

**Original
Article**

Respiratory Complications during Mid- and Long-Term Follow-Up Periods in Patients Who Underwent Pneumonectomy for Non-Small Cell Lung Cancer

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Background: Pneumonectomy is associated with higher early mortality and morbidity, and it is also known to predispose the patient to respiratory complications during mid- and long-term follow-up. Therefore, the purpose of this study was to identify risk factors associated with respiratory complications during the follow-up period after pneumonectomy.

Methods: We retrospectively reviewed 98 patients who underwent pneumonectomy for non-small cell lung cancer (NSCLC) between Jan 1995 and Dec 2005. Univariate and multivariate analyses were used to identify risk factors of late respiratory complications among preoperative and intraoperative data.

Results: The median follow up duration of 98 patients was 33.1 months (4.2–180.0 months). The late mortality rate was 68.4% ($n = 67$). Causes of late death were cancer specific in 37 patients (55.2%) and respiratory specific in 25 patients (37.3%). Compared with 59 patients who had no respiratory infection after pneumonectomy during mid- or long-term follow-up, being male, a lower BMI ($<22 \text{ kg/m}^2$), presence of chronic obstructive pulmonary disease (COPD) and preoperative pneumonia were significant risk factors by univariate analysis. Multivariate analysis revealed that presence of preoperative pneumonia was the only independent factor associated with late mortality from respiratory complications during the mid- and long-term follow-up periods (OR = 2.41, 95% CI = 1.10–5.32, $p = 0.028$).

Conclusion: Respiratory infection was a comparable risk factor of mortality in the mid- and long-term after pneumonectomy with cancer recurrence. The presence of preoperative pneumonia was an independent factor related to respiratory infection. Careful follow-up for these patients may be required.

Keywords: lung cancer, pneumonectomy, pneumonia, respiratory infections

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Introduction

Pneumonectomy is known to be an appropriate surgical therapy for advanced or centrally located non-small cell lung cancer (NSCLC). Although pneumonectomy can achieve its oncologic goal in the management of NSCLC, it is associated with higher mortality and morbidity rates than other lesser forms of resection. The 30-day mortality rate for pneumonectomy was around 6% in contrast, that for lobectomy due to NSCLC was 2.9%.¹⁾ The causes of death after pneumonectomy are

typically cardiopulmonary in nature, and these include pneumonia, respiratory failure, bronchopleural fistula, myocardial infarction and pulmonary embolism.²⁾ Many studies have identified independent perioperative factors associated with pulmonary complications after pneumonectomy. Old age, smoking status, chronic obstructive pulmonary disease (COPD), and poor pulmonary function have been known to be related with pulmonary complications immediately after pneumonectomy.¹⁻⁴⁾ The mid- and long-term results following pneumonectomy depend not only on the underlying disease for which pneumonectomy was performed but also on the status of the remaining lung. The common causes of death after pneumonectomy are known to be disease progression due to recurrence of the initial disease and restrictive respiratory insufficiency by loss of the alveolar surface.²⁾ However, little is known about respiratory complications during mid- and long-term follow-up for patients after pneumonectomy. Although some authors have reported late morbidities due to pneumonectomy, most of them have focused on postpneumonectomy empyema or syndrome. However, a large portion of pneumonectomized patients suffer from respiratory complications due to respiratory infection, and most of them cannot recover even though maximal treatment is given. In considering these findings, we thought that investigating the outcomes of these patients and risk factors of respiratory complications during mid- and long-term follow-up would be worthy in order to prevent these complications. Therefore, we evaluated the incidence of late respiratory complications of these patients and identified the factors associated with late respiratory complications.

Materials and Methods

Between January 1995 and December 2005, 119 patients who underwent pneumonectomy for NSCLC at the Kyungpook National University Hospital were retrospectively included in the study. Twelve patients (10.1%) were lost during follow-up and were excluded from this study. Preoperative studies included medical history, physical examination, pulmonary function test (PFT), bronchoscopy, chest computed tomography (chest CT), and lung perfusion scan. Diagnosis of preoperative pneumonia was made in the same way as that of postoperative pneumonia, when patients had a lung infiltration or consolidation, purulent sputum and documented presence of microorganisms in the

culture, and leukocytosis. COPD was defined as percent predicted forced expiratory volume (FEV) in 1 second (% predicted FEV1) <70%, and FEV1/forced vital capacity (FVC) <70%. If patients showed mediastinal node metastasis or a bulky mass in the central lesion on chest CT which would prevent complete resection, cisplatin and taxane combination neoadjuvant chemotherapy would be performed. After 3 cycles of neoadjuvant chemotherapy were completed, reassessment of resectability was performed. All patients were operated on by the same surgical team through a standard posterolateral thoracotomy. Until 2000 at this hospital, pneumonectomy was the preferred procedure for a tumor located in a main bronchus, indicating stage IB lung cancer, rather than sleeve resection. The bronchial division was performed with a mechanical stapler and the bronchial stump was covered with various materials in all patients. A Pericardial fat had been mainly used to cover bronchial stump before 2003 and the hemostatic agent named Tachocomb have been tried to be utilized afterwards. Pathologic staging was performed according to the 6th edition TNM staging system. There were 25 patients (23.4%) in stage I, 29 patients (27.1%) in II, 51 patients (47.7%) in III, and 2 patients (1.8%) in stage IV. The histological type of NSCLC was as follows: 89 cases of squamous cell carcinoma (SCC); 18 cases of adenocarcinoma. Early morbidity and mortality were defined as those occurring before hospital discharge or within 30 days after pneumonectomy. Follow-up was achieved through regular clinic visits until patients' death. Patients were examined at 3-month intervals for 2 years, 6-month intervals during years 2–5 postsurgery, and annually after 5 years. Cause of late death was defined as cancer specific if due to recurrence, and respiratory specific if due to respiratory complications such as pneumonia or acute respiratory distress syndrome (ARDS). If recurred patients who were under chemotherapy had a respiratory infection and died during same admission period, it would be counted as cancer specific death.

Pre- and intra-operative variables were tested with univariate analysis for respiratory complications and mortality, categorical variables were analyzed using a Pearson's χ^2 test or Fisher's exact test, and continuous variables were compared by using the Student's paired t-test. For survival analysis, the Kaplan Meier method was used and for comparison of the survival rate a log rank test was used. In the multivariate analysis, a Cox logistic regression analysis

was applied. Statistical significance was indicated by a p -value <0.05 , and all statistical analyses were performed by SPSS PC, version 17 (SPSS Inc, Chicago, IL, USA).

Results

Of 107 patients, the early mortality rate was 8.4% ($n = 9$). Causes of early mortality were pneumonia/ARDS in 7 patients, acute myocardial infarction in 1 patient, and surgical bleeding in 1 patient. The remaining 98 patients except for patients who died during the early follow-up period composed the study group. The mean age was 59.0 (range, 32–75) years old and 89 patients (90.8%) were male. Ninety patients (91.8%) were ever-smokers and 8 patients (8.2%) were never-smokers. Of the ever-smokers, 57 patients (58.2%) had smoked more than 40 pack-years (PY). The mean body mass index (BMI) was 21.9 kg/m², and 54 patients (55.1%) were below 22 kg/m². Eighteen patients (18.4%) were satisfied with the criteria of COPD (FEV₁ $<70\%$ and FEV₁/FVC <70). Nineteen patients (19.4%) had preoperative pneumonia, and most of the organisms were α -hemolytic streptococcus. The median carcinoembryonic antigen (CEA) level was 3.04 ng/ml, and it was >5 ng/ml in 22 patients (24.2%). A right side pneumonectomy was performed in 36 patients (36.7%) and the mean anesthetic time was 4.5 hours. Postoperative complications occurred in 15 patients (15.3%), postoperative pneumonia in four patients, hoarseness in four patients, bleeding required reoperation in three patients, and atrial fibrillation in two patients (**Table 1**). The risk factors of preoperative pneumonia were SCC ($p = 0.017$), more than 40 PY ($p = 0.002$), low FVC ($<80\%$, $p = 0.022$), and presence of COPD ($p = 0.021$) (**Table 2**).

The median follow-up duration of 98 patients was 33.1 months (4.2–180.0 months). The 1-, 3-, 5-year overall survival rates were 87.8%, 63.3%, and 42.5%, respectively. Of 31 surviving patients (31.6%), 23 patients had neither recurrence nor cardiopulmonary disorders, 3 patients had cardiac disorders, 2 patients had second primary cancer, 2 patients had history of respiratory complications, and one patient with recurrence. The late mortality rate was 68.4% ($n = 67$). The causes of late mortality were cancer specific in 37 patients (55.2%), respiratory complication specific in 25 patients (37.3%), and others in 5 patients (7.5%) without disease progression or respiratory infections. The mean survival

Table 1 Basic characteristic of patients who underwent pneumonectomy for NSCLC

Variables	No. of patients (%)
Male patients	89 (90.8)
Age, years	59 + 8.3
Smoking, ever-smoker	90 (91.8)
PY, >40	57 (58.2)
BMI, <22 kg/m ²	54 (55.1)
COPD	18 (18.4)
Preoperative pneumonia	19 (19.4)
CEA, median, ng/ml	3.04
Side of operation, Right	36 (36.7)
Operating time, mean, hour	4.5
Complications	15 (15.3)
Postoperative pneumonia	4 (4.1)
Hoarseness	4 (4.1)
Bleeding	3 (3.1)
Atrial fibrillation	2 (2.0)

NSCLC: non-small cell lung cancer; PY: pack-years; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CEA: carcinoembryonic antigen

Table 2 Risk factors of preoperative pneumonia

Variables	No. of patients (%)	p value
Cell type		0.017
Squamous cell carcinoma	16 (84.2)	
Adenocarcinoma	3 (15.8)	
Smoking		0.002
≤ 40 PY	2 (10.5)	
>40 PY	17 (89.5)	
FVC		0.022
$\geq 80\%$ of predicted value	9 (47.4)	
$<80\%$ of predicted value	10 (52.6)	
COPD		0.021
Yes	12 (63.2)	
No	7 (36.8)	

PY: pack-years; FVC: forced vital capacity; COPD: chronic obstructive pulmonary disease

times of cancer specific and respiratory infection specific cases lost were 57.1 months and 58.0 months, respectively. The 1-, 3-, and 5-year cancer specific survival rates were 92.4%, 73.3%, and 56.6%, and respiratory specific survival rates were 93.6%, 86.1%, and 72.5%, respectively. When the causes of death were evaluated according to survival time, respiratory infection occurred more commonly than cancer recurrence in patients who survived >36 months. In contrast, in patients who survived <36 months, cancer recurrence was more common than respiratory infection. Recurrence occurred in 51 patients (52.4%), and 37 patients of them (72.5%) were dead from disease progression.

Recurrence sites were locoregional in 10 patients, and distant metastasis in 41 patients. The mean time to development of respiratory infection from operation was 23 months in 39 patients who had respiratory complications due to infection during follow-up, of those 25 patients (64.1%, 25/39) who succumbed to deaths of respiratory complications.

Compared with 59 patients who had no respiratory infection after pneumonectomy during mid- or long-term follow-up, male sex, lower BMI, presence of COPD and preoperative pneumonia were significant risk factors by univariate analysis (**Table 3**). Multivariate analysis revealed that presence of preoperative pneumonia was an independent factor associated with mortality from respiratory complications during the mid- and long-term follow-up periods (**Table 4**).

Discussion

In patients undergoing pneumonectomy for NSCLC, postoperative pulmonary complications are common and related with high mortality. The incidence of pulmonary complications after pneumonectomy was up to 50%, and an old age, poor pulmonary function, COPD, and a prolonged anesthetic time have been known to be independent predictors.¹⁻⁵⁾ However, most studies have focused on immediate postoperative periods and early mortality within 30 days. Despite the presence of similar recurrence rates in the pneumonectomy and lesser lung resection groups, the long-term survival rate of patients with pneumonectomy was poor. Alexiou et al. showed that the survival difference between pneumonectomy and lesser resection continues to increase over the first 2 to 3 postoperative years and concluded that this might simply reflect the higher operative mortality of pneumonectomy.⁶⁾ The present study, therefore, aimed to evaluate the risk factors of respiratory complications during the medium and late periods after pneumonectomy. These periods were thought to be recovery phase from surgical stress and pulmonary functions of this time were up to 80% of the postoperative predicted value. In general, the main causes of death other than disease progression after pneumonectomy were found to be respiratory complications and cardiac dysfunction. This study also showed that cancer recurrence and respiratory failure were the main causes of late death after pneumonectomy for NSCLC. Although two patients had myocardial infarction, late mortality was not attributable to cardiovascular insufficiency. Rocco

Table 3 Univariate analysis for late respiratory infection

Variables	No	Yes	<i>p</i> value
Sex, male	0 (0%)	39 (43.8%)	0.006
Age, 60 year	17 (32.7)	22 (47.8)	0.127
BMI, <22 kg/m ²	12 (27.3)	27 (50.0)	0.022
Smoking, ever-smoker	1 (12.5)	38 (42.2)	0.140
Smoking, PY > 40	14 (34.1)	25 (43.9)	0.333
COPD	27 (33.8)	12 (66.7)	0.010
Side, Rt	23 (37.1)	16 (44.4)	0.474
Preoperative pneumonia	26 (32.9)	13 (68.4)	0.005
Neoadjuvant therapy	32 (38.1)	7 (41.7)	0.208
Adjuvant therapy	21 (33.9)	18 (50)	0.116

BMI: body mass index; PY: pack-years; COPD: chronic obstructive pulmonary disease

Table 4 Multivariate analysis for late respiratory infection

Variables	Odds ratio	95% CI	<i>p</i> value
Sex, male	1.010	0.499–2.044	0.978
BMI, <22 kg/m ²	0.924	0.452–1.889	0.829
COPD	0.866	0.381–1.970	0.732
Preoperative pneumonia	2.418	1.099–5.320	0.028

CI: confidence interval; BMI: body mass index; COPD: chronic obstructive pulmonary disease

et al. also revealed that late cardiac insufficiency related to adverse physiological consequences of pneumonectomy is uncommon.⁷⁾ Therefore, respiratory complications were the most important prognostic factor of late mortality and its risk factors have to be elucidated in order to prevent late death after pneumonectomy. Those factors which are significant risk factors of respiratory complications after the early phase of pneumonectomy may also function as risk factors of respiratory complications during the late phase. This study showed that male sex, lower BMI (<22 kg/m²), presence of COPD, and preoperative pneumonia were significant risk factors by univariate analysis for late respiratory complications. However, preoperative pneumonia was the only independent risk factor of respiratory complications by multivariate analysis.

COPD was shown to be a risk factor of postoperative pneumonia in patients who underwent resection to any extent. Shiono et al. reported that a preoperative FEV₁% of less than 70% was a significant risk factor for postoperative pneumonia by multivariate analysis.⁸⁾ Therefore, our results suggest that COPD has a strong impact on deterioration of pulmonary condition after surgery and, in the long run, is associated with worsening pulmonary function. Patients with COPD are more prone to pneumothorax, pneumonia, and chronic

hypoxemia because of impaired total distance of the alveolar surface to the capillary endothelium, reduced area of gas exchange, and reduction of surface capillary area and hemoglobin concentration.⁹⁾ Another reason is that distal airways were frequently colonized in clinically stable populations with lung cancer (42%), COPD (83%), or bronchiectasis (88%).¹⁰⁾ Therefore, COPD patients who underwent pneumonectomy for lung cancer might have had bacterial colonization even though clinical symptoms or infective signs were not present. Because minimal respiratory infection or disturbance of immunity could cause overwhelming respiratory infection, respiratory failure occurred easily in pneumonectomized patients who had marginal pulmonary function.

Poor pulmonary function is also known to be a major risk factor of pulmonary complications immediately and over the long-term especially in patients with pneumonectomy. Leo et al. showed that overall 5-year survival was 17.5% in elderly patients (>70 year) and 53.6% in younger patients, and 37.5% were unrelated to cancer in elderly patients and 13.8% in younger patients. They concluded that the only factor affecting long-term survival in the elderly was preoperative respiratory function.¹¹⁾ Deduced from the results of Leo et al., among patients with older age and poor lung function more deaths unrelated to cancer but rather due to respiratory dysfunction after pneumonectomy might occur. This may be because the postoperative pulmonary condition had severely deteriorated and chronic bronchitis and frequent pulmonary infection occurred.

Close attention should be paid to preoperative pneumonia as an independent risk factor of pulmonary complications during the late phase. Although the mechanisms were not clearly elucidated, bronchial bacterial colonization may be frequent in patients with lung cancer as most of these patients have underlying COPD and this might be a cause. Cabello et al. reported that 42% of patients with pulmonary carcinoma had bronchial colonization with commensal or potential pathogenic micro-organisms.¹⁰⁾ Frequency of bacterial colonization is not known to differ between lobectomy and pneumonectomy. However, preoperative bacterial colonization might be higher in patients with pneumonectomy than those with lobectomy due to bronchial obstruction by a centrally located tumor. Ioanas et al. reported that a central tumor was a statistically significant risk factor of bronchial colonization.¹²⁾ In this study, preoperative pneumonia was present in

19 patients (19.4%) and the risk factors were SCC, heavy smoker (>40 PY), low FVC, and COPD. Of those with postoperative respiratory infections, patients with preoperative pneumonia were twice as common as those without (68.4% vs. 32.9%). Although the presence of causative preoperative microorganisms was not exactly consistent with that of postoperative microorganisms in patients with respiratory infection, preoperative pneumonia was meaningful in predicting late respiratory complications. The authors suggest that unilateral obstruction by central lesion may be a predisposing factor for accumulation of secretions above the obstructed airway and consequent aspiration of colonized secretions to the contralateral lung. As a result, it is possible that colonization with commensal or potential pathogenic organism survive in the remained lung after the surgery. The bacterial colonization may have an effect on late pulmonary complications.

In the present study, every patient with preoperative pneumonia has received the operation after the recovery of pneumonia, which was defined to be both the symptomatic improvement of fever and chills, and the normalization of white blood cell and C-reactive protein levels. In this context, chest physiotherapy is highly recommended to prevent pulmonary complications after lung resection by some investigators. Algar et al. reported that chest physiotherapy is highly recommended to prevent pulmonary complications after pneumonectomy.¹³⁾

Neoadjuvant chemotherapy is known to be a major risk factor of perioperative complications after pneumonectomy as well as lobectomy. Busch et al. found a significant increase in major pulmonary complications in patients who had received induction chemotherapy.¹⁴⁾ As neoadjuvant therapy is being studied in earlier stage lung cancer and may be applied more broadly in the future, the exact mechanism of perioperative complications caused by induction chemotherapy has to be elucidated. Roberts et al. concluded that the most common life-threatening complication in patients receiving neoadjuvant chemotherapy was the failure to respond to antibiotics given for pneumonia.¹⁵⁾

This study has several limitations. First, because patients who underwent pneumonectomy had reached a more advanced stage than those with lobectomy, most patients received adjuvant therapy. Therefore, many patients had experienced poor general condition, which can make patients more susceptible to respiratory infection.

It is difficult to differentiate respiratory complications derived from risk factors inherent to patient health and demographics from those by chemotherapy. Second, a large portion, 10% of our patients were lost during the follow-up period in our study. However, these patients might have died more likely due to respiratory complications than to recurrence. Third, this study has failed to come up with a solution in patients who had preoperative pneumonia in order to prevent respiratory infections/failure over the long term. We plan to study the effect of respiratory rehabilitation on early and late respiratory complications after pneumonectomy.

Conclusion

From these results, careful prophylactic treatment of COPD patients with preoperative pneumonia are critical for prolonging survival after pneumonectomy for non-small cell lung cancer.

Disclosure Statement

The authors report no conflicts of interest in the writing of this report.

References

- 1) Deslauriers J, Ginsberg RJ, Piantadosi S, et al. Prospective assessment of 30-day operative morbidity for surgical resections in lung cancer. *Chest* 1994; **106**: 329S-330S.
- 2) Klemperer J, Ginsberg RJ. Morbidity and mortality after pneumonectomy. *Chest Surg Clin N Am* 1999; **9**: 515-25.
- 3) Wada H, Nakamura T, Nakamoto K, et al. Thirty-day operative mortality for thoracotomy in lung cancer. *J Thorac Cardiovasc Surg* 1998; **115**: 70-3.
- 4) Harpole DH, Liptay MJ, DeCamp MM, et al. Prospective analysis of pneumonectomy: risk factors for major morbidity and cardiac dysrhythmias. *Ann Thorac Surg* 1996; **61**: 977-82.
- 5) Iwamoto K, Ichiyama S, Shimokata K, et al. Postoperative pneumonia in elderly patients: incidence and mortality in comparison with younger patients. *Intern Med* 1993; **32**: 274-7.
- 6) Alexiou C, Beggs D, Onyeaka P, et al. Pneumonectomy for stage I (T1N0 and T2N0) nonsmall cell lung cancer has potent, adverse impact on survival. *Ann Thorac Surg* 2003; **76**: 1023-8.
- 7) Rocco G, La Rocca A, De Rosa V, et al. The use of a bone substitute composite in the management of a post-pneumonectomy bronchopleural fistula. *Eur J Cardiothorac Surg* 2009; **36**: 415-6.
- 8) Shiono S, Yoshida J, Nishimura M, et al. Risk factors of postoperative respiratory infections in lung cancer surgery. *J Thorac Oncol* 2007; **2**: 34-8.
- 9) Sekine Y, Behnia M, Fujisawa T. Impact of COPD on pulmonary complications and on long-term survival of patients undergoing surgery for NSCLC. *Lung Cancer* 2002; **37**: 95-101.
- 10) Cabello H, Torres A, Celis R, et al. Bacterial colonization of distal airways in healthy subjects and chronic lung disease: a bronchoscopic study. *Eur Respir J* 1997; **10**: 1137-44.
- 11) Leo F, Scanagatta P, Baglio P, et al. The risk of pneumonectomy over the age of 70. A case-control study. *Eur J Cardiothorac Surg* 2007; **31**: 780-2.
- 12) Ioanas M, Angrill J, Baldo X, et al. Bronchial bacterial colonization in patients with resectable lung carcinoma. *Eur Respir J* 2002; **19**: 326-32.
- 13) Algar FJ, Alvarez A, Salvatierra A, et al. Predicting pulmonary complications after pneumonectomy for lung cancer. *Eur J Cardiothorac Surg* 2003; **23**: 201-8.
- 14) Busch E, Verazin G, Antkowiak JG, et al. Pulmonary complications in patients undergoing thoracotomy for lung carcinoma. *Chest* 1994; **105**: 760-6.
- 15) Roberts JR, Eustis C, Devore R, et al. Induction chemotherapy increases perioperative complications in patients undergoing resection for non-small cell lung cancer. *Ann Thorac Surg* 2001; **72**: 885-8.