Pneumonectomy for lung cancer

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Abstract: Pneumonectomy is associated with an increased risk of mortality compared with lobectomy or sublobar resections. Despite advancements in thoracic surgery and perioperative management, complete removal of a lung can still represent a challenge for both the surgeon and the patient. Currently, parenchymal-sparing pulmonary resections have equivalent oncologic results to pneumonectomy and therefore, when possible, are favored. However, there are circumstances in which pneumonectomy remains the best oncologic procedure for the patient. Thorough preoperative workup and aggressive postoperative management are mandatory to optimize recovery. In this paper, we review pneumonectomy-related preoperative evaluation, operative techniques, and postoperative management.

Keywords: Non-small cell lung cancer (NSCLC); pneumonectomy; sleeve lobectomy; review

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Introduction

Lung cancer is the leading cause of cancer-related death in the United States; each year, more than 25,000 procedures are performed to treat this disease (1). The 5-year overall survival for all patients with lung cancer is a dismal 18% (2,3). In 2019, 228,150 new cases of lung cancer were estimated to be diagnosed as well as 142,670 projected deaths from the disease (4).

Non-small cell lung cancer (NSCLC) accounts for 84% of all primary bronchogenic carcinomas. Surgical resection remains the cornerstone of treatment for early-stage and locoregionally advanced NSCLC (stages I through IIIA). Only 25% to 30% of patients present with early-stage disease, and an additional 25% to 30% of patients are eligible for surgical resection with curative intent (5). Five-year overall survival rates for patients with NSCLC who have undergone surgery range from 75% for stage IA disease to 25% for stage IIIA disease (6).

Pneumonectomy accounts for 7.5% of all major lung resections (7). Common indications for pneumonectomy for lung cancer include locally advanced, central tumors with invasion of vascular and/or bronchial structures (8-10). Although the use of pneumonectomy for N2 disease has been described, this indication remains controversial and is restricted to select patients who have undergone neoadjuvant treatment, often in the context of a clinical trial (11,12). Stage-related 5-year survival rates after pneumonectomy for NSCLC may be as high as 44% for stage I, 37.5% for stage II, and 29% for stage III disease (13-15). However, when the overall survival rates are calculated, these range from 21% to 31% (16,17).

Table 1 Relevant dates, personnel, and events during the development of pneumonectomy

Year	Surgeon	Country	Events
1903	Ferdinand Sauerbruch	Germany	Designed a negative-pressure chamber that allowed for surgery in the pleural cavity
1908	Willy Meyer	US	Designed a negative and positive “differential” pressure chamber in the management of open thoracotomy
1931	Rudolph Nissen	Germany	Performed the first successful pneumonectomy for a patient with chronic empyema
1932	Cameron Haight	US	Performed the first successful pneumonectomy in the US
1933	Evarts Graham	US	Performed the first successful pneumonectomy for a patient with lung cancer
1938	Richard Overholt	US	Performed the first successful right pneumonectomy and described the technique of hilar dissection
1938	Clarence Crafoord	Sweden	Published a monograph focusing on the standardization of the technical aspects of pneumonectomy, “On the Technique of Pneumonectomy in Man”
1993	William Walker	UK	Performed the first thoracoscopic pneumonectomy

History of pneumonectomy

In 1903, Ferdinand Sauerbruch designed a negative-pressure chamber that allowed for the performance of surgery in the pleural cavity under open pneumothorax without collapse of the lung. In 1908, in New York, Willy Meyer modified the machinery to work with both positive and negative pressures. It was not until 1931, in Berlin, that Rudolph Nissen performed the first successful pneumonectomy (18). A year later, Cameron Haight performed the first successful pneumonectomy in the Western hemisphere (19).

The first successful pneumonectomy for lung cancer was performed by Evarts Graham in 1933 and became, at that time, the definitive procedure for this disease (20). In 1938, Richard Overholt reported his experience on 22 pneumonectomies (21). Meanwhile, Clarence Crafoord published a monograph focusing on the standardization of the technical aspects of pneumonectomy, including the periscapular incision with subperiosteal resection of the fifth rib, individual vessel ligation, suture closure of the bronchus, and a new rhythmic ventilatory technique that included the use of bronchial blockers (22). Overholt described the technique of hilar dissection, emphasizing the advantage of bronchial transection before dissecting the hilar vessels; with this technique, he achieved a reported mortality for patients with lung cancer of 33% (21). Following these reports and for the next two decades, pneumonectomy became the standard treatment for lung cancer and accounted for 30% of lung resections until the 1990s (*Table 1*).

In 1993, William Walker performed the first thoracoscopic pneumonectomy (23). The pulmonary artery and veins were divided using a linear stapler, and a clamp was preliminarily applied to the main arterial truncus to control possible bleeding. The lung was removed via minithoracotomy in the fifth intercostal space. The patient was discharged on the fifth postoperative day, without complications (23). Since then, several authors have described in detail the various options for pneumonectomy by minimally invasive approaches, with acceptable morbidity, mortality, and oncologic outcomes (24-26).

Indications for pneumonectomy

The standard indication for pneumonectomy for lung cancer is represented by an extent of disease that is not amenable to lung-sparing resection in the presence of sufficient cardiopulmonary reserve. Examples typically include centrally located tumors and interlobar invasion. In addition, the involvement of the mainstem bronchus, ipsilateral pulmonary artery, or both ipsilateral pulmonary veins, as well as the presence of synchronous ipsilateral upper and lower lobe malignancies, can often require a pneumonectomy.

Preoperative evaluation

Preresection functional assessment should include the patient’s performance status as well as a formal geriatric evaluation in the elderly patient. Cardiopulmonary reserve should be assessed by pulmonary function testing and

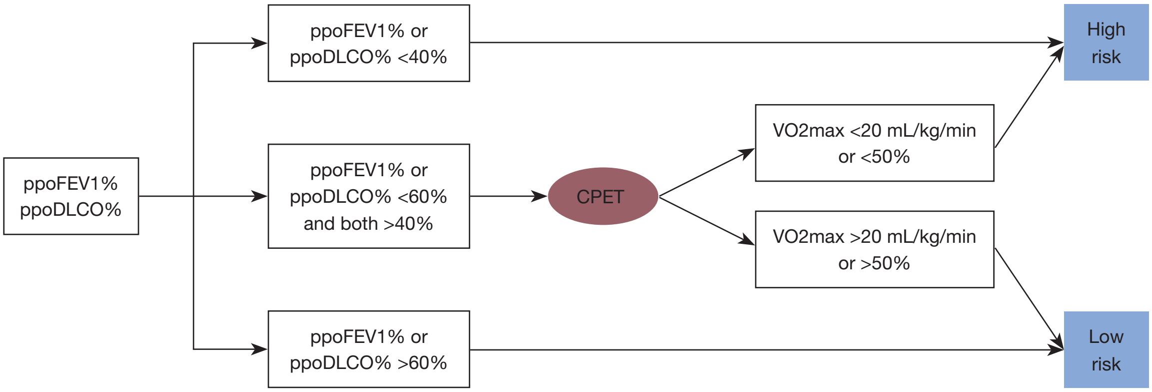

Figure 1 Algorithm of operability for pneumonectomy (28,30-33). CPET, cardiopulmonary exercise testing; ppo, predicted postoperative; VO2 max, maximal oxygen consumption.

electrocardiography along with an echocardiogram (27). Predicted postoperative forced expiratory volume in one second (FEV1) and diffusing capacity of the lungs for carbon monoxide (DLCO) should be calculated, as these have been shown to greatly influence postoperative morbidity and mortality as well as quality of life parameters (i.e., long-term dyspnea, need for permanent oxygen therapy) (28).

Patients with a preoperative FEV1 >2 L and predicted postoperative FEV1 >800 mL are considered to be eligible for pneumonectomy (29). In patients with borderline pulmonary parameters (FEV1 <2 L), a quantitative perfusion scan should be performed (30). A predicted postoperative FEV1 or DLCO of <40% indicates an increased risk of perioperative complications (31). In selected patients with poor performance on the stair climbing test, cardiopulmonary exercise testing should be performed (32). Simple cardiopulmonary exercise testing assessment can be in the form of stair climbing, 6- and 12-min walk tests, or the shuttle walk test. However, more commonly, cardiopulmonary exercise testing with cycloergometry is used to measure maximal oxygen consumption (VO2 max). Pneumonectomy candidates consuming <20 mL/kg/min or VO2 max <50% of predicted are at higher risk for postoperative morbidity and mortality (33). Finally, smoking cessation should be strongly encouraged, and a program should be in place to provide support with both counseling and approved pharmacologic adjuncts (*Figure 1*).

Clinical staging

Preresection oncologic evaluation should include a PET-CT and MRI of the brain to rule out distant metastases. Fiberoptic bronchoscopy, endobronchial ultrasound-guided biopsy, or mediastinoscopy to assess N2/3 disease should be performed (34). If indicated, an anterior mediastinotomy or thoracoscopy can be useful to determine involvement of nodal stations 5 and 6. Central tumors with concurrent pleural effusions should be subjected to thoracoscopic assessment of the pleural surfaces before committing to pneumonectomy.

Surgical decision-making: pneumonectomy versus sleeve lobectomy

Despite the high incidence of lung cancer and the number of patients with stage II and III disease, rates of pneumonectomy are declining, largely secondary to the emergence of induction therapies and the use of parenchymal-sparing resections. Sleeve resection of the bronchus, the pulmonary artery, or both has the advantage of providing complete tumor resection while avoiding pneumonectomy and has been proven to be a valid oncologic approach, as discussed below (35).

In 1947, Clement Price Thomas reported the first bronchial sleeve resection (36). In 1960, Donald Paulson presented encouraging survivals after bronchoplasty procedures performed for hilar tumors (37). Initially proposed for patients with lung cancer and poor cardiopulmonary function, sleeve lobectomy has progressively gained acceptance and is a reasonable alternative to pneumonectomy in select patients (38). The most common anatomic location for sleeve resections is the upper lobe (39-41). Sleeve lobectomy is oncologically

Table 2 Morbidity, mortality, and survival after sleeve lobectomy *vs.* pneumonectomy

Study	PSM	No. of patients		Induction therapy (%)		Mortality (%)		Morbidity (%)		5-year survival (%)	
		SL	PN	SL	PN	SL	PN	SL	PN	SL	PN
Okada (46) 2000	Yes	60	60	NA	NA	0	2	10	22	48	29
Lausberg (47) 2000	No	81	40	NA	NA	1.2	7.5	NA	NA	61.9 (2-year)	56.1 (2-year)
Martin-Ucar (48) 2002	No	38	81	NA	NA	10.5	9.9	NA	NA	64 (1-year)	73 (1-year)
Deslauriers (35) 2004	No	184	1046	NA	NA	1.3	5.3	NA	NA	52	31
Bagan (49) 2005*	No	66	151	0	0	4.5	12.6	28.8	29.9	72.5	53.2#
Kim (50) 2005	No	49	200	12	0	6.1	4.1	51	35	53.7	59.5
Ludwig (51) 2005	No	116	194	NA	NA	4.3	4.6	37.9	25.8	39.0	27.0
Takeda (52) 2006	No	62	110	25.8	16.8	4.8	3.6	45.2	40.9	54.3	32.9
Park (44) 2010	Yes	105	105	17.1	15.2	1.0	8.6	33.4	29.5	58.4	32.1
Gómez-Caro (53) 2011	No	55	21	20.0	9.5	3.6	4.7	32.3	33.3	61	31
Berry (39) 2014	No	35	52	0	0	5.7	3.9	49	58	65.2 (3-year)	46.8 (3-year)
Cusumano (54) 2014	No	51	68	100.0	100.0	3.9	2.9	47.0	48.6	53.8	43.1
Abdelsattar (43) 2017	Yes	1,713	1713	9.6	9.2	1.6	5.9	NA	NA	NA	NA
Pagès (55) 2017	Yes	794	794	20	21	4.99	5.89	NA	NA	71.86 (3-year)	60.76 (3-year)

*Only right upper sleeve lobectomy vs. right pneumonectomy in this trial; #Right pneumonectomy with N0-1 disease or only skip metastasis. PSM, propensity score matching; SL, sleeve lobectomy; PN, pneumonectomy; NA, not available.

equivalent to pneumonectomy, with comparable tumor recurrence rates. Maurizi *et al.* reported 5-year overall and disease-free survival for patients with centrally located NSCLC following sleeve resection of 55.1% and 62.9%, respectively (42). Abdelsattar *et al.* compared the results of sleeve resection (n=1,713; 7.2%) and pneumonectomy (n=22,251; 92.9%) for NSCLC in a multilevel propensity-matched observational study (43). The authors observed lower rates of 30-day (1.6% *vs.* 5.9%; P<0.001) and 90-day (4% *vs.* 9.4%; P<0.001) mortality and improved overall survival following sleeve resection. Sleeve resection was associated with 73% less mortality at 30 days and 57% less mortality at 90 days. Deslauriers *et al.* reported results of 1,230 consecutive patients with NSCLC who underwent sleeve resection (n=184) or pneumonectomy (n=1,046). Five-year overall survival was 52% following sleeve lobectomy and 31% after pneumonectomy (P<0.0001) (35). In a matching analysis performed by Park *et al.*, postoperative mortality was substantially lower after sleeve procedures (1% *vs.* 8.6%), with greatly improved 5-year overall survival (58.4% *vs.* 32.1%) (44). Balduyck *et al.* demonstrated superior quality of life after sleeve lobectomy, with lower incidence of dyspnea, general pain, thoracic pain, and shoulder dysfunction (45). Collectively, if equivalent oncologic outcomes are anticipated, sleeve lobectomy is favored over pneumonectomy. The differences in morbidity, mortality, and survival after sleeve lobectomy versus pneumonectomy are highlighted in *Table 2*.

Nodal involvement

In the absence of lymph node involvement (N0), sleeve lobectomy is clearly superior to pneumonectomy. However, the use of sleeve lobectomy is slightly more controversial in cases of N1 involvement. This is because most patients with N1 disease die because of distant metastases rather than local recurrence (56). Therefore, N1 disease should not be considered a contraindication for a sleeve resection (56). Berry *et al.* concluded that, compared with pneumonectomy, sleeve lobectomy for NSCLC with N1 nodal disease does not compromise long-term survival (39).

Although several studies have reported an increased risk of recurrence after sleeve lobectomy, compared with pneumonectomy, for tumors with hilar adenopathy (50,56), other evidence suggests that the presence of N1 or N2 disease does not necessarily mandate pneumonectomy, and sleeve lobectomy can achieve complete tumor resection without a significantly increased risk of local recurrence or difference in survival (57-59). In fact, Okada *et al.* concluded that sleeve lobectomy should be performed, instead of pneumonectomy, regardless of nodal status (46).

The role of chemotherapy and radiation in pneumonectomy

The Intergroup trial (INT0139) performed in North America and reported in 2009 remains one of the most influential studies to evaluate surgery for stage III NSCLC (60). Patients received concurrent chemotherapy plus radiation to 45 Gy with or without surgical resection. Thirty percent of patients underwent pneumonectomy, with an observed 5-year overall survival of 22% and no improvement in long-term outcomes. Overall perioperative mortality rate was 26%, with 38% for right-side and 12% for left-side pneumonectomy, suggesting that pneumonectomy is a "high-risk" procedure in patients with stage III NSCLC who have received induction therapy (60). However, multiple, single-institution, retrospective studies have shown acceptable perioperative risk for pneumonectomy in the setting of induction chemotherapy and radiotherapy (61-65). In addition, when the literature is investigated for short-term mortality after pneumonectomy, there is no difference in 30-day mortality between patients who underwent neoadjuvant therapy (5.6%) and those who did not (6%) (66).

In 2012, Kim *et al.* published a meta-analysis that investigated 27 trials for perioperative mortality after pneumonectomy with induction chemotherapy and radiation (67). Mortality rates at 30 and 90 days were 7% and 12%, respectively, with no difference between patients whose induction regimen included radiation and those whose did not. The best prospective, contemporary data regarding safety of pneumonectomy following induction therapy comes from the SAKK trial, where 232 patients with resectable IIIA N2 disease were treated with either induction chemotherapy or chemotherapy and sequential radiation (68). Pneumonectomy was performed in 20% of patients in the trimodality group and 25% of patients in the bimodality group, with a low perioperative mortality of 4.5%. Again, no difference in survival was noted between the tri- and bimodality groups. A phase II trial published in 2009 reported a 5-year survival of 40% in patients who underwent induction chemoradiotherapy followed by surgery for stage IIIB disease (69). Pneumonectomy was performed in 48% of patients with a 30-day mortality rate of 5.7% and median overall survival of 29 months. *Table 3* lists the study details and mortality and survival rates for phase III trials involving neoadjuvant therapy followed by pneumonectomy. Given these results, if oncologically indicated, the evidence strongly supports that a pneumonectomy can safely be performed following induction chemotherapy with or without radiation for locoregionally advanced NSCLC.

Operative technique

A standard muscle-sparing posterolateral thoracotomy in the fifth or occasionally fourth intercostal space provides optimal exposure. The latissimus dorsi muscle is divided, and the serratus anterior muscle is retracted superiorly. The rib can be transected posteriorly to facilitate exposure. Preservation of the intercostal muscle should be done at this time in case it is needed to cover the bronchial stump. On entering the pleural space, absence of pleural effusion and intrathoracic metastatic spread should be confirmed. Thoracoscopic evaluation can be used for this purpose as well. Thoracoscopy helps to identify pleural metastases that may not be identified by conventional imaging techniques and can also be used for surgical planning to determine the optimal incision used for resection (76).

Left-sided pneumonectomy

We initially perform a complete mediastinal lymph node dissection including stations 5, 6, 7, 9, and, if enlarged or FDG-avid, 4L and 8. Particular attention should be paid to the recurrent laryngeal and phrenic nerves to avoid injury during the dissection. The pulmonary veins and main pulmonary artery (PA) are then isolated and divided using the stapler. Safe dissection of these structures is always facilitated by first removing the hilar N1 nodes whenever possible. With central tumors, the hilar dissection can be challenging, and it may require opening the pericardium. Given the short intrapericardial length of the left pulmonary artery, identification and division of the ligamentum arteriosum may be performed to maximize length on the main PA.

The left mainstem bronchus is circumferentially dissected, with care being taken not to devascularize the airway. Again, a complete station 7 nodal dissection should be performed, as this makes the subsequent bronchial dissection relatively easy. The endobronchial extent of

Table 3 Randomized phase III trials assessing preoperative therapy followed by surgery for stage III NSCLC

Study	Eligibility	Study arms	Preoperative RT	Dose (Gy)	No. of patients			Mortality (no. %)			5-year survival (%)
					All	Right	Left	All	Right	Left	
Albain (60) 2009, Intergroup 0139	T1-3pN2	Induction RT-CHT + S *vs.* CHT + RT	Yes	45	54	29	25	14 (26%)	11 (38%)	3 (12%)	22
van Meerbeeck (70) 2007, EORTC 08941	III/N2 (inoperable)	Induction CHT + S *vs.* CHT + RT	No	NA	72	38	33	5 (7%)	2 (5%)	3 (9%)	NA
Stephens (71) 2005	T3N1, T1-3N2 (inoperable)	Induction CHT + S *vs.* RT	No	NA	2	NA	NA	2 (100%)	NA	NA	NA
Johnstone (72) 2002, RTOG 89-01	T1-3pN2	Induction CHT + S *vs.* CHT + RT	No	NA	NA	NA	NA	NA	NA	NA	NA
Eberhardt (73) 2015, ESPATUE	IIIA (pN2), selected IIIB	Induction CHT + RT-CHT + S *vs.* Induction CHT + RT-CHT	Yes	45	23	NA	NA	0 (0%)	NA	NA	NA
Pless (68) 2015, SAKK	T1-3pN2	Induction CHT + RT + S *vs.* Induction CHT + S	Some	44	25 (CRS arm)	NA	NA	0 (0%)	0 (0%)	0 (0%)	NA
					19 (CS arm)	NA	NA	3 (16%)	2 (NA)	1 (NA)	NA
Katakami (74) 2012, WJTOG9903	T1-3pN2	Induction CHT + RT + S *vs.* Induction CHT + S	Some	40	0 (CRS arm)	0	0	NA	NA	NA	NA
					1 (CS arm)	NA	NA	0 (0%)	NA	NA	NA
Thomas (75) 2008, GLCCG	T1-3N2 or central T3N0-1, T4N1-3 or T1-4N3	Induction CHT + RT-CHT + S *vs.* Induction CHT + S + PORT	Some	45	50 (Inter arm)	19	31	7 (14%)	NA	NA	NA
					54 (Control arm)	20	34	3 (6%)	NA	NA	NA

CHT, chemotherapy; S, surgery; RT, radiotherapy; NA, not available; CRS arm, Induction CHT + RT + S arm; CS arm, Induction CHT + S arm; PORT, postoperative radiotherapy; Inter arm, Induction CHT + RT-CHT + S arm; Control arm, Induction CHT + S + PORT arm.

the tumor determined by preoperative bronchoscopy is taken into consideration before division of the bronchus. Bronchial margins are then sent for frozen section analysis. The bronchial stump should be <2 cm and is then tested for pneumostasis by submerging it under water. If no leak is identified, the bronchial stump may be bolstered with soft tissue (intercostal muscle, pericardial fat pad, or pedicled pericardium) to help prevent bronchopleural fistula. For left-sided pneumonectomies, we do not routinely cover the bronchus as it is covered in large part by the arch of the aorta. However, if induction radiation was administered or adjuvant radiation is being considered, bronchial stump coverage may be performed.

Right-sided pneumonectomy

Surgical principles and approach are similar to those previously described for left-sided pneumonectomy. Following exposure, we perform a complete mediastinal lymph node dissection including stations 2R, 4R, 7, 9, and occasionally level 8 nodes. Assessment of the hilum and vascular control is performed next. The azygous vein is not routinely divided, but this can be performed to facilitate exposure to the proximal right main PA and the mainstem bronchus. The superior vena cava is mobilized to gain control of the main PA. If that proves challenging secondary to tumor location or treatment effect, one should open the pericardium and obtain control medial to the superior vena cava. If significant resection of the pericardium is required to achieve an R0 resection, the pericardium should be reconstructed with prosthetic material such as Gore-Tex mesh or polypropylene mesh. This is done to prevent cardiac herniation—a potentially highly lethal complication (77,78).

Postoperative management, complications, and outcomes

Initial management of patients following pneumonectomy consists of early extubation (preferably in the operating room), adequate pain relief (usually with an epidural catheter), aggressive pulmonary toilet, early ambulation, and venous thromboprophylaxis (79). Despite this, 33% to 44% of patients experience a complication after pneumonectomy (80-82). One of the most common complications is atrial dysrhythmia, occurring in approximately 20% to 40% of patients following pneumonectomy (81,83). More severe complications after pneumonectomy, such as empyema, acute respiratory distress syndrome (ARDS), and bronchopleural fistula (BPF), are less common but are independent risk factors for death. A recent report of the Memorial Sloan Kettering (MSK) experience with pneumonectomy considered 355 patients over an 18-year period who underwent pneumonectomy for NSCLC. In this series, an incidence of BPF of 3.7% was found (84), which is similar to rates (8%) in other studies (82,85). Postpneumonectomy ARDS occurred in 2.3% of cases (84), compared with rates of 2.7% to 12% in other studies (81,82,86,87). Postpneumonectomy ARDS is associated with postoperative mortality of almost 70% and 5-year overall survival of 17.6% (88). Primary risk factors for developing BPF and ARDS are older age and right-sided pneumonectomy (81,82,85). Right-sided pneumonectomy is associated with a higher risk of death, compared with left-sided pneumonectomy, especially after neoadjuvant therapy (89). Although induction chemoradiation was found to be an independent risk factor for major adverse events following pneumonectomy in a large study from the Society of Thoracic Surgeons General Thoracic Surgery Database (90), other studies have not supported this association (82,85). Mortality rates after pneumonectomy also appear to be influenced by hospital volume. The unadjusted in-hospital mortality for 90,088 patients undergoing pneumonectomy in the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database was 2.7% in the highest-volume decile of hospitals versus 4.9% in the lowest-volume decile (91). As a comparison, in the MSK series, the reported 30-day mortality was 4.6% (84). Moreover, the mortality burden after pneumonectomy should not be overlooked in the post-hospital discharge setting. Schneider *et al.* reported that more than half of postpneumonectomy deaths occurred during the first 90 days after discharge from the hospital (92). In the MSK series, 13 of 24 deaths within the first 90 days occurred while in-hospital (84).

In general, factors associated with adverse long-term survival include increased age, advanced stage, extended resection, adenocarcinoma, lymphatic vessel microinvasion, lymph node involvement, and residual disease (93). Conversely, sex, pneumonectomy laterality, and tumor size do not predict long-term survival (93,94). Fernandez *et al.* observed that, although right-sided pneumonectomy was associated with an approximately 2-fold increase in perioperative mortality, compared with left-sided pneumonectomy, 3-year survival rates were similar (39% for right *vs.* 41% for left) (92).

Conclusions

Pneumonectomy is an increasingly less common surgical procedure and is often the last resort for patients with NSCLC not amenable to lung-sparing resection. Sleeve resection has shown promise as an alternative to pneumonectomy, although in cases of centrally located tumors, involvement of vascular structures, or bulky hilar adenopathy, pneumonectomy may be unavoidable. In these cases, pneumonectomy can be performed with acceptable operative morbidity and mortality, even after induction therapy.

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Footnote

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