = .0042) were also higher among the patients treated with induction chemotherapy (Roberts *et al.*, 2001).

Although this study was criticized because there was no matching by stage between the two groups, and patients in the chemotherapy group had a higher stage, it was the first study that raised the concern of postoperative complications after induction chemotherapy.

In another retrospective study of 106 patients, Venuta et al demonstrated neoadjuvant chemotherapy did not increase complications in experienced surgeon's hands (Venuta *et al.*, 2007).

Among the results of several studies trying to assess the risk of complications after neoadjuvant chemotherapy, it is important to discuss the results found by Mansour et al. They analyzed 306 patients who underwent pneumonectomy from January 1999 to July 2005 after neoadjuvant chemotherapy and they found no increased postoperative mortality (Mansour *et al.*, 2007). However, Martin et al, reviewing Memorial Sloan Kettering Cancer Center database, from 1993 to 1999 found an increased mortality (23.9 %) in patients who underwent a right pneumonectomy after induction chemotherapy (Martin *et al.*, 2001).

With this information, it became a classical recommendation to avoid right pneumonectomy after neoadjuvant chemotherapy.

3. Neoadjuvant versus adjuvant chemotherapy

Another question that remains unanswered is the best timeline for chemotherapy administration in relationship with surgery. Specifically, should chemotherapy be given prior to surgery (neoadjuvant) or after recovery from surgery (adjuvant).

Many authors have tried to address this issue with randomized controlled trials.

Among them, the Neoadjuvant/Adjuvant Taxol (paclitaxel) Carboplatin Hope (NATCH) trial from the Spanish Lung Cancer group, included patients with stage I (> 2 cm), II, and T3, N1 NSCLC. The study candidates were randomized to neoadjuvant or adjuvant carboplatin/paclitaxel or surgery alone. The preliminary results from the neoadjuvant arm demonstrated neoadjuvant chemotherapy could be a safe alternative to those patients with resectable NSCLC (Felip *et al.*, 2007).

The final results of this trial were reported in 2009, at the World Congress on Lung Cancer (Felip *et al.*, 2010).The study included a total of 624 patients and among them there was no significantly different progression-free or overall survival observed. In the groups of induction chemotherapy, adjuvant chemotherapy, and surgery alone, the 5-year progression-free survival rates were 38.3 %, 36.6 %, and 34 %, and the 5-year overall survival rates were 46.6 %, 45.5 %, and 44 %, respectively. There were multiple limitations in the study, including the fact that most of the patients included were staged as IA and IB. Also, a lot of patients included in the adjuvant chemotherapy group were not able to receive the originally planned three cycles of treatment due to postoperative morbidity. The implication of this trial is that adjuvant therapy may be comparable to neoadjuvant therapy for stage I and II non-small cell lung cancer. That would have implications for timing of sleeve and bronchoplastic procedures.

The Chinese Society of Lung Cancer also designed the Survival Study of Docetaxel and Carboplatin as Neoadjuvant vs Adjuvant Chemotherapy in Early-Stage NSCLC (NCT00321334) with similar controversial results (Yang *et al.*, 2013).

The International Adjuvant Lung Cancer Trial Collaborative Group randomized a total of 1867 patients diagnosed with NSCLC who underwent complete resection of their malignancies. 36.5 % were diagnosed with pathological stage I disease, 24.2 % with stage II, and 39.3 % with stage III disease. 932 patients underwent cisplatin based adjuvant chemotherapy, with etoposide in 56.5 % of patients, vinorelbine in 26.8 %, vinblastine in 11.0 %, and vindesine in 5.8 %. The median duration of follow-up was 56 months. Patients assigned to chemotherapy had a significantly higher survival rate than those assigned to observation (44.5 % versus 40.4 % at 5 years [469 deaths versus 504] $P<0.03$). Patients assigned to the chemotherapy arm also had a significantly higher disease-free survival rate than those assigned to observation alone (39.4 % vs. 34.3 % at 5 years [518 events versus 577]; $P<0.003$). There were seven deaths related to chemotherapy toxicity (0.8 %) and there was no neoadjuvant therapy arm, but the conclusions favored significantly the administration of cisplatin-based chemotherapy after completely resected NSCLC (International Adjuvant Lung Cancer Trial Collaborative, 2004).

Another systematic review of 31 randomized trials, including 21 with postoperative chemotherapy and 10 with induction chemotherapy, with more than 10000 patients analyzed, was not able to find any differences in patients' mortality and morbidity, disease-free survival and overall survival between both groups, suggesting the timing of chemotherapy, after of before the surgery has very little impact in postoperative results (Lim *et al.*, 2009).

4. Role of radiation therapy in NSCLC

Radiation therapy has an important and well-established role in the management of NSCLC. Although, most of the times it is recommended with concurrent chemotherapy, it can be administered alone (Mohiuddin and Choi, 2005).

Radiation treatment is currently well accepted for six major indications: medically inoperable stage I and II NSCLC, postoperative radiation therapy for stage II and III, neoadjuvant treatment with chemotherapy for marginally resectable stage III disease, definite treatment for bulky stage II and stage III disease, neoadjuvant treatment for superior sulcus tumors and palliation (Mohiuddin and Choi, 2005).

For this topic, we will just focus in marginally resectable stage III disease where radiation therapy is administered with concurrent chemotherapy to try to downstage those patients who would be good candidates for a surgical resection, trying to provide, with both together, a better overall survival (Albain *et al.*, 1995).

A lot of improvements have been achieved since the 1980's where, according to several surgical series, only few patients could undergo a complete surgical resection after neoadjuvant treatment (Mohiuddin and Choi, 2005). Martini et al (Martini *et al.*, 1980) reported in 1980 a series of 445 patients who underwent neoadjuvant chemotherapy and radiation for marginally resectable stage III disease. All the patients were clinically and pathologically staged and among them, 241 underwent surgical exploration. Of these, 80 patients had complete surgical resections, leading to a 3-year survival among this select group of 49 %, compared with the overall survival rate of 13 % among all patients with N2 disease. Among those patients who did not receive neoadjuvant treatment, only 7 % were able to undergo a complete resection.

Following the lead of these results, the phase II trial from the Cancer and Leukemia Group B (CALGB) 8935 showed that those patients who were included in the multimodality treatment arm (neoadjuvant chemotherapy and adjuvant sequential chemotherapy followed by radiation therapy) achieved better survival than with historical benchmarks of surgery alone (17 % versus 13 % 5- year overall survival). This study included mediastinoscopy-staged N2 patients who received two cycles of chemotherapy followed by thoracotomy followed by

2 additional cycles of chemotherapy and 54.0 to 59.4 Gy of postoperative radiation therapy (Sugarbaker *et al.*, 1995).

The next important trial was the small phase II study designed by Fleck et al (Fleck *et al.*) In this trial, authors compared the addition of radiation to chemotherapy as neoadjuvant treatment versus chemotherapy alone. In the study, two cycles of cisplatin and continuous infusion 5 FU with 30 Gy of radiation in 15 fractions resulted in a higher response rate (67 % versus 44 %), resection rate (52 % versus 31 %), and 3-year progression free survival (40 % versus 21 %) than chemotherapy alone.

It was clear after these studies that the main benefit from concurrent chemoradiation therapy was downstaging.

Another study from the Massachusetts General Hospital showed this advantage in detail. 42 patients with mediastinoscopy proven N2 disease underwent neoadjuvant treatment with cisplatin, vinblastine, and 5 FU along with 21 Gy at 1.5 Gy bid with a 10-day break for esophagitis recovery followed by another 21 Gy bid. After surgery, additional radiation was administered (12 to 18 Gy, with a total dose of 54 to 60 Gy) and one more cycle of chemotherapy was added. Almost 89 % of the patients had a complete resection of their tumors and two thirds of the patients diagnosed with stage IIIA (N2) disease were downstaged to N0 and N1. Downstaging was related again with an improvement of 5-years overall survival from 18 % to 42 % (Choi *et al.*, 1997).

The Southwestern Oncology Group (SWOG) 8805 trial was a phase II study designed to analyze the effects of concurrent neoadjuvant chemoradiation therapy followed by surgery in locally advanced NSCLC (Albain *et al.*, 1995). 126 patients were included in the study. Among them, 75 were diagnosed with stage IIIA (with N2 involvement) and 51 were staged as IIIB disease. Patients received two cycles of chemotherapy with cisplatin and etoposide and concurrent radiation therapy with 45 Gy. Patients with good response to the treatment or at least stable disease underwent surgical resection, whereas those with disease progression continued to receive further chemoradiation. The overall 3-year survival rate was 26 % with the trimodality treatment. Among those patients who underwent surgery, the 3-years survival rate was 44 % when the nodal disease had been eradicated by the neoadjuvant treatment and 18 % in those patients with persistent mediastinal disease.

This study was designed based on a previous study by Friess et al (Friess *et al.*, 1987) from 1987 that included patients with advanced NSCLC. Patients underwent four 1-month cycles of cisplatin and etoposide along with radiation therapy up to 60 Gy. The median survival achieved in the study was 16 months, with a 30 % 2-year survival rate.

In the Intergroup 0139 (Albain *et al.*, 2009) trial, 396 patients were included. They were diagnosed with stage IIIA (pathological N2) NSCLC. Patients were randomized to two arms, one receiving induction cisplatin/etoposide with concurrent 45 Gy of radiation followed by surgery and two more cycles of chemotherapy afterwards and the other arm receiving cisplatin/etoposide with 61 Gy of radiation followed by two more cycles of chemotherapy.

The progression free survival was higher in the trimodality treatment arm (12.8 months versus 10.5 months, p= 0.017). On the other hand, in the trimodality treatment there was only minimal benefit in the 5-years survival rate (27.2 % versus 20.3 %). Similar to the results of the SWOG 8805 study, the downstaging to pN0 at the time of the surgery predicted the long-term survival. Five-year survival was 41% in patients with pN0 at the time of surgery and 24 % in patients with residual mediastinal disease.

One of the most important findings of the Intergroup 0139 study was the increased mortality when performing a pneumonectomy after induction chemoradiation therapy. 7.9 % of patients in the trimodality group had a treatment related death versus 2.1 % of the patients in the chemotherapy alone group. Almost 5 % of the deaths in the trimodality arm occurred within 30 days from the surgery and 9 out of 10 deaths were in patients who had undergone a pneumonectomy.

These findings were correlated with an increased risk of mortality of pneumonectomy after induction chemoradiation and led to a stratified analysis. Those patients in the study who had undergone a lobectomy did better when compared to those who needed a pneumonectomy. The 5-years survival of those patients who had undergone a lobectomy was 36 % and decreased to 22 % in pneumonectomy patients.

Other investigators also reported increased mortality among pneumonectomy patients when neoadjuvant chemoradiation was administered (Deutsch *et al.*, 1994; Martin *et al.*, 2001).

Gaissert at al (Gaissert *et al.*, 2009) further investigated the role of pneumonectomy after neoadjuvant chemoradiation therapy. In their retrospective study, they included 183 patients who underwent pneumonectomy, 46 of them after concurrent chemoradiation. The 46 patients who received neoadjuvant treatment had disease ranging from IIB to IV, but they were also younger and with better cardiac and pulmonary function. Hospital mortality was 4.3 % after neoadjuvant therapy and 6.6 % after resection only. Although they concluded pneumonectomy after neoadjuvant chemoradiation therapy is a safe option in carefully selected patients, they also recommended avoiding it when possible, in favor of lung parenchyma sparing operations.

Overall, preoperative concurrent chemoradiation seems a valid option to help downstage patients with NSCLC, facilitating in most of the cases the performance of a complete resection or of a parenchyma sparing operation. However, the inflammatory, immune and systemic responses to radiation therapy and the impact they could have in the healing of the anastomosis after sleeve resection are not yet well understood.

In their study from 2000, Yamamoto et al (Yamamoto *et al.*, 2000) investigated the role of neoadjuvant radiation in bronchial mucosal blood supply and consequently in healing. They included 90 patients and divided them in 3 groups: patients who did not have any neoadjuvant treatment, patients who had chemotherapy alone and patients who had chemoradiation (60 Gy). They measured the bronchial mucosal blood flow preoperatively, intraoperatively, and postoperatively (days 8-10) with a laser Doppler flowmeter.

They observed that bronchial mucosal flow was preserved among patients who did not receive any neoadjuvant treatment and among those who received chemotherapy alone, regardless of the extent of the lymphadenectomy. However, the blood flow was compromised in those patients who underwent neoadjuvant radiation and it decreased still farther after the lung resection. Although they only observed one bronchopleural fistula among their patients, they recommended routine coverage of the bronchial stump with a pedicled flap in those patients who had undergone radiation therapy.

Different studies have shown the effects of the surgical anastomosis and radiation on the bronchial vasculature, ranging from congestion and edema in the acute period (within 4 weeks from radiation) to hyalinization of arterioles and fibrosis in the subacute and late periods (Yokomise *et al.*, 1989; Inui *et al.*, 1993; Sundset *et al.*, 1993; Korpela *et al.*, 1995; Muehrcke *et al.*, 1995; Hyytinen and Halme, 2000).

Although the bronchial microcirculation has two blood sources, the bronchial arteries and the pulmonary circulation (Kröll *et al.*, 1987), it is difficult to predict in which patients an increase in pulmonary blood flow would be able to compensate for the decrease in bronchial circulation (Sundset *et al.*, 1993).

Another factor that seems to be related with the incidence of bronchial complications after neoadjuvant chemoradiation is the radiation dose, especially when it exceeds 35 or 40 Gy (Tsubota *et al.*, 1975; Warram, 1975; Mathisen *et al.*, 1988). Inui and colleagues experimental findings support this theory (Inui *et al.*, 1993), leading to the conclusion that the safer radiation dose would be 36 Gy or less. According to their data, the healing of the bronchial anastomosis was directly related to the bronchial mucosal blood flow. When the radiation dose increased over 36 Gy, the blood flow decreased at least 60 % compared to the preoperative level, leading to an increased rate of bronchial complications. Other authors have recommended laser Doppler flow to try to predict the incidence of bronchial complications, and although it has been used to assess microvascular perfusion in other organs, its clinical implications in sleeve reconstructions remain unclear (Ahn *et al.*, 1985; Kvernebo *et al.*, 1986; Yokomise *et al.*, 1989; Sundset *et al.*, 1993; Korpela *et al.*, 1995; Hyytinen and Halme, 2000).

To summarize, neoadjuvant chemotherapy has shown to be an acceptable option for those patients that have a good response to it and can tolerate a surgical resection. Careful consideration of avoiding neoadjuvant radiation therapy should be given to those cases requiring a pneumonectomy or a bronchial anastomosis because of the side effects that radiation therapy can have in bronchial circulation and consequently in bronchial healing.

d) <u>Quality of life after pneumonectomy and sleeve resection</u>

There are very few studies analyzing quality of life after pneumonectomy and sleeve resection, none of them randomized and just some of them compare quality of life between both types of surgeries.

It seems accepted that quality of life in patients undergoing lung resection for NSCLC tend to deteriorate with the extent of the resection, especially with pneumonectomy (Hamberger and Pichlmaier, 1996; Möller and Sartipy, 2012; Pompili, 2015). Zieren et al in their study in 1996, found more shortness of breath on exertion among those patients who had undergone a pneumonectomy compared to those who had a lobectomy. When compared to the preoperative assessment, quality of life deteriorated significantly at discharge, but was restored within 3 to 6 months after pneumonectomy (Zieren *et al.*, 1996).

Author and questionnaire	QoL scales	Time of follow up (Months)	Differences (Points)
Schulte et al[133] (EORTC QLQ C30 and LC13)	PF	3	<10
	SF	3-6	
	RF	3-6-12	
	GH	3-6	
	Pain	6	
Balduyck et al[134] (EORTC QLQ C30 and LC13)	PF	1-3-6-12	8-14-15-9
	RF	1-3-6-12	32-34-37-32
	CF	12	18
	Shoulder dysf	6-12	17-24
	Pain	6	6
Sartipy[135] (SF 36)	PF	6	19
	Vitality	6	18
	PCS	6	15

Table 13: Differences in the main quality of life scores between pneumonectomy and lobectomy (Pompili, 2015). (EORTC: European Organization for Research and Treatment of Cancer; PF: Physical function; SF: Social function; RF: Role function; GH: General Health; CF: Cognitive function; PCS: Physical composite score, Shoulder dysf: Shoulder dysfunction)

Although it is tempting to assume that the QoL outcomes of sleeve lobectomy are comparable to those of lobectomies, this remains unclear and data concerning sleeve lobectomy are minimal. Ferguson et al in 2003, compared sleeve lobectomy and pneumonectomy in a meta-analysis. They included 99 studies and afterwards calculated postoperative quality-adjusted life years (QALY) using a statistical decision model. With their analysis, they concluded that sleeve lobectomy provided a favorable overall QoL and QALY advantage when compared to pneumonectomy (Ferguson and Lehman, 2003).

Schulte et al found worse reported postoperative quality of life among those patients who had undergone a pneumonectomy, with significantly worse postoperative values (statistical difference in physical function at 3 months, social function at 3-6 months, role function at 3-6-12 months, general health at 3-6 months and pain at 6 months) compared to those who had had a lobectomy or a bilobectomy (Table 13) (Schulte *et al.*, 2009).

Balduyck et al in 2007, confirmed this finding. They studied 100 pneumonectomy patients and found that they were not able to recover their baseline values in physical function, role function, pain, shoulder dysfunction and dyspnea scales in a 12-month period (Balduyck *et al.*, 2007). A year later, the same group published one of the rare prospective quality of life studies comparing pneumonectomy with sleeve resection (Balduyck *et al.*, 2008). In this study, sleeve lobectomy patients recorded a one-month temporary decrease in physical function and social function after surgery. Global quality of life, symptom, and pain related scores returned to preoperative values approximately one month after sleeve lobectomy. On the other hand, pneumonectomy patients were not able to return to their baseline in physical and role function in a 12-month follow up period.

Leo et al also confirmed the negative impact of pneumonectomy in quality of life, with 25 % of patients after pneumonectomy experiencing impaired quality of life after the surgical resection (Leo *et al.*, 2010).

Sartipy also was able to identify the extent of the parenchymal resection as the strongest predictor of physical quality of life decline 6 months after the operation (Sartipy, 2009). However, the mental components did not differ between patients undergoing a lobectomy or a pneumonectomy.

Brunelli et al also reported similar results, finding significantly lower physical composite score among patients with pneumonectomy, but similar mental composite score 3 months after the operation (Brunelli *et al.*, 2007).

Although there is still much room for improvement in measuring quality of life after lung resection and there are rare studies comparing sleeve resection and pneumonectomy, based on the current evidence, it seems clear pneumonectomy has the worst effects in quality of life among all the anatomical lung resections, making appropriate, when possible, to suggest other parenchymal sparing operations.

4. HYPOTHESIS

HYPOTHESIS:

The hypothesis of this study is:

Neoadjuvant chemoradiation therapy may be associated with an increased risk of postoperative pulmonary and airway complications after sleeve resection of the lung and these complications may have a negative impact on the overall survival of this group of patients.

5. OBJECTIVES

OBJECTIVES:

a) Main objectives:

1. Analyze the association between the incidence of postoperative pulmonary complications and airway complications in patients undergoing pulmonary sleeve resection with or without the use of neoadjuvant chemoradiation therapy.

2. Analyze the overall survival of the patients who underwent sleeve resection with and without neoadjuvant chemoradiation therapy and specifically in those patients who were diagnosed with NSCLC.

b) Secondary objectives:

1. Analyze the characteristics of the population of patients submitted to sleeve resection of the lung.
2. Analyze the distribution of the risk-related variables in the studied population.
3. Analyze the incidence of postoperative pulmonary complications among patients who underwent a sleeve resection of the lung in the whole series and by type of resection.
4. Analyze the incidence of airway complications among patients who underwent a sleeve resection of the lung in the whole series and by type of resection.

6. MATERIALS AND METHODS

MATERIALS AND METHODS:

a) Choice of Data Set

The operative experience of the Brigham and Women's Division of Thoracic Surgery in Boston was chosen as the data set to test these hypotheses. This data set provided a very large clinical volume with a standardized approach to patient care.

b) Studied population

We have reviewed a prospective cohort of 143 patients who underwent sleeve resection for any indication in our Institution between January 1998 and December 2016. The considered exposure was the administration of neoadjuvant chemoradiation prior to the sleeve resection. All the information was retrieved from a prospectively recorded database with double quality audit of the data introduced.

The flow diagram showing the population selection is shown in Figure 16.

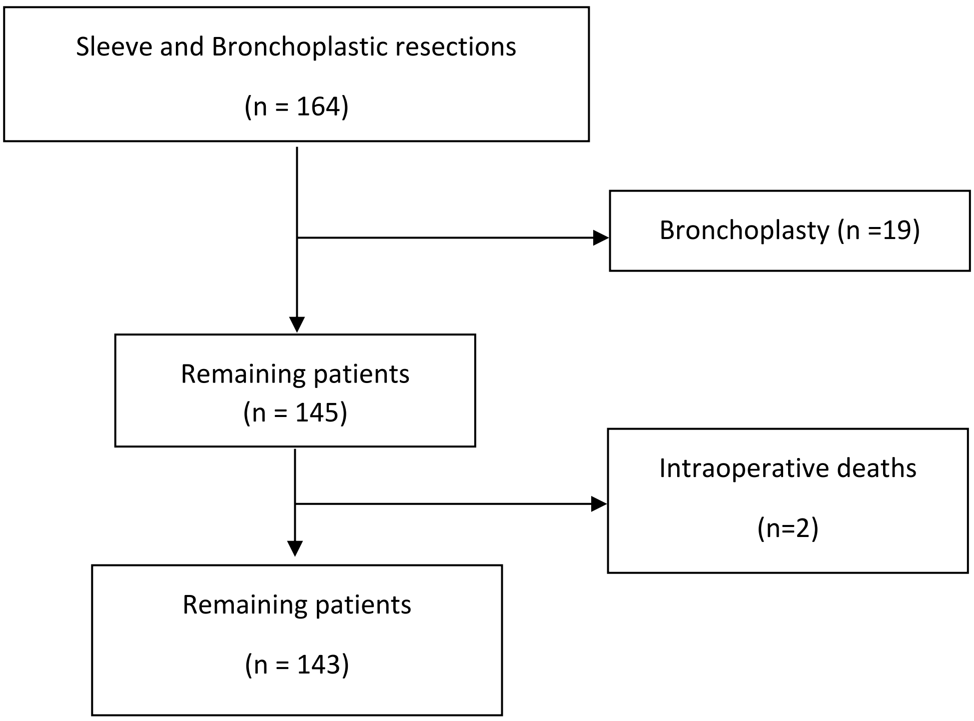

Figure 16: Inclusion criteria flow diagram

c) Perioperative management

Before the operation, patients' work up included physical examination, hematological and biochemical tests, electrocardiogram, chest X-rays, CT scan of the chest, PET-CT, bronchoscopy and EBUS or cervical mediastinoscopy when needed. Other tests were only indicated if previously obtained results suggested them.

Pulmonary function tests were routinely indicated in all patients. In this study, we have analyzed FEV1 % and DLCO % values according to age, gender and height of the patient.

All patients with previous history of relevant cardiovascular disease were referred to the cardiologist for further assessment and a stress test was routinely ordered. As a common practice, coronary stenoses were stented or by-passed before lung surgery.

Perioperative management was uniform for all the patients along the study period. All cases were anesthetized and operated on under the supervision of the same team of senior cardio-thoracic anesthetists and thoracic surgeons, respectively. Prophylactic antibiotic regimen was based on a standard dose of Cefazolin 2000 mg that was repeated 6 hours later if surgery continued.

The surgical technique has been described elsewhere (Mentzer *et al.*, 1993; Mentzer, 1998; Konstantinou *et al.*, 2009) but briefly, it consisted in a preoperative flexible bronchoscopy to assess endobronchial tumor extension and plan the needed resection. It includes circumferential dissection of the bronchus or the pulmonary artery or both, with the best possible oncologic margins and paying attention, in the case of the bronchus, to preserve an appropriate blood supply. The bronchial anastomosis was performed using either a continuous running monofilament suture or interrupted Vicryl™ suture. In general, the posterior aspect of the anastomosis is performed first along the mediastinal face of the bronchus starting at the cartilaginous–membranous juncture. Sewing is continued to the middle of the cartilaginous ring. Circular pulmonary artery anastomosis was performed when needed, using 5/0 polypropylene suture. All the anastomoses were systematically covered by intercostal muscle flaps harvested during the thoracotomy, pleural flaps or pericardial fat pad flaps depending on the surgeon's preferences. Before extubation, a routine bronchoscopy was performed to check the anastomosis and to clean up remaining secretions.

All the patients were extubated in the operating room and, after approximately 6 hours in the recovery room, they were transferred to the TICU. Postoperative analgesia consisted of an epidural catheter with bupivacaine and fentanyl infusion during the first 3 days or until the chest tube was removed, oral oxycodone or dilaudid, and non-steroid anti-inflammatory drugs and narcotics, when needed, thereafter. Nursing care was homogeneous in all cases and included chest physiotherapy and early mobilization of the patients.

d) Variables and outcomes

The outcomes selected as dependent variables were the occurrence of postoperative pulmonary complications and the occurrence of airway complications.

Among the postoperative pulmonary complications, any of the following postoperative events were considered: pulmonary atelectasis requiring bronchoscopy, pneumonia or both. Positive diagnosis was provided if any of the postoperative chest radiographs reported consolidation or atelectasis, when leukocytosis (WBC over 11000 x 10^6/L) and fever (Body temperature >38ºC) of pulmonary origin according to the attending surgeon, when a positive sputum culture was present or there was a change in the quality of the sputum respect to the preoperative sputum and, finally, if respiratory insufficiency (Sp02<90 % on room air) is present measured by a peripheral pulsioximetry (American Thoracic Society and Infectious Diseases Society Of America, 2005).

Among the airway complications, stenosis requiring dilation, bronchopleural fistula, bronchovascular fistula and need for completion pneumonectomy for anastomosis breakdown were considered.

Definitions for each type of postoperative complication were agreed in advance by all team members and all adverse events were recorded at patient's discharge on real time.

Completeness and accuracy of all records were audited by a data manager at the time of patient's discharge.

The independent variables included in the analysis were: Age, BMI, FEV1 %, FVC %, DLCO %, the presence of coronary artery disease, NSCLC diagnosis and the neoadjuvant treatment status.

Although we planned to include renal insufficiency as an independent variable in the analysis, we decided to exclude it given the low number of patients diagnosed with it.

e) <u>Statistical considerations</u>

The dataset includes 143 independent patients who were submitted to a surgical procedure, in this case sleeve resection, at the Brigham and Women´s Hospital between January 1998 and December 2016.

The studied intervention was the administration or not of neoadjuvant chemoradiation treatment and the outcomes of interest were the incidence of postoperative cardiopulmonary complications and airway complications and the overall survival.

To analyze the outcomes, logistic regression methodology was selected, including as covariates general demographic features of the patients (age, gender, date of surgery, weight, height, FEV1 %, FVC %, DLCO %, Coronary artery disease) and clinical variables as diagnosis of NSCLC, clinical and pathological stage and type of surgery.

The complications studied were defined in advance and submitted to a double quality audit when coding them on the database. Furthermore, they were coded individually as pneumonia, atelectasis, stenosis, bronchopleural fistula, bronchovascular fistula and need for completion pneumonectomy and they were grouped in postoperative pulmonary complications and airway complications for analysis purposes.

The distribution of the continuous numerical variables in the population was studied with the Skewness/Kurtosis test.

Multicollinearity was also tested using the tolerance (an indicator of how much collinearity a regression analysis can tolerate) and VIF (variance inflation factor, an indicator of how much of the inflation of the standard error could be caused by collinearity) (Mansfield and Helms, 1982).

Once multicollinearity was dismissed, all the selected variables were kept in the model. Each model´s fit was tested with the Hosmer and Lemeshow's goodness-of-fit test (Hosmer Jr *et al.*, 2013).

1. Estimation and comparison of postoperative pulmonary complication rates

The incidence of postoperative pulmonary complications was determined for the whole series and for both groups: the patients who had received neoadjuvant treatment and those who had not. Finally, a logistic regression model was created, including the incidence of postoperative pulmonary complications as dependent variable and Age, BMI, FEV1 %, FVC

%, DLCO %, the presence of coronary artery disease, NSCLC diagnosis and the neoadjuvant treatment status as independent variables.

2. Estimation and comparison of airway complication rates

The incidence of airway complications was determined for the whole series and for both groups: the patients who had received neoadjuvant treatment and those who had not. Finally, a logistic regression model was created, including the incidence of airway complications as dependent variable and Age, BMI, FEV1 %, FVC %, DLCO %, the presence of coronary artery disease, NSCLC diagnosis and the neoadjuvant treatment status as independent variables.

3. Estimation and comparison of overall survival rates

The overall survival was determined for both groups and for the subset of patients that were diagnosed with NSCLC. Kaplan Meier overall survival curves were designed for this purpose for both, the whole series, and the patients diagnosed with NSCLC. The curves were tested with log rank test.

All calculations, tables and curves were performed using Stata/IC 15 (StataCorp, Texas, USA).

7. RESULTS

RESULTS

Between January 1998 and December 2016, 143 patients underwent sleeve resection at the Brigham and Women's Hospital in Boston.

The characteristics of the variables studied in the population are as follows:

Age: Continuous numerical, years (Skewness/Kurtosis test for normality: p= 0.0276).

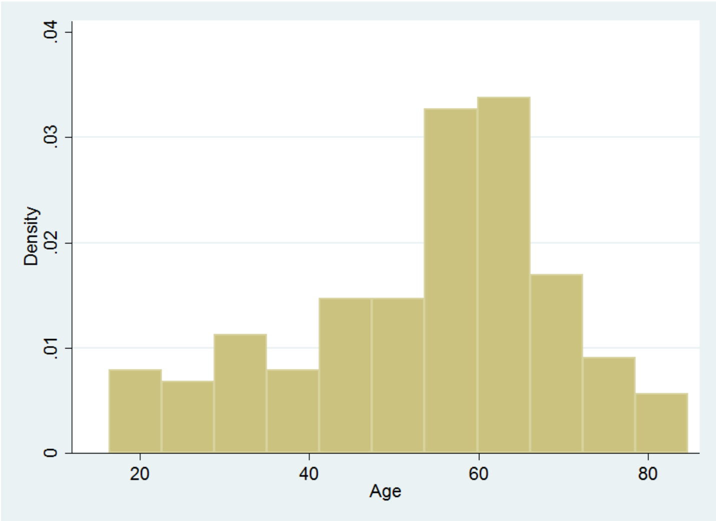

Figure 17: Distribution of variable Age in the studied population.

Gender: Categorical (Codified as 0: Male, 1: Female).

BMI: Continuous numerical, kg/m^2 (Skewness/Kurtosis test for normality: p= 0.0000).

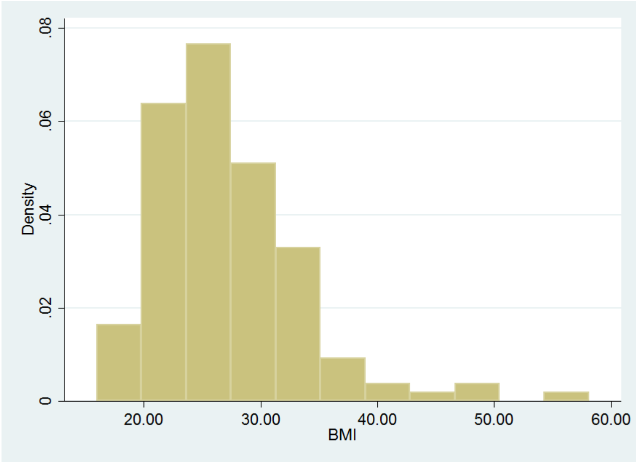

Figure 18: Distribution of variable BMI in the studied population.

FEV1 %: Continuous numerical (Skewness/Kurtosis test for normality: p= 0.1736).

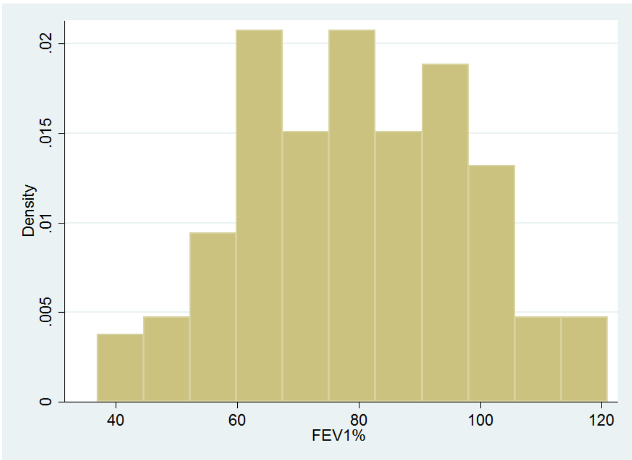

Figure 19: Distribution of variable FEV1 % in the studied population.

FVC %: Continuous numerical (Skewness/Kurtosis test for normality: p= 0.1044).

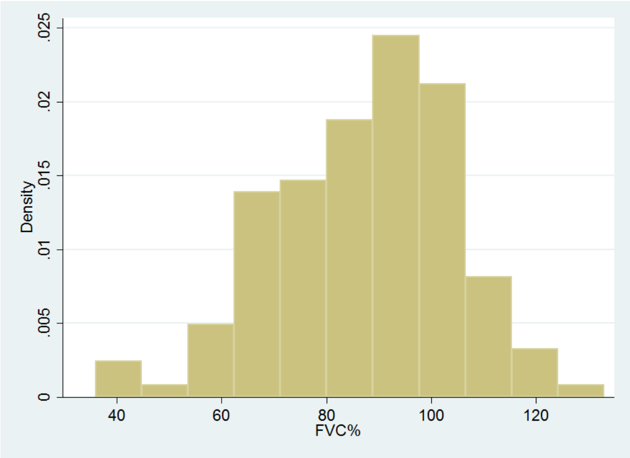

Figure 20: Distribution of variable FVC % in the studied population.

Tiffeneau-Pinelli index: Continuous numerical (Skewness/Kurtosis test for normality: p= 0.0000).

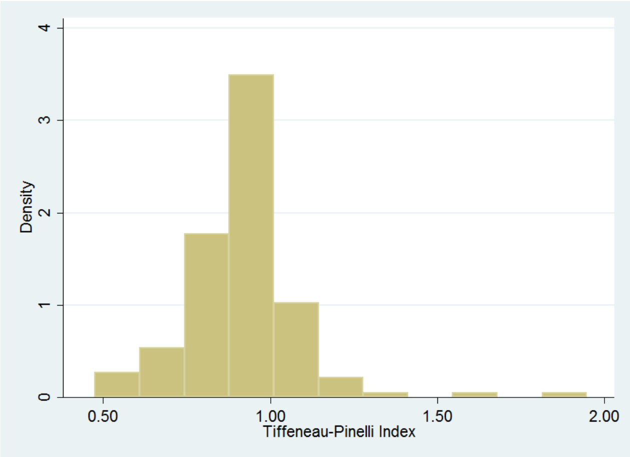

Figure 21: Distribution of variable Tiffeneau-Pinelli index in the studied population.

DLCO %: Continuous numerical (Skewness/Kurtosis test for normality: p= 0.8726).

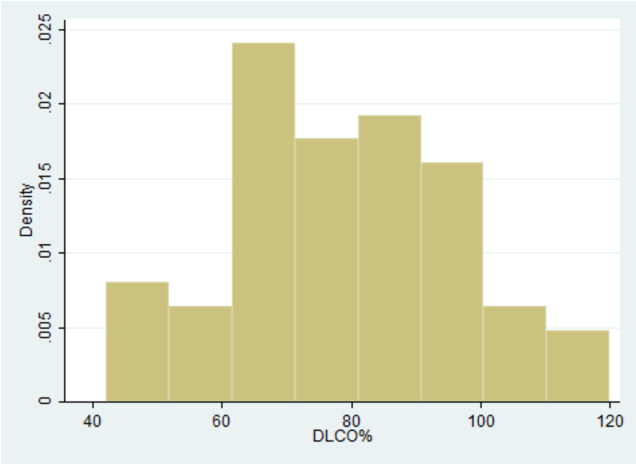

Figure 22: Distribution of variable DLCO % in the studied population.

Coronary Artery Disease (CAD): Categorical (Codified as 0: No, 1:Yes).

Renal insufficiency, Serum Cr>1.2 mg/dL: Categorical (Codified as 0: No, 1:Yes).

Radiation Dose, Gy: Continuous numerical.

Diagnosis (NSCLC versus others): Categorical (Codified as 0: Others, 1: NSCLC).

Survival: Continuous numerical, months.

Pneumonia: Categorical (Codified as 0: No, 1: Yes).

Atelectasis: Categorical (Codified as 0: No, 1: Yes).

Postoperative pulmonary complications: Categorical (Codified as 0: No, 1: Yes).

Stenosis: Categorical (Codified as 0: No, 1: Yes).

Bronchopleural fistula: Categorical (Codified as 0: No, 1: Yes).

Bronchovascular fistula: Categorical (Codified as 0: No, 1: Yes).

Need for Completion pneumonectomy: Categorical (Codified as 0: No, 1: Yes).

The characteristics of the population studied are described in Table 14.

Covariates		No Neoadjuvant Radiation Therapy	Neoadjuvant Chemoradiation Therapy	p-value
Number of patients		n=118	n=25	
Age, years	Mean (SD)	52.55 (16.38)	60.07 (9.18)	0.0305
Gender	Female, n (%)	63 (53.39)	12 (48.00)	0.6240
	Male, n (%)	55 (46.61)	13 (52.00)	
BMI	Mean (SD)	27.41 (6.61)	25.31 (4.53)	0.2049
FEV1 %	Mean (SD)	79.72 (19.21)	79.16 (16.04)	0.8563
FVC %	Mean (SD)	86.60 (16.53)	86.92 (18.36)	0.2012
Tiffeneau-Pinelli index (FEV1/FVC)	Mean (SD)	0.92 (0.02)	0.90 (0.20)	0.0539
DLCO %	Mean (SD)	79.25 (20.44)	71.92 (20.14)	0.1246
Coronary Artery Disease (CAD)	n (%)	12 (10.17)	4 (16.00)	0.4824
Renal Insufficiency, Serum Cr>1.2 mg/dL	n (%)	3 (2.54)	2 (8.00)	0.1787
Radiation Dose, Gy	Mean (SD)	-	57.4 (9.58)	

Table 14: Characteristics of the population.

The mean age of the patients who underwent neoadjuvant therapy followed by sleeve resection was older than those who did not (Mean age 60 vs 53 years old, $p<0.05$) but we did not find any other statistically significant differences regarding the rest of the variables studied (BMI, FEV1 %, FVC %, Tiffeneau index, DLCO %, CAD and renal insufficiency). Among the patients included in the study, 4 underwent neoadjuvant chemotherapy alone, 25 received neoadjuvant chemoradiation therapy and 114 underwent the sleeve resection without any neoadjuvant treatment. 84 of the patients included in the study were histologically diagnosed with NSCLC (84/143, 59 %), one was diagnosed with SCLC, 49 (39 %) underwent the sleeve resection for a carcinoid tumor and the remainder of the patients had a variety of histologies. For the analysis, the 4 patients who underwent neoadjuvant chemotherapy alone had been grouped with patients who did not receive any radiation therapy.

The perioperative 30-day mortality of the series was 3.5 % (5 patients of 143), with 4 patients in the non-neoadjuvant radiation group and 1 patient in the neoadjuvant chemoradiation treatment group. The overall incidence of postoperative pulmonary complications in the whole series was 34.26 % (49 out of 143) with significant differences found between the neoadjuvant chemoradiation therapy group and the other group. 21 of 25 patients in the neoadjuvant group (84.00 %) experienced some type of postoperative pulmonary complications whereas 28 of 118 patients in the non-neoadjuvant radiation therapy group (23.73 %) experienced them ($p < 0.05$). Likewise, the rates of pneumonia, atelectasis, respiratory insufficiency, airway stenosis, prolonged air leak, incidence of bronchopleural fistula and need for completion pneumonectomy (6/24, 25 %) were all higher in the neoadjuvant chemoradiation therapy group when compared to the non-neoadjuvant radiation therapy group ($p < 0.05$, Table 15).

Among the patients who required a completion pneumonectomy, all except for 1 were in the neoadjuvant chemoradiotherapy group, with radiation doses that ranged between 50 and 68 Gy. The median overall survival of those patients who required completion pneumonectomy was 28 months (Range: 7-130, mean: 38.57 months, SD: 41.35).

Covariates		No Neoadjuvant Therapy	Neoadjuvant Chemoradiation Therapy	*p-value*
Number of patients		*n=118*	*n=25*	
Histology	*NSCLC, n (%)*	60 (50.85)	24 (96.00)	*<0.05*
	Carcinoid, n (%)	46 (38.98)	-	
	SCLC, n (%)	1 (0.85)	-	
	Other, n (%)	11 (9.32)	1 (4.00)	
Postoperative Pulmonary Complications	*n (%)*	28 (23.73)	21 (84.00)	*<0.05*
Pneumonia	*n (%)*	15 (12.71)	10 (40.00)	*<0.05*
Atelectasis	*n (%)*	12 (10.17)	15 (60.00)	*<0.05*
Respiratory Insufficiency	*n (%)*	5 (4.24)	7 (28.00)	*<0.05*
Prolonged Air Leak	*n (%)*	6 (5.08)	-	
Postoperative Airway Complications	*n (%)*	8 (6.68)	10 (40.00)	*<0.05*
Stenosis	*n (%)*	5 (4.24)	5 (20.00)	*0.01*
Bronchopleural Fistula	*n (%)*	2 (1.69)	4 (16.00)	*<0.05*
Completion Pneumonectomy	*n (%)*	1 (0.85)	6 (24.00)	*<0.05*
Survival analysis				
Recurrence	*n (%)*	19 (16.10)	15 (60.00)	*<0.05*
***NSCLC patients*	*Median*	62	43	*0.025*

Table 15: Surgical outcomes.

The incidence of postoperative pulmonary complications and airway complications was also analysed by type of resection (Tables 16 and 17), without statistically significant differences among them.

Type of surgery	No, n (%)	Yes, n (%)	Total, n (%)
Airway resection	4 (2.80)	1 (0.70)	5 (3.50)
RUL	30 (20.98)	22 (15.28)	52 (36.36)
ML	13 (9.09)	1 (0.70)	14 (9.79)
RLL	11 (7.69)	4 (2.80)	15 (10.49)
LUL	20 (13.99)	9 (6.29)	29 (20.28)
LLL	13 (9.09)	9 (6.29)	22(15.38)
RN	1 (0.70)	2 (1.40)	3 (2.10)
Lobectomy	2 (1.40)	1 (0.70)	3 (2.10)

Table 16: Postoperative pulmonary complications by type of resection (p = 0.262).

RUL: Right upper lobectomy; ML: Middle lobectomy; RLL: Right lower lobectomy; LUL: Left upper lobectomy; LLL: Left lower lobectomy; RN: Right pneumonectomy.

Type of surgery	No, n (%)	Yes, n (%)	Total, n (%)
Airway resection	5 (3.50)	0 (0.00)	5 (3.50)
RUL	44 (30.77)	8 (5.59)	52 (36.36)
ML	14 (9.79)	0 (0.00)	14 (9.79)
RLL	13 (9.09)	2 (1.40)	15 (10.49)
LUL	25 (17.48)	4 (2.80)	29 (20.28)
LLL	20 (13.99)	2 (1.40)	22(15.38)
RN	2 (1.40)	1 (0.70)	3 (2.10)
Bilobectomy	2 (1.40)	1 (0.70)	3 (2.10)

Table 17: Postoperative airway complications by type of resection (p = 0.570).

The VIF and tolerance test did not show multicollinearity of the variables studied (Table 18).

Variable	VIF	Tolerance (1/VIF)
Age (Years)	1.37	0.73
BMI (kg/m^2)	1.16	0.87
FEV1 %	2.40	0.42
FVC %	2.24	0.45
DLCO %	1.18	0.85
CAD	1.14	0.88
nCRT	1.19	0.83
NSCLC	1.66	0.60

Table 18: Multicollinearity among the variables included in the model (Note that a tolerance of 0.1 or less, equivalent to VIF of 10 or greater would have warranted further investigations).

Logistic regression analysis showed that in our population, only age and neoadjuvant chemoradiation therapy were related with an increased risk of postoperative pulmonary complications (p= 0.046 and p= 0.01 respectively, Table 19).

Hosmer-Lemeshow goodness of fit for the model showed good adjustment, with p=0.84.

Variable	Odds ratio	95 % Confidence interval	p Value
Age (Years)	1.06	0.001-0.12	0.046
BMI (kg/m^2)	0.92	-0.20-0.04	0.168
FEV1 %	0.97	-0.18-0.11	0.658
FVC %	1.02	-0.13-0.17	0.788
DLCO %	1.01	-0.01-0.04	0.382
CAD	0.62	-2.60-1.66	0.667
nCRT	25.66	1.25-5.22	0.01
NSCLC	0.34	-2.89-0.72	0.239

Table 19: Logistic regression model for postoperative pulmonary complications.

Likewise, the logistic regression model showed that only the administration of chemoradiation therapy was related to an increased risk of airway complications (p=0.022, Table 20).

Hosmer-Lemeshow goodness of fit for the model showed good adjustment to the data, with p=0.43.

Variable	Odds ratio	95 % Confidence interval	p Value
Age (Years)	1.068807	.969289-1.178543	0.182
Type of surgery	.9961078	.622978-1.592722	0.987
BMI (kg/m^2)	1.030618	.8810293-1.205605	0.706
FEV1 %	.9786335	.9038942-1.059553	0.594
FVC %	.970315	.9037569-1.041775	0.406
DLCO %	.9993192	.9560094-1.044591	0.976
CAD	.6204765	.0438233-8.785083	0.724
nCRT	17.36375	1.522785-197.9923	0.022
NSCLC	.4355181	.0155103-12.22906	0.625

Table 20: Logistic regression model for airway complications.

The histologic characteristics as well as the stage of studied patients with NSCLC are shown in Table 21.

Covariates		No Neoadjuvant Therapy	Neo-adjuvant Therapy	p-value
Carcinoma Histology		n=54	n=24	
Adenocarcinoma	n (%)	14 (23.33)	9 (37.50)	0.1884
Squamous Cell	n (%)	38 (63.33)	14 (58.33)	0.6699
Mucoepidermoid	n (%)	4 (6.67)	-	-
Neuroendocrine	n (%)	1 (1.67)	-	-
Pleomorphic	n (%)	1 (1.67)	-	-
Poorly Differentiated	n (%)	2 (3.33)	1 (4.17)	0.8525
Clinical Stage				
IA	n (%)	18 (30.00)	4 (16.67)	0.2093
IB	n (%)	20 (33.33)	1 (4.17)	0.0053
IIA	n (%)	11 (18.33)	2 (8.33)	0.2523
IIB	n (%)	4 (6.67)	3 (12.50)	0.3822
IIIA	n (%)	6 (10.00)	13 (54.17)	0.0011
IIIB	n (%)	1 (1.67)	-	-
IV	n (%)	-	1 (4.17)	-
Pathology Stage				
0	n (%)	-	5 (20.83)	-
IA	n (%)	11 (18.33)	7 (29.17)	0.2743
IB	n (%)	12 (20.00)	2 (8.33)	0.1949
IIA	n (%)	25 (41.67)	1 (4.17)	0.0008
IIB	n (%)	3 (5.00)	2 (8.33)	0.5597
IIIA	n (%)	9 (15.00)	7 (29.17)	0.1352

Table 21: Histologic and clinic-pathologic features of NSCLC patients.

The overall median survival for the whole series was 157 months for the patients who did not receive any neoadjuvant therapy (including those with carcinoid tumors) and 43 months for the patients who did (p= 0.000). Among patients with NSCLC the median overall survival was 62 months for those who did not receive neoadjuvant therapy and 43 months for those who received neoadjuvant chemoradiation treatment (p=0.0256, Figures 23 and 24).

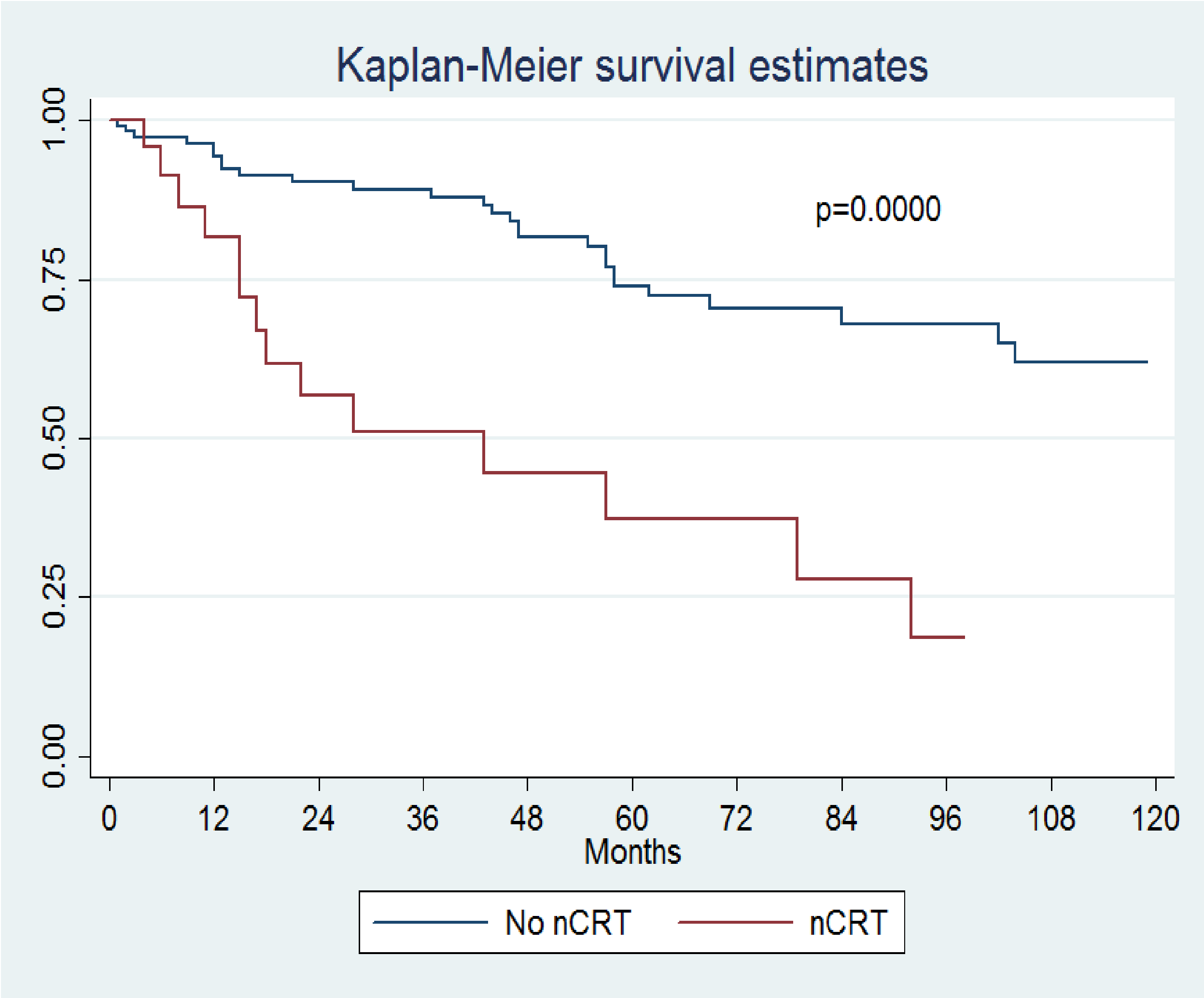

Figure 23: Overall median survival of all the series.

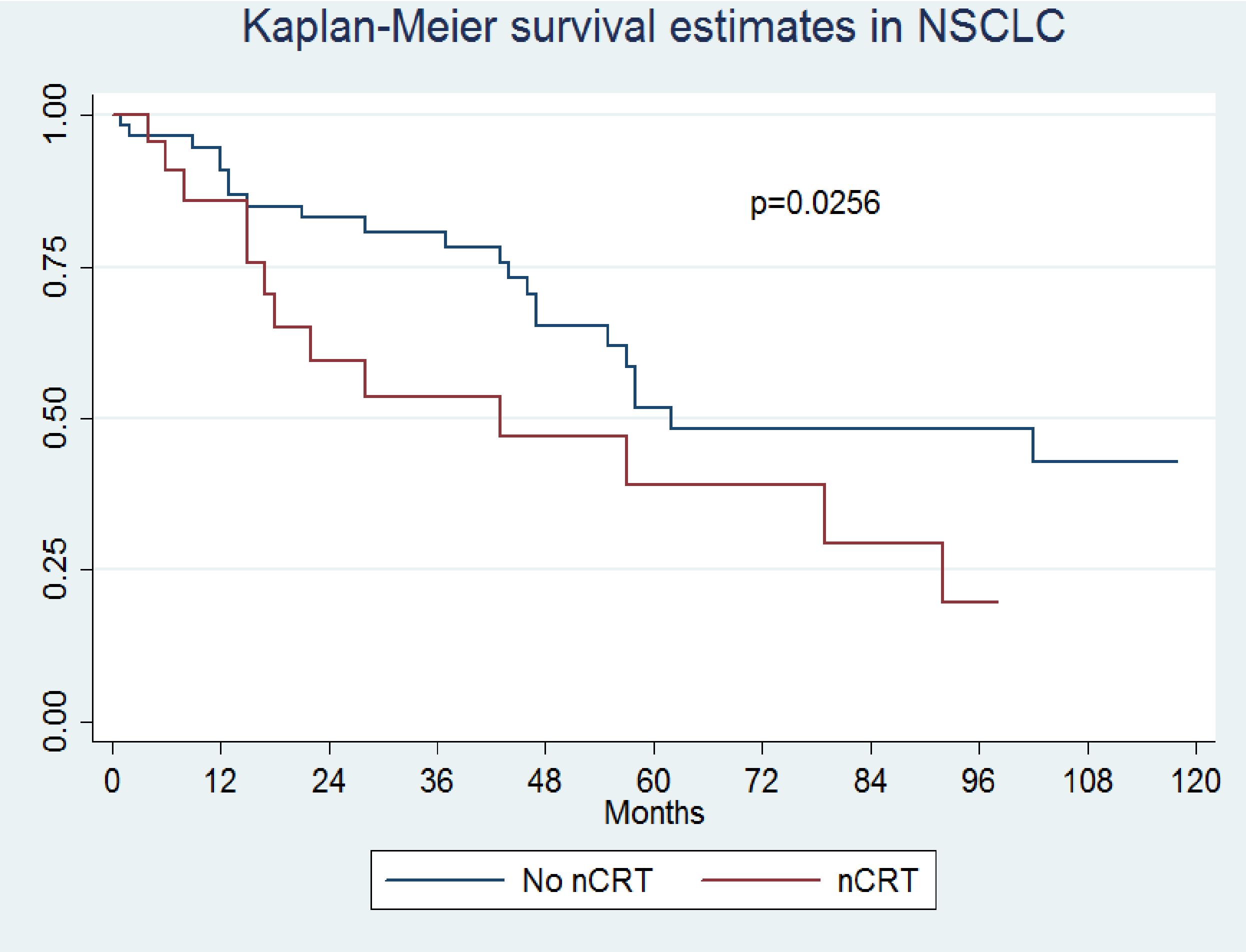

Figure 24: Overall median survival of the patients diagnosed with NSCLC.

8. DISCUSSION

DISCUSSION

Despite multiple advances in NSCLC treatment, surgical resection remains the treatment of choice for those patients who are fit enough to undergo surgery and whose tumors are resectable (Ettinger *et al.*, 2017).

Pneumonectomy has proven to be a suitable oncologic operation for centrally located tumors and those affecting the airway. However, perioperative risk (death within 30 days of surgery) for pneumonectomy remains as high as 7 %, almost 3 times the risk of lobectomy (ESTS, 2012) and quality of life is also significantly impaired (Ferguson and Lehman, 2003). In previously published works, it has been shown that N0 and N1 patients who underwent sleeve lobectomy have better surgical outcomes when compared to patients who underwent a pneumonectomy (Jiménez *et al.*, 2006). Also, perioperative mortality risk in pneumonectomy is increased, being long-term (6 months) mortality risk as high as 24.7 % for right sided pneumonectomy patients (Rodríguez *et al.*, 2013). In our study of 263 patients who underwent a pneumonectomy, multivariate analysis showed that the laterality of the pneumonectomy and the presence of any cardiorespiratory complications were the main factors leading to death after hospital discharge (Rodríguez *et al.*, 2013). In another study, the authors proved that pneumonectomy offered worse overall survival than lobectomy or sleeve lobectomy in stage IB (7^{th} Edition) (Goldstraw *et al.*, 2007) NSCLC patients (Rodríguez *et al.*, 2015). It is true that in both cases, as they were retrospective analysis, I was not able to analyze the causes leading the authors to perform a pneumonectomy. These results, however, and the surgical training I have received, have influenced my clinical practice and the practice of my faculty in Boston. As other authors have recommended (Doddoli *et al.*, 2005), we have tried to avoid pneumonectomies when possible. The Brigham and Women´s Hospital large volume and lung transplant experience have provided the faculty with extensive airway reconstruction experience.

It is under these circumstances, while trying to avoid a pneumonectomy in centrally located tumors, when both neoadjuvant therapy and sleeve resections become valuable (Ma *et al.*, 2016).

Sleeve resection has become the established alternative for pneumonectomy regardless of the pulmonary function. Although technically more challenging, it has been shown that the number of pneumonectomies performed in an institution tends to decrease with increased surgeons' expertise in bronchoplastic and angioplastic techniques (Martin-Ucar *et al.*, 2002; Gómez-Caro *et al.*, 2011). Sleeve resections are performed for approximately 5 % to 8 % of patients with resectable NSCLC (Tedder *et al.*, 1992) but rates as high as 13 % have also been published (Okada *et al.*, 2000; Gómez-Caro *et al.*, 2011).

The perioperative mortality and morbidity after sleeve resection has been shown to be better than in pneumonectomy, with significantly improved quality of life, even in the elderly (Yoshino *et al.*, 1997; Okada *et al.*, 2000; Ferguson and Lehman, 2003; Ma *et al.*, 2007; Bölükbas *et al.*, 2010; Schirren *et al.*, 2011). In recent studies the perioperative mortality of sleeve resection ranged from 2 % in the series of Merritt et al (Merritt *et al.*, 2009) to 4.1 % in the studies by Ferguson et al (Ferguson and Lehman, 2003) and Yildizeli et al (Yildizeli *et al.*, 2007). In a meta-analysis published in 2012 by Shi et al (Shi *et al.*, 2012), sleeve resection patients had lower mortality when compared with pneumonectomy patients with similar morbidity and locoregional recurrence rates. Furthermore, sleeve lobectomy patients had a better overall survival, less loss of pulmonary function and better quality of life than pneumonectomy patients did.

On the other hand, it seems clear that neoadjuvant therapy benefits patients and improves survival in stage IIIA and some IIIB situations (mediastinal downstaging and tumor shrinkage allowing for parenchyma sparing operations) with careful selection of surgical candidates (Thomas *et al.*, 2008; Albain *et al.*, 2009; Cerfolio *et al.*, 2009).

Several studies have shown the feasibility and the safety of sleeve resection after neoadjuvant treatment (Burfeind *et al.*, 2005; Bagan *et al.*, 2009; Milman *et al.*, 2009; Gómez-Caro *et al.*, 2012), although other authors found opposite results (Rea *et al.*, 2008), specifically after neoadjuvant radiotherapy (Hampel *et al.*, 2010). These adverse results have been attributed most of the time to the effects that neoadjuvant treatment, specifically radiation, has on the blood supply, directly affecting the bronchial anastomotic healing (Yamamoto *et al.*, 2000; Hampel *et al.*, 2010).

In our study, the perioperative mortality observed among patients who underwent sleeve resection was 3.5 % (3 % among patients without neoadjuvant radiation treatment and 4 % in the patients with neoadjuvant chemoradiotherapy treatment), comparable to the rates reported in the literature. As expected and supported by the evidence of radiotherapy impairing bronchial healing, most of the airway complications and the completion pneumonectomies occurred among the patients treated with neoadjuvant chemoradiation therapy.

Data in the literature studying specifically the incidence of postoperative pulmonary complications after sleeve resections are minimal, but our results can be compared to those obtained by Rea et al (Rea *et al.*, 2008) and Doddoli et al (Doddoli *et al.*, 2005) in their series.

Although coronary artery disease, FEV1 %, FVC %, DLCO % and renal insufficiency have already been proved to be directly related with the incidence of complications after major anatomical lung resections (Brunelli *et al.*, 2010; Ferguson *et al.*, 2014; Brunelli *et al.*, 2015), in our population only the age and the administration of neoadjuvant chemoradiation therapy were related with an increased risk of postoperative pulmonary complications and only the administration of neoadjuvant therapy was related with an increase in airway complications. The minimal impact of coronary, pulmonary, and renal diseases may be related to the ability to identify these problems and improve them pre-operatively at the Brigham and Women's Hospital.

Furthermore, in order to try to control the possible confounders related to the preoperative risk factors and to obtain the most accurate results in the logistic regression model, we chose the 'manual method' to introduce the independent variables, keeping in the model all those clinically relevant variables that could have a negative impact in outcomes after pulmonary resection. We did so because after estimating multicollinearity of the variables with the VIF and tolerance tests they did not show any correlation among them (Mansfield and Helms, 1982).

Whether or not the effect of neoadjuvant chemoradiation was related to the combination of both chemotherapy and radiation or radiation alone, could not be determined in our study, as all the patients treated with radiotherapy received it in combination with chemotherapy and only 4 patients received chemotherapy alone. Based on Yildizeli et al (Yildizeli *et al.*, 2007) and Hampel et al (Hampel *et al.*, 2010) studies, we could hypothesize those results are secondary to the effects induced by radiation therapy, but our data does not allow that analysis.

It is remarkable that the incidence of postoperative pulmonary complications and airway complications among our neoadjuvant therapy patients is consistently higher than those already reported (Rendina *et al.*, 1997; Veronesi *et al.*, 2002; Massard, 2009) being notable for a 25 % of completion pneumonectomy rate. This may be related to an institutional bias in favor of radiation doses near 54 Gy in the neoadjuvant setting.

Although multimodality treatment can have deleterious effects on the patients, before, during and after the operation, we have not been able to find an objective explanation for the 84 % complication rate among the neoadjuvant chemoradiotherapy Brigham patients. One explanation of this fact could be the meticulously defined and prospectively recorded Brigham database of complications and adverse events. The Division of Thoracic Surgery has advocated aggressively identifying minor and moderate complications to prevent postoperative deaths.

When analyzing the completion pneumonectomy rate within the Brigham series, I have sought out similar experiences by other authors. Although airway complications are not a systematically reported outcome in the literature, some authors have similar rates of completion pneumonectomy when trying to solve airway problems or treat complex bronchopleural fistulas (Rea *et al.*, 2008).

In this series, the incidence of bronchopleural fistula was 4.19 %, similar to those rates already reported (Kutlu and Goldstraw, 1999; Ludwig *et al.*, 2005; Yildizeli *et al.*, 2007; Merritt *et al.*, 2009). Some authors (Rendina *et al.*, 2002) have shown that pedicled flaps may have an important role in reducing the incidence of airway complications but, in the Brigham practice, bronchial anastomosis coverage depends on attending preferences and includes pleura, azygous vein, pericardium and pericardial fat pat. As it is an inconsistent and a very heterogeneous variable, I decided to exclude it from this study.

Different authors consider the protection of the bronchial anastomosis with a pedicled flap a mandatory part of the operation (Yildizeli *et al.*, 2007). Others do not perform it routinely, even after high doses of radiation (Storelli *et al.*, 2012). Even with pedicled flaps, the rates of reported bronchopleural fistula range from 2 % to 6.9 % (Ludwig *et al.*, 2005; Yildizeli *et al.*, 2007; Merritt *et al.*, 2009). Kutlu et al (Kutlu and Goldstraw, 1999), in their series of 100 cases, gave more importance to the careful handling of the airway and the preservation of the peribronchial tissue than to wrapping the anastomosis. In their series, without any protection of the bronchial anastomosis, Konstantinou et al (Konstantinou *et al.*, 2009) did not register any airway complications. Moreover, the incidence of airway complications after lung transplantation has not been affected by wrapping the anastomosis with omentum or internal mammary pedicled flaps (Khaghani *et al.*, 1994; Weder *et al.*, 2009).

When explaining the limited overall survival of patients who received neoadjuvant chemoradiation treatment in our series, it is difficult to determine if it is secondary to the increased complications after neoadjuvant therapy or to the inclusion of advanced stages of NSCLC.

The long-term results and local control after sleeve resection are still a matter of debate. Reported 5-year survival rates for sleeve resection in N1 patients range from 0 to 64 % (Van Den Bosch *et al.*, 1981; Deslauriers *et al.*, 1986; Van Schil *et al.*, 1991), very similar to the results observed in this series. This heterogeneity has been related to different intraoperative techniques for staging and resection (Veronesi *et al.*, 2002). No statistically significant differences were found in survival and recurrence in N0 and N1 patients when systematic lymphadenectomy was performed (Deslauriers *et al.*, 1986; Van Schil *et al.*, 1991; Mehran *et al.*, 1994). Likewise, no differences in overall survival were found between pneumonectomies and sleeve lobectomies (Weisel *et al.*, 1979; Okada *et al.*, 2000). Even with disappointing survival reported in N2 patients after sleeve lobectomy (Naruke, 1989; Mehran *et al.*, 1994), it would have been difficult to achieve better results with a pneumonectomy, as the main pattern for recurrence were distant metastases (Naruke, 1989; Kumar *et al.*, 1996).

Local recurrence has been another concerning factor after sleeve lobectomy and, although not included in my analysis, it ranges from 4 % (Deslauriers *et al.*, 1986) to 42 % (Rendina *et al.*, 1999) in extended resections. Although Tedder at al (Tedder *et al.*, 1992) reported higher local recurrence after sleeve lobectomy (12.5 %) than after sleeve pneumonectomies (4 %), this information remains difficult to interpret as most of the authors did not specify what the site of recurrence was.

Unfortunately, although this thesis analyzes one of the largest series of sleeve resections after neoadjuvant treatment, the number of patients included remains small, making it difficult to draw definitive treatment recommendations on this group of surgical candidates. The heterogeneity of the population, the different neoadjuvant therapy regimens, as well as the technical aspects of a challenging surgical procedure could have affected the results obtained. The lack of pneumonectomy patients within the chosen dataset has made it impossible to compare the outcomes between the resections.

The lack of analysis by NSCLC stage could have played a role as a confounding factor when analyzing the overall survival. Due to the limited number of patients studied, we were not able to determine if the decreased overall survival in this subset of patients is related to the effects of the neoadjuvant treatment or to an advanced pathological stage. Further analysis with a larger number of patients included is required to help illuminate this matter. Such an analysis might require pooling of large datasets from multiple institutions.

The analysis of this dataset leads us to conclude that selection and preoperative preparation of patients appears to be satisfactory. Details of the operative technique might be improved if it led to less airway complications. Aggressive pulmonary toilet postoperatively, including bronchoscopy where indicated, is a necessary part of patient care. Despite these limitations, this analysis provides new insight that might affect treatment paradigms. For instance, a multimodality treatment option that might be considered could be neoadjuvant chemotherapy followed by surgery, then chemoradiation in the adjuvant setting.

9. CONCLUSION AND CLOSING REMARKS

CONCLUSION AND CLOSING REMARKS:

In conclusion:

1. In this population of patients submitted to sleeve lung resection, I have shown that the administration of neoadjuvant therapy, probably radiotherapy, has a negative impact in the incidence of both respiratory complications and airway complications.

2. It is remarkable to note a 25 % risk of completion pneumonectomy to treat airway complications among those patients who received neoadjuvant chemoradiation therapy in a high surgical volume center.

3. Although we have not been able to conclude the causative effect of neoadjuvant chemoradiation therapy or of the advanced stage at the time of the resection, the patients who required a sleeve resection after neoadjuvant treatment suffered a significantly decreased overall survival when compared to those who did not require neoadjuvant chemoradiation therapy.

4. Considering these results, careful consideration of neoadjuvant chemoradiation treatment in those patients who are surgical candidates but who might require a sleeve resection at the time of the operation, should be made.

5. In case neoadjuvant treatment cannot be avoided, mediastinal restaging and detailed discussion of the increased perioperative risk of complications becomes mandatory.

6. Furthermore, extreme care should be paid to the surgical technique and directed perioperative strategies to avoid respiratory complications such as intensive chest physiotherapy and aggressive pulmonary toilet in order to improve the outcomes of this subgroup of patients.

10.RESUMEN DE LA TESIS

RESUMEN DE LA TESIS

a) Introducción

Las resecciones broncoplásticas son una alternativa válida a la neumonectomía en pacientes con carcinoma de pulmón no microcítico resecable cuando éste se encuentra en la proximidad de la vía aérea. Aunque han demostrado su equivalencia a la neumonectomía en lo que a control local y a distancia de la enfermedad se refiere, debido a su naturaleza y a su mayor complejidad técnica, continúa debatiéndose si la incidencia de complicaciones pulmonares postoperatorias y de la vía aérea, especialmente tras la administración de tratamiento neo-adyuvante con quimio y radioterapia, es mayor que en aquellos pacientes que no reciben tratamiento neo-adyuvante.

Algunos estudios han demostrado el impacto negativo de la radioterapia sobre la circulación bronquial, lo que influye directamente en la cicatrización de las anastomosis, mientras que otros, en su mayoría con un número pequeño de pacientes, no han sido capaces de encontrar diferencias.

b) Estado actual del tema:

La administración de tratamiento neo-adyuvante con quimio y radioterapia ha demostrado ser una opción aceptable en aquellos pacientes con carcinoma de pulmón no microcítico de localización central o localmente avanzado que pueden tolerarlo.

Consideración especial requieren aquellos pacientes que pueden necesitar una neumonectomía o una resección broncoplástica para su tratamiento definitivo, ya que este tratamiento, especialmente la radioterapia, puede presentar efectos deletéreos en la cicatrización de la sutura bronquial.

c) Hipótesis:

La administración de tratamiento neo-adyuvante con quimio y radioterapia en pacientes que van a ser sometidos a una resección pulmonar broncoplástica aumenta la incidencia de complicaciones pulmonares postoperatorias, así como de complicaciones de la vía aérea y estas complicaciones podrían tener un efecto negativo en la supervivencia a largo plazo de este grupo de pacientes.

d) Objetivos:

1. Analizar la asociación entre la incidencia de complicaciones pulmonares y de la vía aérea postoperatorias en pacientes sometidos a resección pulmonar broncoplástica con la administración de tratamiento neo-adyuvante con quimio y radioterapia.

2. Analizar si estas complicaciones se relacionan negativamente con la supervivencia de estos pacientes.

e) Material y métodos:

Hemos estudiado una cohorte prospectiva de 143 pacientes sometidos a resección pulmonar broncoplástica en Brigham and Women´s Hospital entre Enero de 1998 y Diciembre de 2016. Se ha considerado como exposición la administración de tratamiento neo-adyuvante antes de la resección pulmonar. Toda la información se obtuvo de una base de datos prospectiva con doble control de calidad de los datos introducidos.

Tras analizar la distribución de las variables objeto de estudio en la muestra y tras descartar colinearidad entre ellas mediante el cálculo de VIF (Variable Inflation Factor) y Tolerancia, se diseñó un modelo de regresión logística para cada tipo de complicaciones. Las variables dependientes consideradas en cada modelo fueron la incidencia de complicaciones pulmonares postoperatorias y la incidencia de complicaciones de la vía aérea, respectivamente.

Se definieron las complicaciones pulmonares postoperatorias como la incidencia de atelectasia pulmonar que requiriera broncoscopia, neumonía o ambas.

Las complicaciones de la vía aérea incluyen estenosis que requiriera dilatación, fístula bronco-pleural, fístula bronco-arterial y la necesidad de completar la neumonectomía por cualquier problema relacionado con la anastomosis.

Las variables independientes introducidas en cada modelo fueron: Edad, BMI, FEV1 %, FVC %, DLCO %, la presencia de enfermedad coronaria, diagnóstico de carcinoma de pulmón no microcítico y la administración o no de tratamiento neo-adyuvante.

Posteriormente se calculó la supervivencia de toda la serie y de los pacientes diagnosticados de carcinoma de pulmón no microcítico. Se estimaron las diferencias en la supervivencia mediante el test log rank.

Todos los cálculos se realizaron utilizando STATA/IC 15.

f) Resultados:

En total se analizaron 143 pacientes que se sometieron a resección pulmonar broncoplástica en nuestra Institución. Los pacientes que recibieron tratamiento neo-adyuvante eran mayores que los que no lo recibieron (Media: 60 años frente a 53, $p < 0,05$), pero no encontramos diferencias estadísticamente significativas en el resto de las variables. 84 de los 143 pacientes estudiados presentaron el diagnóstico de carcinoma de pulmón no microcítico, 1 fue diagnosticado con carcinoma microcítico, 49 con tumores carcinoides y el resto con histologías variadas.

La mortalidad a 30 días de la serie fue 3,5 % (5 pacientes de 143). La incidencia de complicaciones pulmonares postoperatorias en toda la serie fue 34,26 % (49 pacientes), con diferencias estadísticamente significativas entre el grupo de pacientes que recibió tratamiento neo-adyuvante y el que no lo recibió (84,00 % de complicaciones entre los pacientes que recibieron quimio y radioterapia neo-adyuvante frente a 23,73 % entre los que no la recibieron, $p <0,05$).

Así mismo, la incidencia de neumonía, atelectasia, insuficiencia respiratoria, estenosis de la vía aérea, fístula bronco-pleural y necesidad de completar la neumonectomía (6/24) fueron mayores entre los pacientes que recibieron tratamiento neo-adyuvante ($p<0,05$).

Los pacientes que requirieron completar la neumonectomía se encontraban, excepto 1, en el grupo de tratamiento neo-adyuvante, con dosis de radioterapia que iban desde los 50 hasta los 68 Gy.

La mediana de supervivencia de los pacientes que requirieron completar la neumonectomía fue de 28 meses (Rango: 7 a 130 meses, media: 38,57 meses, SD: 41,35).

Tras el análisis de regresión logística, solo la edad y la administración de tratamiento neo-adyuvante se relacionaron con un aumento de las complicaciones pulmonares postoperatorias (p= 0,046 y p= 0,01 respectivamente, Hosmer-Lemeshow test de bondad de ajuste del modelo: p=0,84).

De la misma manera, otro modelo de regresión logística demostró que solo la administración de tratamiento neo-adyuvante se relaciona con el aumento en la incidencia de complicaciones de la vía aérea (p=0,022, Hosmer-Lemeshow test de bondad de ajuste del modelo: p=0,43).

La mediana de supervivencia de toda la serie fue 157 meses en los pacientes que no recibieron tratamiento neo-adyuvante (incluyendo aquellos con tumores carcinoides) y 43 meses para los pacientes que sí lo recibieron (p=0,000). Entre los pacientes diagnosticados con carcinoma de pulmón no microcítico, la mediana de supervivencia fueron 62 meses para aquellos pacientes que no recibieron tratamiento neo-adyuvante y 43 meses para aquellos que lo recibieron (p=0,0256, Figuras 23 and 24).

11.CONCLUSIONES

CONCLUSIONES

En conclusión:

1. En este grupo de pacientes sometidos a resección pulmonar broncoplástica, la administración de terapia neo-adyuvante, probablemente radioterapia, supone un impacto negativo tanto en la incidencia de complicaciones pulmonares como en la incidencia de complicaciones de la vía aérea.

2. En esta serie procedente de un centro de alto volumen quirúrgico y con un programa consolidado de trasplante pulmonar, la necesidad de completar una neumonectomía para tratar las complicaciones de la vía aérea es de hasta un 25 % en los pacientes que recibieron quimio y radioterapia neo-adyuvantes.

3. Aunque no hemos sido capaces de diferenciar si se debe a la terapia neo-adyuvante en sí o a un estadio oncológico avanzado en el momento del diagnóstico, los pacientes que recibieron tratamiento neo-adyuvante presentan una menor supervivencia cuando se comparan con los que no lo recibieron.

4. Estos resultados apoyan la evaluación cuidadosa de la administración de quimio y radioterapia neo-adyuvantes en todos aquellos pacientes que sean candidatos a una resección en manguito.

5. Cuando el tratamiento neo-adyuvante sea estrictamente necesario y teniendo en cuenta tanto los resultados que presentamos aquí como los presentados anteriormente por otros autores, debe llevarse a cabo una re-estadificación mediastínica sistemática.

6. Dado el mayor riesgo postoperatorio que presentan estos pacientes, su discusión en comités multidisciplinares ha de ser obligatoria, así como una técnica quirúrgica especialmente cuidadosa y la implementación de

estrategias postoperatorias como la fisioterapia respiratoria para prevenir algunas de estas complicaciones.

12. REFERENCES

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13.APPENDIX 1: TABLES AND FIGURES IN ORDER OF APPEARANCE

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14.APPENDIX 2: LIST OF ABBREVIATIONS

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NSCLC: Non small cell lung cancer.

FEV1 %: Forced expiratory volume in the first second.

FVC %: Forced vital capacity.

CT: Computed tomography.

PET-CT: Positron emission tomography–computed tomography.

EBUS: Endobronchial ultrasound.

DCLO %: Diffusing or transfer factor of the lung for carbon monoxide.

PEEP: Positive end-expiratory pressure.

ECMO: Extracorporeal membrane oxygenation.

QoL: Quality of life.

EORTC: European Organization for Research and Treatment of Cancer.

PF: Physical function.

SF: Social function.

RF: Role function.

GH: General Health.

CF: Cognitive function.

PCS: Physical composite score.

Shoulder dysf: Shoulder dysfunction.

QALY: Quality-adjusted life-year.

CAD: Coronary artery disease.

RI: Renal insufficiency.

BMI: Body mass index.

TICU: Thoracic intermediate care unit.

RUL: Right upper lobectomy.

ML: Middle lobectomy.

RLL: Right lower lobectomy.

LUL: Left upper lobectomy.

LLL: Left lower lobectomy.

RN: Right pneumonectomy.

nCRT: Neoadjuvant chemo-radiation therapy.

VIF: Variance inflation factor.

CPNM: Carcinoma de pulmón no microcítico.