Chapter

Bronchopleural Fistula after Pulmonary Resection: Risk Factors, Diagnoses and Management

Kristina Jacobsen

Abstract

Bronchopleural fistula (BPF) after a pulmonary resection is rare with some of the most life-threatening consequences and a high mortality rate. Contamination of the pleural space resulting in empyema and spillage of the infected fluid into the remaining lung leading to respiratory distress remain the biggest concerns with BPF postoperatively. There are many patient characteristics and risk factors that can be evaluated to decrease the chance of a postoperative BPF. Presentation of BPF can be early or late with the late BPF more difficult to diagnosis and manage. Many options to treat BPF include surgical repair, conservative management, and endoscopic treatment.

Keywords: bronchopleural fistula, pneumonectomy, empyema, lung cancer, thoracic surgery

1. Introduction

Bronchopleural fistula (BPF) is defined as a central fistulous connection of inspired air between trachea, major, lobar, or segmental bronchus into the pleural space [1, 2]. Or a BPF can occur peripherally when there are connections between the distal segmental bronchus or lung parenchyma and the pleural space [1, 2]. Although rare, managing a BPF is challenging and represents a high morbidity and mortality.

2. Etiology

After an anatomical lung resection, a BPF is rare but severe complications can occur and may be fatal. The BPF incidence after a pneumonectomy for lung cancer is between 4.5% and 20% and 0.5–1% after a lobectomy [1, 3, 4]. The mortality rate after a pneumonectomy is estimated to be 18–71% with a much lower rate for lobectomy [2, 4]. The pleural space is exposed to the endobronchial bacterial flora with the pleural effusion leaking into the major airway and into the peripheral alveolar space. The main cause of death is aspiration pneumonia, empyema, and subsequent respiratory distress [4, 5]. Treatment for BPF after surgery requires emergency

treatment due to patient's lung volume loss and short-term poor respiratory function with surgical damage to the respiratory muscles [5].

The less common causes of BPF include suppurative lung processes such as septic pulmonary emboli, infected pulmonary infarctions, or tuberculosis [6]. Neoplasms with tumor invasion into the pleural space may also lead to BPF. Iatrogenic etiologies due to complications with chest tube insertion, thoracentesis or lung biopsies may result in BPF [6].

When considering different surgical approaches and incidence of BPF, one study evaluated the Society of Thoracic Surgeons and General Thoracic Surgery Database (STS-GTD) to compare outcomes of video-assisted thoracoscopic surgery (VATS) and robotic-assisted lobectomy (RATS) for primary clinical stage I or II non-small cell lung cancer (NSCLC) at high volume centers from 2009 to 2013. This study identified 1,220 RATS and 12,378 VATS patients. The incidence of BPF between these two groups was not statistically significant (0.6% vs. 0.3%, $p = 0.08$) [7]. Another study that included 737 cases of VATS lobectomies and 748 cases of open lobectomies for the surgical treatment of resectable non-small cell lung cancer showed no statistical difference in incidence of BPF postoperatively [8].

3. Risk factors

Certain anatomic, technical, and patient factors lead to increased risk for BPF (**Table 1**). Generally, right-sided pneumonectomy is associated with high risk of BPF. Devascularization of the bronchial stump, diabetes, malnutrition, steroids, neoadjuvant chemoradiotherapy, stump closure, residual carcinomatous tissue, presence of empyema and postoperative mechanical ventilation all lead to increased risk of bronchial stump dehiscence [9, 10].

3.1 Right sided surgery and right pneumonectomy

Generally, right-side pneumonectomy and right lower lobectomy are associated with high risk of BPF and are multifactorial. The right upper pulmonary artery is made up of the apical, anterior, and posterior ascending branches [11]. The apical and anterior branches are located in the front of the hilum and the posterior is located at the posterior segment of the horizontal fissure [11]. The right lower pulmonary artery is divided into the dorsal and basilar segment and is located at the corresponding position of the posterior ascending branch in

Anatomic Factors
Right pneumonectomy
Technical Factors
Devascularization of bronchial stump
Long bronchial stump
Stump closure
Residual carcinoma at bronchial margin
Patient Factors
Preoperative radiotherapy
Presence of empyema
Postoperative mechanical ventilation
Diabetes
Chronic Steroid Use
Nutritional status

Table 1.
Risk factors for bronchopleural fistula after pulmonary resection.

the horizontal fissure [11]. This single bronchial artery supplies the entire right mainstem bronchus whereas the left mainstem bronchus has a vascular supply by two bronchial arteries [9]. During lymphadenectomy if the single artery of the right bronchus is damaged, the bronchial stump becomes ischemic [4].

After a right pneumonectomy, the risk for BPF increases due to the diversion of the entire cardiac output going through the smaller left lung and increased load on the right ventricle [12]. This compensation results in decreasing circulating blood volume, pulmonary hypertension, increased pulmonary pressures, increased pulmonary vascular resistance and right ventricular failure [12, 13]. Loss of the larger right lung may compromise pulmonary function resulting in respiratory failure predisposing the patient to the postpneumonectomy edema syndrome [12, 14, 15]. Larger perioperative fluid resuscitation causes overload of the pulmonary circulation and right ventricle and has been reported to be a poor outcome predictor [14, 15].

Anatomical differences in the right bronchus versus the left are significant factors in increased risk of BPF. The right main bronchus is more vertical and wider than the left increasing the accumulation of secretions in the bronchial stump [4]. The right mainstem bronchus is not naturally buttressed by mediastinal tissue coverage and therefore likely to be exposed to the thoracic pleural free space [9, 15]. The left main bronchial stump tends to be protected and covered by the aortic arch with its surrounding vascularized mediastinal tissue [9, 15]. The left bronchial stump retracts within that tissue under the aortic arch after dissection giving protection from the pleural free space.

3.2 Lymph node dissection

The surgical approach to mediastinal lymph node dissection at the time of pulmonary resection for NSCLC has been a subject of interest for several decades. Accurate pathologic lymph node examination offers the most accurate staging and survival benefit and provides the most significant prognostic factor [16]. Accurate nodal staging increases survival by improved risk categorization, increased detection of candidates for adjuvant therapy and possibly resection of oligometastatic disease [17]. Staging NSCLC may have lymph node metastases even after appearing localized by imaging which makes the extent of mediastinal lymph node removal controversial [18]. Patients with negative nodes by systematic lymph node dissection with early stage NSCLC did not have improved survival with complete mediastinal lymph node dissection [17–19]. Intraoperative lymph node sampling is removal of one or more lymph nodes decided by preoperative or intraoperative findings and is determined by the surgeon [19]. Systematic nodal dissection contains all mediastinal tissue containing lymph nodes and is removed systematically within anatomical landmarks. To meet minimal recommendations, for right-sided cancers, mediastinal lymphadenectomy should contain stations 2R, 4R, 7, 8, and 9. Left side stations 4 L, 5, 6, 7, 8 and 9 should be included [17–19]. Patients should have N1 and N2 node resection with a minimum of N2 stations sampled [17–19]. Some argue that systematic mediastinal lymph node sampling versus mediastinal lymph node dissection is adequate for staging and that complete dissection does not provide survival advantage as most patients with N2 disease die from systemic disease [18, 19].

Lymph node dissection removes tissue from adjacent organs and skeletonization of intrathoracic structures. It includes enblock removal of tissues with cancer cells that includes lymph nodes and fatty tissue within bronchus, trachea, superior vena cava, aorta, pulmonary vessels, and pericardium [17, 20].

Healing of the bronchial stump is delayed due to decreased post-operative blood supply after lymph node dissection. Superior and inferior mediastinal lymph node

dissection for NSCLC is widely performed adjunct to pulmonary resection [21]. Vascular supply to the suture line is watershed from the descending thoracic aorta across the mediastinum and is decreased after mediastinal lymph node dissection [11]. Ischemic bronchitis after lymph node dissection due to decreased bronchial microvascularization negatively influences bronchial stump healing [11, 21]. Lymph node sampling rather than complete lymphadenectomy leading to devascularization of the bronchial stump can permit adequate blood flow to the bronchial stump [21]. Meticulous technique while dissecting around the bronchus is necessary. Preventing devascularization of the bronchus during lymph node dissection can decrease the incidence of fistulization [9, 21].

3.3 Stump closure

The Sweet principles on bronchial closure, emphasized in 1945 are still followed today. Trauma to the end of the bronchus should be minimized and the blood supply must be preserved all the way to the end cut of the bronchus [22]. The cut edges of the bronchus should be carefully approximated [22]. Tissue reinforcement of the bronchial closure should be provided. Clamps should not be used on the proximal bronchus [22]. The major change to Sweet's original description has been leaving the posterior membranous wall longer when cutting the bronchus so it can be used as a flap to decrease tension on the closure [22].

Typically, when the bronchus is pulled to place a stapler, an abrupt onset of vagal-induced atrial fibrillation or bradycardia may occur, along with hypotension that leads to releasing the bronchus [23]. There is a natural tendency with the next attempt to reduce bronchial traction allowing for a longer stump. Using a Roticulator linear stapler is useful to suture and clip the main bronchus close to the carina [23]. To avoid pooling of secretions within the bronchial stump, the stump should be resected back to its origin and for a pneumonectomy divided as close to the level of the carina as possible [9, 24]. This is critical to avoid secretions pooling resulting in infection and stump breakdown.

When closing a very proximal right bronchial stump or thickened bronchial wall, attention must be directed to ensure there is no closure under tension [25]. Closure under tension can be implicated in right sided BPFs at the point of transection of the right mainstem bronchus as it is generally larger than the left [25]. By the Law of LaPlace, the tension on the curved cartilaginous membranes and the fluid within the crenelated surface is higher in the larger orifice of the right bronchial stump [18, 26, 27]. Elimination of the stump diverticulum may reduce surgical line tension [18, 26, 27]. The cartilaginous ring at the origin of the right mainstem bronchus tends to keep the bronchus open and closure should be parallel to the bifurcation spur of the resected bronchus [21, 28]. This decreases the intraluminal deformity of the remaining bronchi with the straightened angle of the longitudinal axes [21,28].

3.3.1 Suture vs. staple closure

The surgical technique of bronchial closure remains controversial and has been studied extensively. The preferred technique of pulmonary hilum vessel ligation and bronchial stump closure has troubled thoracic surgeons for years. In 1909, regarding bronchial stump closure, Meyer advised his inversion technique [29]. In 1945, Sweet described the longitudinal, single interrupted silk suture closure [29, 30]. Dr. Mark Ravitch started using staplers in the United States in 1964 after having observed their early development in Russia [29]. In 1970, Kirksey reported 147 patients who underwent pulmonary resection with disposable and plastic

American staplers called Thoraco-Abdominal (TA) [29]. Reluctance to use vascular staplers due to fear of fatal hemorrhage because of malfunction continued the debate concerning pulmonary hilum vessel manual ligation versus stapled division for many decades [29]. The cessation of the alarm resulted after Asamura et al., in 2002 published results of 842 vascular divisions using endoscopic staples with 0.1% incidence of stapling failure and Yano et al., in 2013 reported 3393 pulmonary vein and artery stapling uses with a failure rate of only 0.27% [29].

It is decided by the surgeon perioperatively to use either manual suturing or stapling methods [31]. None of these have proven superiority in reducing the incidence of BPF and around a 4% rate of BPF has been reported for mechanical stapling and suture technique [31, 32]. Ucvet et al., 2011 reported the weakest part of the line are the end points of the stapler and it may incompletely close the tissue [31]. The staple line that exceeded the length of the bronchus caused a detachment in this end site creating a microfistula. These microfistulas can lead to large BPF along with infections [31]. To provide stump safety, lateral suturing to the weak and risky stump end points was required [31].

Endoscopic staplers have 2 differences compared to conventional TA type staplers: proximal and distal ends can be closed, both division and stapling can be performed simultaneously in one firing motion [31, 33]. The advantages of using endostaplers during a pulmonary resection are: (1) Time required for closure can be reduced, compared to the TA stapler when closure of the distal end of the bronchus and division are required; (2) Both proximal and distal ends of the bronchi are simultaneously and tightly closed without purulent or contaminated discharge which minimizes contamination of the operative field; (3) By selecting the appropriate cartridges, endostaplers can be used safely in vascular division [31, 33].

Suture closure is considered when the bronchial wall is hardened due to calcification [10, 21, 33]. Suture closure is also used with position difficulty due to hilar adenopathy or when the tumor is close to the pulmonary hilum due to a more extensive proximal dissection or a technically difficult bronchial stump [10, 21, 33]. Manual suturing may have the advantage of allowing inspection and assessment of the bronchial mucosa quality. Tumor fragments may also be recovered after the main bronchus is clamped [34].

3.4 Tissue coverage of the bronchial stump

Generally, wound healing has three phases: (1) inflammatory phase (2) proliferation phase (3) remodeling phase [35]. The inflammatory phase is marked by the aggregation of platelets, infiltration with leukocytes and coagulation. This phase begins soon after injury and is followed by the proliferation phase. The proliferation phase is characterized by reepithelialization, fibroplasia, angiogenesis, and wound contraction. Persistent inflammation can last about 2 weeks and likely causes robust adhesion. The remodeling phase takes place over months when the epithelium produces collagen and matrix proteins responding to the injury [35]. The phase of wound healing needs to be considered when deciding which type of bronchial closure is used.

Several options are available for coverage of bronchial closure. To reduce the incidence of postpneumonectomy BPF with soft tissue buttressing after bronchial closure has been debated. Many suggest stump reinforcement in patients with increased risk factors for BPF [36]. Cerfolio et al., 2005 suggests the best way to treat postoperative complications is to prevent it [37]. Local soft tissue coverage may provide vascular ingrowth to promote stump healing and effectively contain a small bronchial stump dehiscence [38]. Algar et al. 2001, found that the absence of bronchial stump tissue coverage was an independent predictor of BPF in the final multivariable model ($p = 0.039$) [32].

3.4.1 Intercostal muscle flap

The intercostal muscle flap causes no functional disability, is easy to harvest, has adequate length to reach most sites, has adequate vascularity and is harvested through the same thoracotomy incision [39]. Sfyridis et al., discovered the group that received an intercostal muscle flap had a lower incidence of development of BPF (0% versus 8.8%; $p < 0.02$) [40]. This flap is harvested prior to chest retraction to not crush the flap and cause damage to the blood supply. The use of cautery to harvest this flap is necessary because it is lacking periosteum and over time will not calcify [9, 37, 40]. The intercostal muscle flap is harvesting by cutting approximately two-thirds of the posterior aspect of the latissimus dorsi and the entire serratus anterior muscle is spared [37]. The rib is not shingled or cut. For harvesting, rib instruments are not used. The intercostal muscle flap, usually overlying the sixth rib is harvested using cautery prior to chest retraction from the under surface of the fifth rib. Starting at the distal end of the muscle under the serratus anterior muscle, cautery is lowered from 40 to 70 and carefully the muscle is dissected with both hot and cold cautery. So the intercostal vein is not injured, the cautery tip is positioned so it is almost parallel with the surface of the fifth rib. The intercostal is posteriorly freed from the sixth rib, past the lumbar-dorsal fascia but not freed from the undersurface of the fifth rib past this structure due to risk of injury to the vein posterior of the fifth rib with any further dissection. The bronchial stump is then tested [37].

3.4.2 Pericardial fat pad

In a retrospective study, Taghavi et al., found 93 patients who underwent pneumonectomy for primary lung cancer, identified no BPF during follow up after using a pedicled pericardial flap for bronchial stump coverage [41]. A pericardial fat pad is harvested from the anterolateral pericardium, pedicled at its cranial part, avoiding inclusion or injury to the phrenic nerve [9, 42]. A wide based pedicle should be used to assure vascularity of the flap. Careful attention should be used to avoid twisting the pedicle. The flap is attached caplike over the bronchial stump with numerous single mattress stitches to avoid devascularization when tied down over the four corners of the bronchial stump. The defect in the pericardium is then reconstructed with mesh [9, 42].

3.4.3 Serratus anterior flap

Bronchopleural fistula is exceedingly rare when a pedicled muscle flap is used to buttress the lobar bronchus, even after preoperative radiation doses of 60Gy or higher are administered [43]. To provide sufficient protection after preoperative radiation, using omental or serratus as a prophylactic buttress for the highly irradiated right main stem bronchus after a right pneumonectomy is recommended [43].

If the patient is believed to be at extraordinary risk of stump complications, larger muscle or omental flaps are used. The serratus anterior flap and omental flap are also used to treat a postoperative bronchopleural fistula to close the fistula [43, 44].

The serratus anterior muscle, one of the workhorse flaps is easily harvested, reliable, often preserved during the initial pneumonectomy due to its utility in dealing with potential complications [44]. The vascular pedicle that runs on the lateral undersurface of the scapula is where the serratus anterior muscle is based [25]. This muscle is mobilized and placed between the ribs in the second or third interspace where it will reach the hilum without tension. The thoracodorsal vascular pedicle is protected throughout the dissection [44]. With tight interspaces, compromising the

vascular supply of the flap, a segment of the third rib can be removed to allow the flap to enter the pleural space easily [25]. The serratus anterior flap is secured with interrupted absorbable sutures to the mediastinal areolar or peribronchial tissue [25] (**Figure 1**). This tissue helps with infection control and healing due to its blood supply emanating from regions beyond the inflamed field [25]. The flap is placed over the bronchial stump with uninterrupted suture to secure the closure [9, 25, 44].

3.4.4 Omental flap

The omentum has superior blood supply and plasticity which allows for a very safe and easy bronchus closure even in the presence of fibrotic tissue or infection [45]. The omentum with a rich blood supply assures adequate antibiotic and oxygen delivery [46]. Delivering potent angiogenic factors, the omentum improves neovascularization of the bronchial suture lines in experimental models. Omental transposition does not impair muscle function or produce chest wall deformities seen with major muscle flaps [46].

The disadvantage of tradition omental flap transposition extends the surgical procedure into the abdomen, requiring laparotomic access. Usually the omentum is mobilized through the upper midline abdominal incision, transposed into the chest via a substernal or anterior transdiaphragmatic route [46]. This description applies a transdiaphragmatic harvesting technique of the greater omentum performed through the standard thoracotomy [46].

The five centimeter incision in the diaphragm is performed radially between its anterior insertion and central tendon through the standard thoracotomy [46, 47]. Oval forceps are used to slide through the diaphragm into the abdominal cavity. Once confirmation the omentum is free of adhesions, the greater omentum gently can be retracted through the diaphragm into the chest. The omental insertion of the transverse colon is identified and divided as extensively as possible. The most distal omental extremity is identified in the chest cavity by gentle traction and subsequently isolated carefully inspecting its vascular supply. After confirming the omental flap has no traction on the stomach or colon, the omentum is sutured to the bronchial stump in the usual fashion. The diaphragmatic incision is closed leaving a large enough opening to avoid strangulation of the omentum. The omental flap is sutured with interrupted sutures to the diaphragmatic opening to further relieve

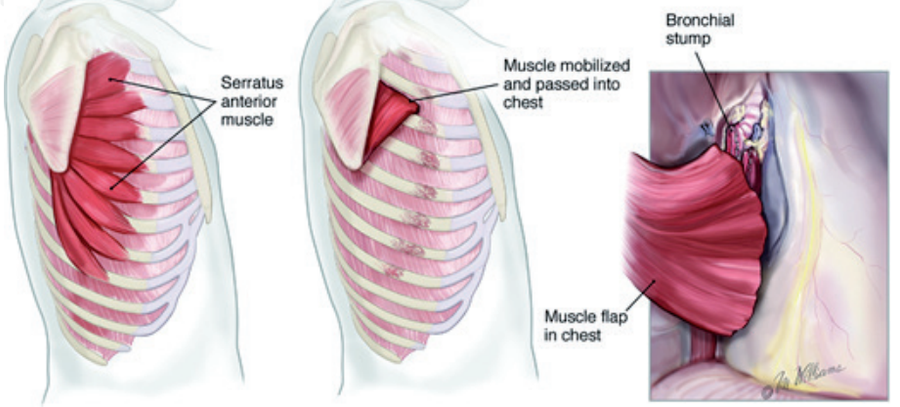

Figure 1.
The serratus anterior muscle is harvested and mobilized into the chest between the ribs in the second or third interspace with rib segmentation. (Sugarbaker D, Bueno R, Burt B, et al, editors. Adult chest surgery. 3rd edition. New York: McGraw-Hill Education; 2020; with permission).

any tension. This technique is appropriate to reinforce the bronchial stump and can be large enough to fill the pleural space [46, 47].

3.5 Residual carcinoma at bronchial margin

Residual disease is characterized by residual carcinomatous tissue within the margin of resection either under visible inspection or under microscopy [48]. Residual disease at the bronchial stump may cause poor prognosis with the increased risk of lung cancer recurrence both distantly and locally [48]. It may also decrease the bronchial stump anastomosis which can lead to a fatal bronchopleural fistula or empyema [48, 49]. In all pulmonary resections, the estimated incidence of residual disease left at the bronchial stump is 4–5% [49]. Asamura et al. reported in 2359 patients that the most important risk factor for a BPF was resection type, followed by presence of residual microscopic tumor at the resection margin ($p < 0.01$) [28]. Survival is worse in patients with bronchial margin residual disease; 1 and 5 year survivals range between 20 and 50% and 0–20% respectively [48]. Mediastinal lymph node involvement is associated with the poor survival in 75–85% of patients with residual bronchial margin disease [48]. Radiotherapy or reoperation may be considered in these patients [48, 49].

3.6 Neoadjuvant chemoradiotherapy

Neoadjuvant chemoradiotherapy is a crucial strategy in multidisciplinary treatments to improve the survival rate and resectability for patients with lung cancer [50]. Especially for patients with advanced lung cancer, chemoradiotherapy can eliminate or reduce the micro-metastasis. Previously published randomized control trials have been integrated with recent systematic reviews and have concluded that neoadjuvant chemoradiotherapy can significantly benefit the survival outcomes in operable patients [50]. Relative to other pulmonary resections, pneumonectomy has been associated with increased morbidity and mortality. The mortality for a pneumonectomy after neoadjuvant therapy has reports with very low mortality (<5%) countered by other reports with alarmingly high mortality (>20%) [51]. For the patient with N2 disease who requires a pneumonectomy, the correct approach can be unclear with the postoperative and intraoperative complications remaining a debate [50, 51]. Bronchial mucosa ischemia is induced by radiotherapy but the mucosal blood flow can recover in eight to ten days after completion of therapy. Early effects of radiation can cause mucosal edema and inhibit capillary angiogenesis [52]. Late effects of radiation cause fibrotic small vessel disease through radiation vasculopathy [52]. Radiation pneumonitis, poor wound healing, and fibrosis can occur in previously irradiated bronchial tissue with a higher perioperative and postoperative complication leading to a bronchopleural fistula [53, 54]. Induction therapy may cause injury to the bronchial microvascularization predisposing to airway complications but published literature does not support the notion that all pneumonectomies after therapy are associated with postoperative mortalities [51, 55].

3.7 Empyema

Empyema is the presence of purulent fluid in the postpneumonectomy pleural space. Postpneumonectomy empyema occurs in 2–16% of patients and can be life threatening [55]. This postoperative complication is associated with BPF which can further increase morbidity and mortality [56]. Most BPFs associated with empyema is monomicribial with most pathogens being Streptococcus or

Staphylococcus species and occur within 10 to 14 days of surgery [52, 57]. A late empyema can occur more than three months to 40 years after a pneumonectomy and is most often acquired via a hematogenous route [52, 57]. After a pneumonectomy, to avoid spillage of infected fluid into contralateral lung the patient should be kept upright at least 45 degrees [52]. An early empyema withing 10 to 14 days after surgery presents with expectoration of purulent sputum and fever [57]. Radiographic findings show a shift of the mediastinum away from the post-pneumonectomy space, development of a new or sudden change in the existing air-fluid level, and failure of the mediastinum to shift normally in the immediate postoperative period [57]. Empyema diagnosis is confirmed by fluid sample in the postpneumonectomy space [57].

3.8 Mechanical ventilation

Mechanical ventilation in patients after a pneumonectomy, subjects the bronchial stump line to increased wall tension and continuous barotrauma [1]. Positive pressure ventilation can be challenging in these patients and the aim is to prevent further lung injury by keeping the airway pressure below the critical opening pressure of the fistula, optimizing pleural suction pressures and provide adequate alveolar ventilation of sufficient gas exchange [58, 59]. To decrease the flow across a BPF, reducing the proportion of minute ventilation provided by the ventilator, minimal levels of positive end expiratory pressure (PEEP), low tidal volumes and respiratory rate are helpful [1, 59]. Adverse effects in mechanically ventilated patients with BPF include loss of effective tidal volume, incomplete lung expansion, inability to remove carbon dioxide and prolonged ventilatory support [59]. The majority of reported studies report a significant relationship between the occurrence of BFP and mechanical ventilation after pneumonectomy [60].

3.9 Diabetes, chronic steroid use, nutritional status

Typically, surgeons consider diabetes mellitus in patients requiring surgical intervention an important contributor to some fatal adverse events [61]. Diabetic microangiopathy alters the vascular bed causing small vessel ischemia impairing proper wound healing [40]. This decreases the oxygen diffusion capacity and the bronchial stump circulation is particularly prone to poor wound healing [52, 61]. The largest retrospective analysis reported by Asamura et al. in 1992, showed statistical results from both univariate and multivariate analysis indicating significantly increased risk of postoperative BPF in patients with diabetes [28].

Preoperative use of corticosteroids is believed to contribute to several postoperative complications which include impaired bronchial healing [62]. In a study by Algar et al. 2001, patients with preoperative steroid therapy were associated with higher risk of BPF ($p < 0.001$) [32]. This same study found hypoalbuminemia to also be related to higher risk of BPF ($p < 0.017$) [32]. Hypoalbuminemia has a negative effect on the healing process, and in order to decrease the BPF risk, an albumin level above 3.5 mg/dl is the goal [63]. Patients requiring a pneumonectomy are usually very catabolic and nutritional assessment is essential in their management [1]. Metabolic alterations induced by the lung cancer tumor affects the nutrition in these patients [64]. These alterations lead to cachexia syndrome with higher levels of the proinflammatory cytokines interleukin-6 and tumor necrosis factor and lower levels of albumin [64]. Malnutrition increases the risk of 90-day mortality rate, postoperative infection and length of hospital stay after a pneumonectomy and a thorough preoperative evaluation is crucial [64].

4. Pathophysiology: clinical features and diagnosis

4.1 Early/acute bronchopleural fistula

An early BPF has a peak incidence within 8 to 12 days after surgery but can occur at any time in the postoperative period [59]. Surgical closure of the BPF is the cornerstone of management. If a BPF is seen within the first 4 days after surgery, it requires exploration as it is likely due to a mechanical failure of the bronchial stump [59]. Early BPFs are normally approached urgently through the previous thoracotomy incision. An acute BPF can be life-threatening due to asphyxiation from pulmonary flooding or tension pneumothorax due to a massive air leak [59, 65, 66] (**Figure 2**). Acute BPF should be suspected in patients who present with fever, dyspnea, subcutaneous emphysema, excessively productive cough of purulent fluid, hypotension, trachea or mediastinal shift, disappearance, or reduction of pleural effusion on the chest radiograph or persistent air leak [25, 59, 65]. Chest radiography monitors the efficacy of BPF therapy and plays an essential role in evaluating the possibility of a BPF after a lung resection [2]. These symptoms appearing should raise the index of suspicion and quick and accurate diagnosis must be made before there is an overwhelming amount of aspiration into the remaining lung [25].

4.2 Late/chronic bronchopleural fistula

Late bronchopleural fistula present in the postoperative period more than 14 days [59]. The subacute and chronic forms present with more insidious symptoms and is characterized by fever, malaise, wasting, minimally productive cough, dullness to percussion on the affected side and reduced air entry with progressive clinical deterioration and varying levels of respiratory compromise [2, 59, 65]. A late BPF is often seen in debilitated or immunocompromised patients with many comorbidities [59]. In the chronic form that is associated with empyema, there is fibrosis of the mediastinum and pleural space preventing the mediastinal shift [59, 65].

Causes of late BPF include foreign body aspiration, refractory infection, chemotherapy and radiotherapy, and blunt chest trauma [67]. The time of interval is 2 months to 20 years between the surgery, therapy or injury and the onset of the late BPF [67].

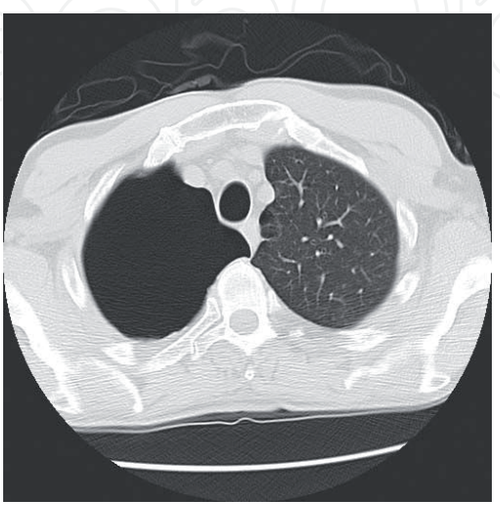

Figure 2.
Axial lung window after right pneumonectomy with large pneumothorax with evidence suggesting communication of the bronchial stump and pleural space. Case courtesy of Radswiki, Radiopaedia.org, rID: 11262.

In late BPF, due to the relatively stable mediastinal structures, conservative treatment is accepted by many investigators as the first step. Closure of the bronchial fistula with endoscopic treatment should be considered [67]. Proper antimicrobial coverage is mandatory along with proper nutrition with patients frequently requiring parenteral or enteral feeding [65]. Aggressive nutritional support and physical rehabilitation should be started early to optimize patients and enhance their recovery [65]. If surgery is indicated for a late BPF, the previous transthoracic approach may be unsafe due to fibrosis with associated inflammation with risk of bleeding and injury to vital structures [68, 69]. With a median sternotomy, approaching well vascularized, healthy, virgin tissues to reach the carina and bronchi may be preferrable and necessary. The advantages to the transsternal approach for BPF closure are avoidance of an inflamed operative field, scarring and adhesions in previous surgical fields and deformities of the thorax with thoracoplasty [68, 69]. The disadvantage of this approach is the infected empyema space is not managed at the time of closure. Previous cardiac surgery is not recommended for this type of approach [68, 69].

Once a BPF is suspected, a Computerized Tomography (CT) Scan with intravenous contrast to map the vasculature and better define the air-fluid levels and the peripheral rind enhancement is necessary [70]. This scan will identify the fistulous tract and will allow evaluation of the potential causes of BPF (i.e. recurrent tumor, staple line dehiscence, pneumonia, abscess, devascularized stump). It will also be simultaneously used to define the anatomic relationship of the adjacent mediastinal structures, vasculature, and diaphragm. A large fistulous tract can be clearly identified and a vigilant search must take place to look for subtle signs of a small BPF such as a change in the appearance of pre-existing pleural air-fluid levels and extraluminal air bubbles adjacent to the bronchial stump. Care must be taken to ensure while the patient is lying flat during the scan that they do not aspirate the pleural fluid through the BPF to the healthy lung [70].

All patients should undergo diagnostic bronchoscopy whether the BPF diagnosis is apparent radiographically or clinically [25]. A large fistula can be visualized but smaller 1 to 2 mm fistulas may be difficult to recognize [25]. Bronchoscopy provides information about the tissue at the level of the stump and condition of the remaining bronchial stump and can assist in deciding definitive repair [25].

5. Management of BPF

Management varies according to the individual patient, but the importance of addressing the risk of contralateral aspiration pneumonia and tension pneumothorax by drainage of the pleural space at time of diagnosis has to be emphasized [69]. The most important action when an acute BPF is suspected is protecting the contralateral lung from spillage of pleural fluid [2]. The primary principle is drainage of the pleural space by chest tube thoracostomy and care should be taken to place the chest tube above the previous thoracotomy incision as the diaphragm will be elevated with the normal thoracic remodeling that occurs after pneumonectomy [25, 59, 71, 72]. Pleural fluid should be sent for total protein, complete blood cell count, glucose, cytology, lactate dehydrogenase, triglycerides, gram stain and culture to evaluate for pleural infection [59]. Although integral for drainage, the chest tube can predispose the pleural space to infection and function as a foreign body [59]. Connecting the chest tube to a digital chest drainage system allows for more accurate and objective assessment of air flow and larger flow values and trend evaluation would provide more detailed information about the size and severity of the BPF [73]. For patients who are mechanically ventilated, the chest tube can

be used for occlusion during the inspiratory phase or to add positive intrapleural pressure during the expiratory phase [59]. These interventions decrease BPF during inspiration and decrease air leak during expiration to maintain positive end-expiratory pressure (PEEP) [59].

5.1 Acute failure of the bronchial stump

Acute failure of the bronchial stump is usually due to bronchial stump dehiscence and expeditious surgical repair with this single-staged intervention is recommended once clinical stabilization is achieved [71, 74, 75]. Given the relative integrity of the tissue, early stage of the infectious process, minimal pleural contamination and no problematic residual space, early reoperation is warranted to reestablish an airtight stump [25, 71, 74, 75]. Exploration with surgical revision by posterolateral thoracotomy with selective intubation and lung isolation of the contralateral mainstem bronchus to prevent further spillage of the remaining lung is recommended [25, 71, 75]. The fistula, if not readily visible can be identified with the assistance of positive pressure ventilation while covering the bronchial stump with irrigation [25]. The pleural space should be completely debrided and irrigated to remove all necrotic tissue [25]. The bronchial stump is refashioned and carefully dissected to decrease trauma to the blood supply [25, 71]. Measured from the carina, all efforts are made to made for the final stump to be less than 1 cm in length [25] (**Figure 3**). The stump may be reclosed with a stapler if their remains sufficient length on initial exploration. In cases where there is too much inflammation to allow stapling, the bronchial stump is mobilized and reclosed with interrupted monofilament sutures [25, 71]. A balance between avoiding too much exposure that may damage blood supply and exposing enough bronchus to avoid tension on the closure much be achieved [25].

5.2 Transposition of muscle flaps to treat BPF

Using a vascularized tissue to reinforce the suture line is the most important aspect of closure [25, 76]. Stump coverage was previously discussed as a preventive measure for BPF. The objective in treating a BPF with vascularized tissue is to obliterate the postpneumonectomy pleural space [25, 71, 75, 77]. Deciding which muscle flap to use depends on which muscle was preserved or damaged from the previous thoracotomy and the amount of space to be filled [71, 75, 77]. The most common muscles used in the pleural space to treat a BPF are serratus anterior, pectoralis major, pectoralis minor, latissimus dorsi, and intercostal muscles [25, 71, 75, 77, 78]. The latissimus dorsi is the most reliable and largest muscle but

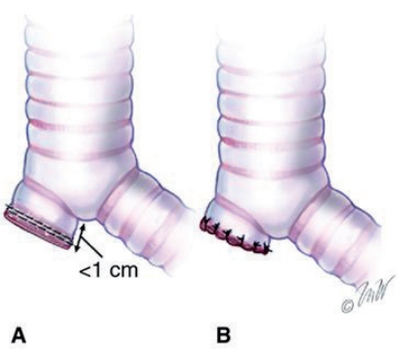

Figure 3.
A. The bronchial stump should be less than 1 cm. After inspection, if there is enough length on the stump, it can be closed with a stapling device. B. With too much inflammation, the stump may need to be sutured closed. (Sugarbaker D, Bueno R, Burt B, et al, editors. Adult chest surgery. 3rd edition. New York: McGraw-Hill Education; 2020; with permission).

may not be sufficient to obliterate the postpneumonectomy cavity if it was already divided in the original thoracotomy [77, 78]. The greater omentum consists of a large fold of peritoneum with excellent blood supply and antibacterial effect, lymphoid tissue, and fat [76, 78]. Using large muscles as the latissimus dorsi, greater omentum and serratus anterior has the advantage to contribute bulk to fill some of the dead postpneumonectomy space sugar [76–78]. In a study by Mazzella et al. 2017, fourteen patients with early BPF were treated with surgical repair of the bronchial stump via thoracoscopy (2) or thoracotomy (12) with omentum and fibrin glue (2) parietal pleural (3), intercostal muscle (1) or pericardial patch (2) with no recurrence of BPF after surgery [79].

5.3 Clagett window and eloesser flap

Treating a BPF with empyema and sepsis may require an Eloesser flap for patients too debilitated or too ill for a decortication or prolonged procedure involving muscle flaps [25, 80, 81]. The difference between the Clagett open-window thoracostomy (OWT) procedure and Eloesser flap is that the Clagett procedure is larger than the Eloesser flap and the Clagett window is temporary to allow complete drainage of purulent drainage in the pleural space [80] (**Figure 4**). The Eloesser flap creates a permanent drainage window in the pleural space [80].

5.3.1 Clagett procedure

In 1963, Clagett and Geraci described a technique as a two-step procedure for the management of postpneumonectomy empyema [81, 82]. This procedure combined an open-window thoracostomy pleural drainage with repetitive irrigation of the infected cavity with obliteration of the space with antibiotic fluid without direct fistula closure [2, 25, 81–84]. The procedure resulted in recurrences of fistulization and prolonged hospitalization and significant mortality. This technique is rarely

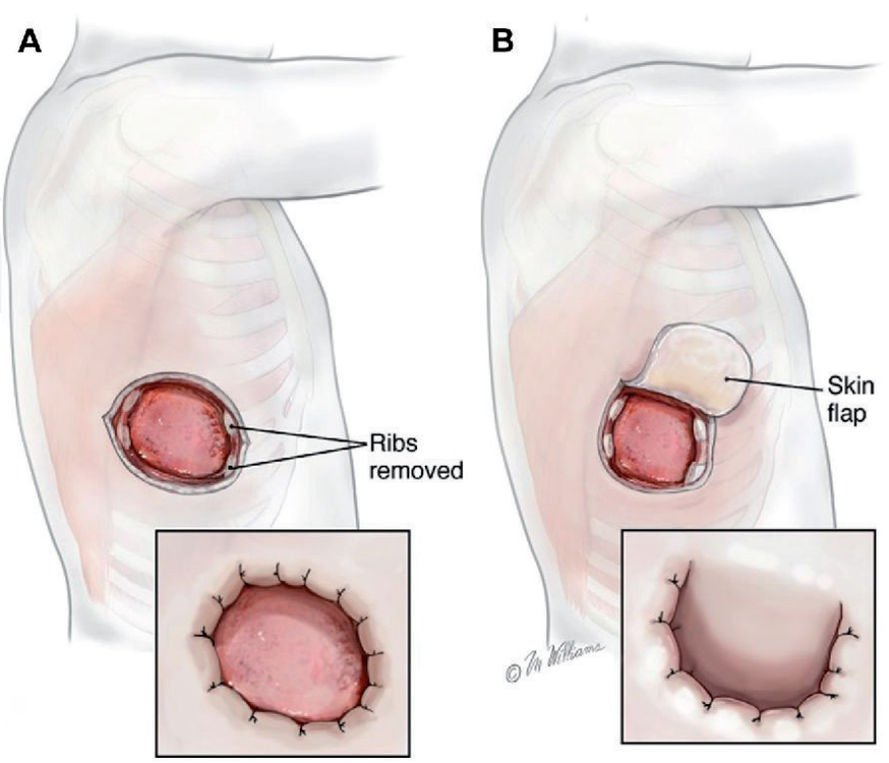

Figure 4.
(A) Clagett window and (B) Eloesser flap. (Sugarbaker D, Bueno R, Colson Y, et al, editors. Adult chest surgery. 2nd edition. New York: McGraw-Hill Education; 2015; with permission).

used and has been modified with initial bronchial stump closure with muscle transposition described earlier [2, 25, 80–84].

Once the BPF is closed and buttressed with muscle transposition, diluted wet povidone-iodine (Betadine) dressings are placed in the thorax and changed every 48 hours in the operating room [81, 83, 84]. This is done for approximately 4 to 6 days until the muscle flap is adherent to the bronchial stump and adjacent mediastinum [81, 83, 84]. Then the pack is changed in the patient's room 3 to 4 times a day. When health granulation is present in the pleural space, the entire cavity is filled with antibiotic solution selected to tailor culture and sensitivity results [25, 81, 83, 84]. In multiple layers to avoid leakage of fluid, the chest is then closed [25, 81, 83, 84].

The modified Clagett procedure involves daily intracavitary dressing changes, lasting for a long period of time and may not allow chest closure. Other ways to accelerate wound healing process were investigated [85]. Wound vacuum-assisted closure (VAC) therapy has recently been evaluated and used in patients with complex infected wounds without the OWT [86]. Bacterial proteinases are microorganisms and play a pathogenic role in an infected wound by consuming oxygen and nutrients that are required for tissue repair [87]. Reducing the bacterial proteinase load in a wound would allow the body to heal [87]. The VAC allows topical solutions to be cyclically flushed into the foam dressing before removal under negative pressure that irrigates, cleans, and removes infectious material from the pleural space [85, 87]. This is done without OWT, decreasing postoperative pain [88]. Recent studies show that as an adjunct to standard therapy, the VAC can decrease pain, hospital length of stay and morbidity in patients with complicated postoperative empyema [85, 88].

5.3.2 Eloesser flap

The Eloesser Flap OWT continues to evolve. A "H" or "U" shaped incision is made above the previous incision over the dependent portion of the space [25, 80]. A segmentary resection of one or two ribs are removed to obtain a window and limit the tendency of the opening to contract and close [25, 79, 80]. Necrotic tissue is debrided and edges of the flap are sutured directly to the parietal pleura with absorbable interrupted sutures to create an epithelized tract which encourages healing and maintains window patency [25, 79, 80]. The window should be not too far inferiorly which may interfere with the diaphragm and not too posterior that would be difficult for the patient to manage [25, 79, 80]. Using moistened gauze, dressing changes are performed until the cavity is decontaminated. Care is taken to prevent cardiac tamponade by excessive gauze inserted in the cavity [25, 79, 80]. The thoracostomy is closed with a thoracomyoplasty when clinical conditions suggest correct timing. In the chest cavity, healthy granulation tissue, improved clinical condition, closure of the bronchial stump and negative cultures of the chest cavity all suggest proper timing [25, 79, 80].

6. Endoscopic treatment of bronchopleural fistula

6.1 Biological glue

Many different biological glues for endoscopic BPF closure are available. Fibrin-based, albumin-glutaraldehyde tissue adhesive, and cyanoacrylate-based glues are the most common [2, 83]. Application technique is performed by a catheter inserted through the flexible bronchoscope and placed above the fistula [2, 83]. The glue is injected into the fistula and creates a plug after a few seconds that occludes the

fistula with instantaneous cessation of air leak expected [2, 83]. Some prefer glue injection with a 21G needle due to less glue displacement and more effective closing of the BPF. This procedure may need to be repeated and endoscopic surveillance and close clinical monitoring is important for signs of failure [2, 83].

Cardillo et al. 2015, reported patients with BPF sized 1 cm or less with a viable bronchial stump were treated endoscopically [89]. The cure rate with endoscopic treatment was 92.3% in very small fistulas <2 mm with mechanical abrasion of the fistula. Cure rate was 71.4% in small fistulas >2 mm and < 3 mm with submucosal injection of 0.5 to 2 mL polidocanolhydroxypolyethoxydodecane at the fistula. This liquid surfactant causes endothelial cell lysis. It induces sclerosis and acts on the venous endothelium via interferences with cell membrane lipids. Cure rate with intermediate fistulas >3 mm and < 6 mm was 80%. Treatment was with n-butyl cyanoacrylate glue injected into the fistula. This mechanically occludes the fistula causing proliferation of the bronchial mucosa and a local inflammatory reaction. Morbidity and mortality rates were 5.8% [89].

6.2 Endobronchial valves

Endobronchial valves (EBV) have been available since 2003 and were originally developed for the reduction of lung volume in patients with emphysema [90, 91]. They were first described by Snell et al., 2005 for BPF [92]. Introduced through a flexible bronchoscope, EBV have a unidirectional valve to prevent airflow into the fistula and will result in atelectasis and collapse of the fistula [90, 91, 93]. This results in decreased or absent air leak. The process of recovery would lead to resolution of the shunt, fibrosis, and eventual extraction of the EBV [90, 91, 93]. Complete elimination of air flow through the BPF does not always occur and does not mean the EBV is unsuccessful. Decreased flows may bring the rate below critical rate flows and allow for fistula healing [91].

6.3 Amplatzer device closure

Many small fistulas (<3 mm) spontaneously heal or heal with glue placed endoscopically [94, 95]. Treatment for BPF endoscopically can bridge to control infection until a patient is able to able to undergo surgical repair [90, 92] (**Figure 5**). Amplatzer

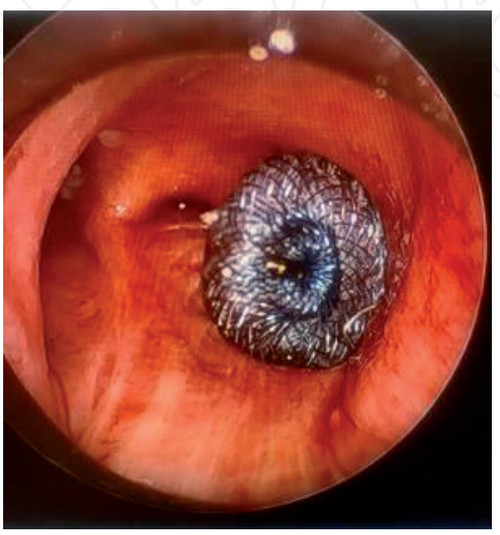

Figure 5.
Amplatzer Muscular VSD Occluder 8mm x 7mm placed to occlude the right mainstem bronchopleural fistula. Image courtesy of Dr. Tarek Dammad, Orlando, Florida.

device is normally used for transcatheter closure of atrial septal defects. This device can contribute to intrabronchial granulation tissue and has good biocompatibility [94, 95]. The tissue growth reduces the risk of displacement. The waist of the Amplatzer device is placed inside the fistula and the two discs are placed at the distal and proximal ends of the fistula [94, 95]. Fruehter et al. 2011 treated nine patients with Amplazter device with BPF and the fistula was successfully closed [96]. After nine months, the results were maintained [96].

7. Conclusion

Improvements in thoracic surgery have decreased the incidence of BPF but mortality remains high. Proactive approaches to risk management and mitigating potential causes for increased chance for BPF preoperatively and intraoperatively are essential to improved outcomes. Expeditious surgical repair for acute BPF, along with new therapies with wound vacuum-assisted closure (VAC) therapy and endoscopic options for small fistulas may all expedite closure of BPF and improve survival.

Conflict of interest

The author declares no conflict of interest.

Thanks

To my colleagues: Dr. Joseph Boyer, Dr. Nayer Khouzam, Dr. George Palmer and Dr. Marcello DaSilva at AdventHealth Orlando, Florida, U.S.A. and to Dr. Steve Talbert at the University of Central Florida. You all have taught me so much, for so many years, and I sincerely thank you.

Author details

Kristina Jacobsen
Division of Cardiothoracic Surgery, AdventHealth Hospital, Orlando, FL, USA

*Address all correspondence to: kristina.jacobsen@adventhealth.com

References

[1] Skekar K, Foot C, Fraser J, Ziegenfuss M, Hopkins P, Windsor M. Bronchopleural fistula: An update for intensivists. Journal of Critical Care 2010; 25: 47-55.

[2] Dal Agnol G, Vieira A, Oliveria R, Antonia P, Figueroa U. Surgical approaches for bronchopleural fistula. Shanghai Chest 2017;1: 1-14.

[3] Fuso L, Varone F, Nachira D, Leli I, Salimbene I, Congedo M, et al. Incidence and management of post-lobectomy and pneumonectomy bronchopleural fistula. Lung 2016; 194: 299-305.

[4] Tokunaga Y, Kita Y, Okamoto T. Analysis of risk factors for bronchopleural fistula after surgical treatment of lung cancer. Ann Thorac Cardiovasc Surg 2020; 26: 311-319.

[5] Okuda M, Go T, Yokomise H. Risk factor of bronchopleural fistula after general thoracic surgery: review article. General Thorac and Cardiovas Surg 2017; 65: 679-685.

[6] Marques P, Andrade G, Granadas J, et al. Iatrogenic Bronchopleural Fistula. Cureus 2020;12:1-8.

[7] Louie B, Wilson J, Kim S, Cerfolio R, Park B, Farivar A, et al. Comparison of VATS and robotic approaches for clinical stage I and II NSCLC using the STS database. Ann Thorac Surg. 2016;102:917-924.

[8] Mei J, Guo C, Xia L, Liao H, Pu Q, Ma L, et al. Long-term survival outcomes of video-assisted thoracic surgery lobectomy for stage I-II non-small cell lung cancer are more favorable than thoracotomy: A propensity score-matched analysis from a high-volume center in China. Transl Lung Cancer Res 2019;8:155-166.

[9] Liberman M, Cassivi S. Bronchial stump dehiscence: Update on prevention and management. Semin Thorac Cardiovasc Surg 2007; 19:366-373.

[10] Sirbu H, Busch T, Aleksic I, Schreiner W, Dalichau H. Bronchopleural fistula in the surgery of non-small cell lung cancer: Incidence, risk factors, and management. Ann Thorac Cardiovasc Surg 2001; 7: 330-336.

[11] He J, Xu X. Thoracoscopic anatomic pulmonary resection. J Thorac Dis 2012; 4: 520-547.

[12] Birdas T, Morad M, Okereke I, Rieger K, Kruter L, Mathur P, et al. Risk factors for bronchopleural fistula after right pneumonectomy: Does eliminating the stump diverticulum provide protection? Ann Surg Oncol 2012; 19:1336-1342.

[13] Elrakhawy H, Alassal M, Shaalan A, Awad A, Sayed S, Saffan M. Impact of major pulmonary resections on right ventricular function: Early postoperative changes. Heart Surgery Forum 2018; 21: 9-17.

[14] Hackett S, Jones R, Kapila R. Anesthesia for pneumonectomy. BJA Education 2019; 19: 297-304.

[15] Darling G, Abdurahman A, Yi Q, Johnson M, Waddell T, Pierre A, et al. Risk of a right pneumonectomy: Role of a bronchopleural fistula. Ann Thorac Surg 2005;79:433-437.

[16] Watanabe S, Asamura H. Lymph node dissection for lung cancer. Significance, strategy, and technique. J Thorac Oncol 2009;4: 652-657.

[17] Ray M, Smeltzer, M, Faris N, Osarogiagbon R. Survival after mediastinal node dissection, systematic

sampling, or neither for early stage NSCLC. J Thorac Oncol 2020;15:1670-1681.

[18] Darling G, Allen M, Decker P, Ballman K, Malthaner R, Inculet R, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: Results of the ACOSOG Z0030 trial. J Thorac Cardiovasc Surg 2011;141:662-670.

[19] Lardinois D, DeLeyn P, Schil P, Porta R, Waller D, Passlick B, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006;30: 787-792.

[20] Mammana M, Marulla G, Zuin Z, Perissinotto E, Camacchio G, Franceschi E, et al. Postpneumonectomy bronchopleural fistula: analysis of risk factors and the role of bronchial stump coverage. Surgery Today 2020;50:114-122.

[21] Benhamed L, Bellier J, Fournier C, Akkad R, Mathieu D, Kipnis E, Porte H. Postoperative ischemic bronchitis after lymph node dissection and primary lung cancer. Ann Thorac Surg 2011;91:355-360.

[22] [22].Wright C, Wain J, Mathisen D, Grillo H. Postpneumonectomy bronchopleural fistula after sutured bronchial closure: Incidence, risk factors, and management. J Thorac and Cardiovasc Surg 1996;112:1367-1371.

[23] Cariata A, Piromalli E, Taviani M. Postpneumonectomy bronchial stump recurrence and bronchopleural fistula. Asian Cardiovasc & Thorac Annals 2012; 20: 439-442.

[24] Algar F, Alvarez A, Aranda J, Salvatierra A, Baamonde C, Lopez-Pujol F. Predication of early bronchopleural fistula after pneumonectomy: A multivariate analysis. Ann Thorac Surg 2001;72:1662-1667.

[25] Sugarbaker D, Bueno R, Burt B, Growth S, Loor G, Wolf A, Williams M, Adams A. Sugarbaker's adult chest surgery. 3rd ed. New York: McGraw Hill Education, c2020.

[26] Hu X, Duan L, Jiang G, Wang H, Liu H, Chen C. A clinical risk model for the evaluation of bronchopleural fistula in non-small cell lung cancer after pneumonectomy. Ann Thorac Surg 2013;96:419-424.

[27] Prange H: LaPlace's law and the alveolus. A misconception of anatomy and a misapplication of physics. Adv Physiol Educ 2003;27:34-40.

[28] Asamura H, Naruke T, Tsuchiya R, Goya T, Kondo H, Suemasu K. Bronchopleural fistulas associated with lung cancer operations. J Thorac Carciovasc Surg 1992;104: 1456-1464.

[29] Potaris K, Kapetanaksi E, Papamichail K, Midvighi E, Verveniotis A, Parissis F, et al. Major lung resections using manual suturing versus staplers during fiscal crisis. Int Surg 2017;102:198-204.

[30] Moura V, Lamdin E, Ferraz F, Turatti R, Jaqueta C, Leme P. Modified method for bronchial suture by Ramirez Gama compared to separate stitches suture: experimental study. Rev. Col Bras Cir 2014; 41: 188-192.

[31] Ucveta A, Gursova S, Sirzaia S, Erbavcub A, Ozturka A, Celana K, et al. Bronchial closure methods and risks for bronchopleural fistula in pulmonary resections: how a surgeon may choose the optimum method. Interact Cardiovasc Thorac Surg 2011; 12: 558-562.

[32] Algar F, Alvarez A, Aranda J, Salvatierra A, Baamonde C,

Lopez-Pujol F. Prediction of early bronchopleural fistula after pneumonectomy: A multivariate analysis. Ann Thorac Surg 2001;72:1662-1667.

[33] Asamura H, Kondo H, Tsuchiya R. Management of the bronchial stump in pulmonary resections: a review of 533 consecutive recent bronchial closures. Eur J Cardiothorac Surg 2000;17:106-110.

[34] Habaut J, Baron O, Al Habash O, Despins P, Duveau D, Michaud J. Closure of the bronchial stump by manual suture and incidence of bronchopleural fistula in a series of 209 pneumonectomies for lung cancer. Eur J Cardiothorac Surg. 1999;16: 418-423.

[35] [35].Makidono K, Miyata Y, Ikeda T, Tsutani Y, Kushitani K, Takeshima Y, et al. Investigation of surgical technique for bronchial stump closure after lobectomy in animal model. Gen Thorac and Cardiovasc Surg 2020;68: 609-614.

[36] Panagopoulosa N, Apostolakisa E, Koletsisa E, Prokakisa C, Hountisb P, Sakellaropoulosc G, et al. Low incidence of bronchopleural fistula after pneumonectomy for lung cancer. Interact Cardiovasc Thorac Surg 2009;9: 571-575.

[37] Cerfolio R, Bryan A, Yamamuro M. Intercostal muscle flap to buttress the bronchus at risk and the thoracic esophageal-gastric anastomosis. Ann Thorac Surg 2005;80:1017-1020.

[38] Kesler K, Hammoud Z, Rieger K, Kruter L, Yu M, Brown J. Carinaplasty airway closure: A technique for right pneumonectomy. Ann Thorac Surg 2008;85:1178-1186.

[39] Goyal V, Gupta B, Sharma S. Intercostal muscle flap for repair of bronchopleural fistula. Lung India 2015;32: 152-154.

[40] Sfyridis P, Kapetanakis E, Baltaviannis N, Bolanos N, Anagnostopoulos D, Markogiannakis A, et al. Bronchial stump buttressing with an intercostal muscle flap in diabetic patients. Ann Thorac Surg 2007;84:967-972.

[41] Caushi F, Quirjako G, Skenduli I, Xhemalaj D, Hafizi H, Bala S, et al. Is the flap reinforcement of the bronchial stump really necessary to prevent bronchial fistula? J Cardiothorac Surg 2020; 15:1-7.

[42] Taghavi S, Marta G, Lang G, Seebacher G, Winkler G, Schmid K, et al. Bronchial stump coverage with a pedicled pericardial flap. An effective method for prevention of postpneumonectomy bronchopleural fistula. Ann Thorac Surg 2005;79:284-288.

[43] Cerfolio R, Bryan A, Jones V, Cerfolio R. Pulmonary resection after concurrent chemotherapy and high dose (60 Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. Eur J Cardiothorac Surg 2009;35: 718—723.

[44] Park J, Eom J, Choi S, Kim Y, Kim E. Use of a serratus anterior musculocutaneous flap for surgical obliteration of a bronchopleural fistula. Interact Cardiovasc Thorac Surg 2015;20: 569-574.

[45] Botianu P. Current indications for the intrathoracic transposition of the omentum. Botianu J Cardiothorac Surg 2019;14:1-6.

[46] Jiang F, Huang J, You O, Yuan F, Yin R, Xu L. Surgical treatment for bronchopleural fistula with omentum covering after pulmonary resection for non-small cell lung cancer. Thorac Cancer 2013;4:249-253.

[47] D'Andrilli A, Ibrahim M, Andreetti C, Ciccone A, Venuta F,

Rendina E. Transdiaphragmatic harvesting of the omentum through thoracotomy for bronchial stump reinforcement. Ann Thorac Surg 2009;88:212-215.

[48] Lia S, Fana J, Zhoub J, Renb Y, Shena C, Che G. Residual disease at the bronchial stump is positively associated with the risk of bronchoplerual fistula in patients undergoing lung cancer surgery: a meta-analysis. Interact Cardiovasc Thorac Surg 2016;22: 327-335.

[49] Wind J, Smit E, Senan S, Eerenberg J. Residual disease at the bronchial stump after curative resection for lung cancer. Eur J Cardiothorac Surg 2007;32: 29-34.

[50] Li S, Fan J, Liu J, Zhou J, Ren Y, Shen C, Che G. Neoadjuvant therapy and risk of bronchopleural fistula after lung cancer surgery: A systematic meta-analysis of 14,912 patients. Japanese J Clinical Onc 2016;46: 534-546.

[51] Kim A, Boffa D, Wang Z, Detterbeck F. An analysis, systematic review, and meta-analysis of the perioperative mortality after neoadjuvant therapy and pneumonectomy for non–small cell lung cancer. J Thorac Cardiovasc Surg 2012;143:55-63.

[52] Clark J, Cooke D, Brown L. Management of complications after lung resection. Prolonged air leak and bronchopleural fistula. Thorac Surg Clin 2020;30:347-358.

[53] Chargari C, Riet F, Mazevet M, Morel E, Lepechoux C, Deutsch E. Complications of thoracic radiotherapy. Presse Med 2013;42:342-351.

[54] VandePas J, Roozendaal L, Wanders S, Custers F, Vissers Y, DeLoos E. Bronchopleural fistula after concurrent chemoradiotherapy. Adv in Radiation Onc 2020;5: 511-515.

[55] Gonzalez M, Litzistorf Y, Krueger T, Popeskou S, Matzinger O, Ris H, et al. Impact of induction therapy on airway complications after sleeve lobectomy for lung cancer. Ann Thorac Surg 2013;96:247-252.

[56] Deschamps C, Bernard A, Nichols F, Allen M, Miller D, Trastek V, et al. Empyema and bronchopleural fistula after pneumonectomy: Factors affecting incidence. Ann Thorac Surg 2001;72:243-248.

[57] Kopec S, Irwin R, Stoller J, Hollingsworth H: Sequelae and complications of pneumonectomy. Uptodate 2013, available from http://www.bsgdtphcm.vn/thamkhao/contents/UTD.htm?31/36/32329

[58] Matthews C, Goswami D, Ramchandani N, Huffard A, Reiger K, Young et al. The influence of airway closure technique for right pneumonectomy on wall tension during positive pressure ventilation: An experimental study. Semin Thoracic Surg 2020;32:1076-1084.

[59] Salik I, Vashisht R, Abramowicz A. Bronchopleural fistula. StatPearls [Internet] 2021. Available from https://www.ncbi.nlm.nih.gov/books/NBK534765/

[60] Toufektzian L, Patris V, Sepsas E, Konstantinou M. Does postoperative mechanical ventilation predispose to bronchopleural fistula formation in patients undergoing pneumonectomy? Interact Cardiovasc Thorac Surg 2015;21:379-382.

[61] Li S, Fan J, Zhou J, Ren Y, Shen C, Che G. Diabetes mellitus and risk of bronchopleural fistula after pulmonary resections: A meta-analysis. Ann Thorac Surg 2016;102:328-339.

[62] Kim H, Paik H, Kim S, Park M, Lee J. Preoperative corticosteroid use and early postoperative bronchial

anastomotic complications after lung transplant. Korean J Thorac Cardiovasc Surg 2018; 51: 384-389.

[63] Suzuki M, Otsuji M, Saitoh Y, Iizasa T, Shibuya K, Sekine Y, et al. Bronchopleural fistula after lung cancer surgery. Multivariate analysis of risk factors. J Cardiovasc Surg 2002;42:263-267.

[64] Bagan P, Berna P, DeDominicis F, Pereira J, Mordant P, DeLaTour B, et al. Nutritional status and postoperative outcome after pneumonectomy for lung cancer. Ann Thorac Surg 2013;95:392-396.

[65] Lois M, Noppen M. Bronchopleural fistulas. An overview of the problem with special focus on endoscopic management. CHEST 2005; 128:3955-3965.

[66] Erwin F, Lakson G, Sarvasti D, Tahalele P. Spontaneous pneumothorax following bronchopleural fistula in geriatric patient: A case report and emergency management. J Widya Medika 2021; 3: 53-61.

[67] Zhang C, Pan Y, Zhang R, Wu W, Liu D, Zhang M. Late-onset bronchopleural fistula after lobectomy and adjuvant chemotherapy for lung cancer: A case report and review of the literature. Medicine 2019;98:1-5.

[68] Topcuogly M, Kayhan C, Ulus T. Transsternal Transpericardial approach for the repair of bronchopleural fistula with empyema. Ann Thorac Surg 2000;69:394-397.

[69] [69].Bal S, Ali K, Haridas B, Shrivastava G, Gupta S. Management of post pneumonectomy bronchopleural fistula: the transpericardial approach. J Vis Surg 2018;4:237-242.

[70] Gaur P, Dunne R, Colson Y, Gill R. Bronchopleural fistula and the role of contemporary imaging. J Thorac Cardiovasc Surg 2014;148:341-347.

[71] Teh E, West D. Bronchopleural fistula: prevention is still best. Shanghai Chest 2017;1:48.

[72] QV J, Chen G, Jiang G, Ding J, Gao W, Chen C. Risk factor comparison and clinical analysis of early and late bronchopleural fistula after non-small cell lung cancer surgery. Ann Thorac Surg 2009;88:1589-1593.

[73] Jacobsen K, Talbert S, Boyer J. The benefits of digital drainage system versus traditional drainage system after robotic-assisted pulmonary lobectomy. J Thorac Dis 2019; 11: 5328-5335.

[74] Cusmano G, Alifano M, Lococo F. Endoscopic and surgical treatment for bronchopleural fistula after major lung resection: an enduring challenge. J Thorac Dis 2019;11:S1351-S1356 .

[75] Bribriesco A, Patterson A. Management of postpneumonectomy bronchopleural fistula. From thoracoplasty to transsternal closure. Thorac Surg Clin 2018;28:323-335.

[76] Okada S, Shimomura M, Tsunezuka H, Ishihara S, Ishikawa N, Kameyama K, et al. One-stage closure of large bronchopleural fistula with pedicledlatissimus dorsi muscle flap after preemptive antibiotics: A case report. International J Surg Case Reports 2020;74:257-259.

[77] He Z, Shen L, Xu W, He X. Effective treatment of bronchopleural fistula with empyema by pedicled latissimus dorsi muscle flap transfer. Two case report. Medicine 2020; 99:41.

[78] Lu C, Feng Z, Ge D, Yuan Y, Zhang Y, Qi F, et al. Pedicle muscle flap transposition for chronic empyema with persistent bronchopleural fistula: Experience of a single clinical center in China. Surg Today 2016;46:1132-1137.

[79] Mazzella A, Pardolesi A, Maisonneuve P, Petrella F, Galetta D,

Gasparri R, et al. Bronchopleural fistula after pneumonectomy: Risk factors and management, focusing on open-window thoracostomy. Semin Thorac Cardiovasc Surg 2018;30:104-113.

[80] Denlinger, C. Eloesser flap thoracostomy window. Oper Tech Thorac Cardiovasc Surg 2010;15:61-69.

[81] Pairolero P, Arnold P, Trastek V, Medland B, Kay P. Postpneumonectomy empyema. The role of intrathoracic muscle transposition. J Thorac Cardiovasc Surg 1990;99:958-968.

[82] Schneiter D, Cassina P, Korom S, Inci I, Al-Abdullatief M, Dutly A, et al. Accelerated treatment for early and late postpneumonectomy empyema. Ann Thorac Surg 2001;72:1668-1672.

[83] Azevedo I, Oliveira R, Ugalde P. Management of postpneumonectomy empyema and bronchopleural fistula. Shanghai Chest 2021;5:15.

[84] Zaheer S, Allen M, Cassivi S, Nichols F, Johnson C, Deschamps C, et al. Postpneumonectomy empyema: Results after the Clagett procedure. Ann Thorac Surg 2006;82:279-287.

[85] Saadi A, Perentes J, Gonzalez M, Tempia A, Wang Y, Demartines N, et al. Vacuum-assisted closure device: A useful tool in the management of severe intrathoracic infections. Ann Thorac Surg 2011;91:1582-1590.

[86] Haghshenasskashania A, Rahnavardia M, Yana T, McCaughan B. Intrathoracic application of a vacuum-assisted closure device in managing pleural space infection after lung resection: Is it an option? Interact Cardiovasc Thorac Surg 2011;13: 168-174.

[87] Gabriel A, Shores J, Bernstein B, DeLeon J, Kamepalli R, Wolvos T, et al. A clinical review of infected wound treatment with vacuum assisted closure® (V.A.C.®) therapy: Experience and case series. Int Wound J 2009; 6:1-25.

[88] Hoffman H, Neu R, Potzger T, Schemm R, Grosseri C, Szoke T, et al. Minimally invasive vacuum-assisted closure therapy with instillation (Mini-VAC-Instill) for pleural empyema. Surgical Innovation 2015;22: 235-239.

[89] Cardillo G, Carbone L, Carleo F, Galluccio G, DiMartino M, Giunti R, et al. The rationale for treatment of postresectional bronchopleural fistula: Analysis of 52 patients. Ann Thorac Surg 2015;100:251-257.

[90] Zo S, Song J, Kim B, Jeong B, Jeon K, Cho J, et al. Surgically intractable bronchopleural fistula treated with endobronchial valve insertion by isolating the tract with indigo carmine: A case report. Resp Med Case Reports 2020;29:100972.

[91] Gaspard D, Bartter T, Boujaoude Z, Raja H, Arya R, Meena N, et al. Endobronchial valves for bronchopleural fistula: Pitfalls and principles. Ther Adv Respir Dis 2017;11:3-8.

[92] Snell G, Holsworth L, Fowler S, Eriksson L, Reed A, Daniels F. et al. Occlusion of a broncho-cutaneous fistula with endobronchial oneway valves. Ann Thorac Surg 2005;80:1930-1932.

[93] Kalatoudis H, Nikhil M, Zeid F, Shweihat Y. Bronchopleural fistula resolution with endobronchial valve placement and liberation from mechanical ventilation in acute respiratory distress syndrome: A case study. Case Rep Crit Care 2017:3092457.

[94] Wu Y, He Z, Xu W, Chen G, Liu Z, Lu Z. The Amplatzer device and pedicle muscle flap transposition for the treatment of bronchopleural fistula with chronic empyema after lobectomy: Two

case reports. World J Surg Onc 2021;19:1-7.

[95] Motus I, Bazhenov A, Basvrov R, Tsvirenko A. Endoscopic closure of a bronchopleural fistula after pneumonectomy with the Amplatzer occluder: A step forward? Interact Cardiovasc Thorac Surg 2020;30:249-254.

[96] Fruchter O, Kramer M, Dagan T, Raviv Y, Abdel-Rahman N, Saute M, et al. Endobronchial closure of bronchopleural fistulae using Amplatzer devices. Our experience and literature review. Chest 2011;139:682-687.