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Citation	Surgery Today, 36(10), 869-873 <a href="https://doi.org/10.1007/s00595-006-3264-z">https://doi.org/10.1007/s00595-006-3264-z</a>
Issue Date	2006-10
Doc URL	<a href="http://hdl.handle.net/2115/14867">http://hdl.handle.net/2115/14867</a>
Rights	The original publication is available at <a href="http://www.springerlink.com">www.springerlink.com</a>
Type	article (author version)
File Information	ST36-10.pdf



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## **Original Article**

### **Title**

# **Long-term Outcomes After Surgical Resection of Non-Small Cell Lung Carcinomas Complicated by Pneumoconiosis**

**Running head;** NSCLC complicated by pneumoconiosis

**Key words;** Pneumoconiosis, NSCLC, Prognosis

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## **Abstract**

*Purpose.* Lung cancer patients with respiratory complications are high risk surgical cases, and thus the operative indication is usually severe, which in turn has resulted in unclear long-term findings. We aimed to clarify the validity of surgery in non-small cell lung cancer (NSCLC) patients with pneumoconiosis.

*Methods.* Clinical and pathological data from 122 patients undergoing surgical resection for NSCLC with pneumoconiosis (n=34: group A) and without pneumoconiosis (n=88: group B) were reviewed to assess treatment outcomes and prognostic factors.

*Results.* Of the treatment factors, intraoperative blood loss was significantly greater in group A (723.2±647.3 ml) than group B (466.4±450.7 ml) (p=0.0067), although operative time (207±103.4 min vs. 196.1±53.5 min, for groups A and B respectively) and postoperative drainage period (8.3±4.2 days vs. 8.5±5.7 days, respectively) did not differ significantly between the two groups (p=0.9466 and p=0.6355, respectively). In postoperative complications, the incidence of postoperative hemorrhage was higher in group A (29.4%) than group B (7.9%) (P=0.0022). The 5-year survival rate did not differ significantly between the two groups (A and B; 45.9% and 55.7%, respectively) (p=0.9424).

*Conclusions.* The presence of pneumoconiosis does not adversely affect postoperative survival or the treatment of NSCLC patients, except in intraoperative blood loss and postoperative hemorrhage. Thus if enough consideration is done to the hemorrhage, surgical treatment of NSCLC patients with pneumoconiosis cannot be excluded as a treatment option.

## **Introduction**

NSCLC is the most common cancer worldwide, and nearly all lung cancer is environmentally induced and thus preventable. Inflammation-induced fibrosis is considered a risk factor for carcinogenesis in multiple organs wherever etiologies exist, e.g., in diseases such as idiopathic pulmonary fibrosis, ulcerative colitis, and liver cirrhosis<sup>1-3</sup>. Pneumoconiosis is an occupational lung disease characterized by irreversible fibrous lesions (silicotic nodules or mixed dust fibrosis) in the lung resulting from chronic inhalation of silica and silicates in dusty workplaces<sup>4,5</sup>. Many studies of silica and mortality from lung cancer have suffered from confounding data due to exposure to other toxins. However, only few reports have outlined the outcomes after surgical treatment of non-small cell carcinomas (NSCLC) complicated by pneumoconiosis. We aimed to clarify the clinicopathological features and review the outcomes, of surgical treatment for NSCLC with pneumoconiosis.

## **Material and Methods**

**Patients.** During the period April 1988 to March 2000, 122 patients (98 males and 24 females, age range 43-84 years) with NSCLC underwent lung resection at Iwamizawa Rosai Hospital, Japan. Patients with evidence of metastasis to other organs and with prior anticancer treatment were excluded. The clinicopathologic stage was determined according to the TNM classification system of the International Union Against Cancer<sup>6</sup>. Pneumoconiosis was diagnosed and categorized for patients with a definite occupational history, according to the International Labour Office (ILO) Classification of Radiographs of Pneumoconioses<sup>7</sup>. In this classification system, parenchymal lung abnormalities on chest radiographs are identified and radiographic severity is classified on a 12-point scale range from 0/- to 3/+ by comparing the radiographs to ILO standard films. Pneumoconiotic patients have been carefully followed by regular medical examinations in Iwamizawa Rosai Hospital. Namely, chest CT was carried out at least every 6 months, while other routine tests, including chest radiography and sputum cytology, were

performed at least every 3 months. Thirty-four (27.9%) patients (group A) with pneumoconiosis and 88 (72.1%) patients without pneumoconiosis (group B) were observed. These comprised 59 cases of squamous cell carcinoma (SCC), 59 adenocarcinomas and 4 large cell carcinomas. Group A comprised 24 patients with SCC and 10 with adenocarcinoma. Of the 122 patients, 14 underwent pneumonectomy, 105 patients underwent lobectomy and 3 patients underwent segmentectomy. The pulmonary function of all patients was examined before surgery. During the postoperative course, the chest drain was removed when next day air leakage was not detected and the drainage was less than 100 ml in a day. Postoperative complications were defined as those occurring within 30 days of thoracotomy. The diagnosis of pneumonia was considered when patients developed a new and persistent lung infiltrate and had purulent tracheal secretions confirmed by a bacterial culture of the sputum. Acute respiratory failure was defined as postoperative ventilator dependence > 24 hour or reintubation for controlled ventilation. Prolong air leakage was defined as air leakage requiring > 10 days of postoperative chest tube drainage. Pneumothorax evidenced on chest radiograph or CT scan and requiring chest tube placement. Bleeding through the chest tubes was considered to be a significant complication when a reoperation was required, or when RBC packs were transfused. Cardiovascular complications were defined as follows: symptomatic cardiac arrhythmia requiring treatment, acute myocardial infarction (ECG and elevation of creatine phosphokinase) or unstable angina. When the controlled ventilation was needed for 14 days or more, the patients had tracheotomy.

**Statistical Analysis.** The chi-squared test, Fisher's test, or the Mann-Whitney U test was used to analyze the correlation between complication with pneumoconiosis and patients' parameters, including histopathologic findings. The Kaplan-Meier method was used to generate survival curves, and survival differences were analyzed with the log-rank test, based on the status of complication with pneumoconiosis. The percentage of predicted value of vital capacity (%VC), force expiratory one second (FEV1.0%), operative time, intraoperative blood loss and

duration of drainage are shown as averages with standard deviation. Probability values of less than 0.05 were regarded as indicating statistical significance. All analyses were performed using statistical analysis software (Statview J version 5.0; SAS Institute Inc. Cary, NC).

## **Results**

### *Patient characteristics*

The correlation between complication with pneumoconiosis and clinical factors are shown in Table 1. The average age in group A was  $69.1 \pm 5.9$  (range 56- 77 years), and group B  $65.1 \pm 9.1$  (range 43- 84 years). All 34 patients in group A were male, while of the 88 patients in group B, 64 were male and 24 were female. Complication with pneumoconiosis was related to gender ( $p=0.0007$ ) and age ( $p=0.0246$ ), however, did not correlate with histological stage, T classification, N classification, type of operation or surgery-related death. Of the various histological types, SCC was the most frequent form of cancer in group A ( $p=0.0072$ ).

### *Perioperative results*

In preoperative pulmonary function, the average %VC of group A was  $102.2 \pm 18.3\%$  (range 70.8- 146.9 %) and of group B  $105.7 \pm 17.9\%$  (range 40.2- 97.7%) ( $p=0.2767$ ), while the average FEV1.0% of group A was  $66.1 \pm 11.3$  (range 40.2- 97.7%) and of group B  $70.5 \pm 11.5$  (range 28.8- 97.6%) ( $p= 0.0250$ ) (Fig. 1). In operative findings, the mean operative time of group A was  $207.8 \pm 103.4$  minutes (range 106- 700 minutes), and of group B  $196.1 \pm 53.5$  minutes (range 66- 360 minutes) ( $p=0.9466$ ), the mean intraoperative blood loss of group A was  $723.2 \pm 647.3$  ml (range 45- 3083 ml), and of group B  $466.4 \pm 450.7$  ml (range 50- 2500 ml) ( $p=0.0067$ ). In postoperative findings, the mean duration of drainage of group A was  $8.3 \pm 4.2$  days (range 3- 21 days), and of group B  $8.5 \pm 5.7$  days (range 2- 35 days) ( $p=0.6334$ ) (Fig. 2). In postoperative complications, the incidence of postoperative hemorrhage was higher in group A (29.4%) than group B (7.9%) ( $P=0.0022$ ) and other complication was similar in these two groups. The re-operation was performed in 2 patients of the postoperative hemorrhage (group A) and in 2 patients of the postoperative hemorrhage, in 2 patients of the bronchopleural fistula (group B)

( $p=0.7595$ ). The tracheotomy was performed in 4 patients in group A and 5 patients in group B ( $p=0.2491$ ). Complication with pneumoconiosis was related to preoperative pulmonary function (FEV1.0%), intraoperative blood loss and postoperative hemorrhage but was not related to surgery-related death.

#### *Long-term results*

The overall survival rate for the 122 patients was 52.5% at 5 years, with a median follow-up period of 29.5 months. Five years survival rates were 45.9% (group A) and 55.7% (group B), no statistically significant difference in survival between the presence or absence of pneumoconiosis was noted ( $p=0.9424$ )(Fig. 3).

#### **Discussion**

The most common estimation of causality between pneumoconiosis and lung cancer was negative in the past. Recently, this suggestion of causality in lung cancer complicated by pneumoconiosis has been gaining support. Some studies have suggested that the k-ras mutation and p53 are related to NSCLC complicated by pneumoconiosis<sup>8,9</sup>. However, the treatment of NSCLC with pneumoconiosis has not been well studied<sup>10</sup>. Patients of lung cancer complicated by pneumoconiosis tend to be excluded from operative indication by reasons of respiratory insufficiency and old age. Therefore, we examined the clinicopathological features, perioperative findings and long-term results after surgery in NSCLC complicated by pneumoconiosis. Patients complicated by pneumoconiosis are significantly older than those without pneumoconiosis, as the number of new patients with pneumoconiosis has been decreasing worldwide. Moreover, new pneumoconiotic patients are expected to be older in the future and thus the indication of lung resection will be more severe. The present results will help in the decision of operative indication in NSCLC complicated by pneumoconiosis.

The histological type of lung cancer complicated by pneumoconiosis is often SCC, with Scarano et al<sup>11</sup> reporting 78.8% and Kojima<sup>12</sup> reporting 54.5% of such patients having SCC. Similarly, in the present study, SCC was statistically significantly the most frequent form

(70.6%) of cancer in the patients with pneumoconiosis, suggesting that the inhalation of carcinogens may play a role of in the pathogenesis of lung cancer.

Analysis of the perioperative findings revealed that intraoperative blood loss and numbers of patients of postoperative hemorrhage in group A was significantly greater than in group B. Adhesion, emphysema of the lung and severe anthracosis in the medulla lymph node all render manipulation difficult during surgery in pneumoconiotic patients. The difference in the duration of drainage was not statistically significant between the two group, which suggests that careful closing of the air leakage hole intraoperation is important for decreasing operative complications.

In the present study, the survival rate did not differ significantly between groups A and B, suggesting that the complication of pneumoconiosis might not increase the surgical risk posed by the either the patient's fitness or the biological features of the tumor.

Recently, as a novel treatment for NSCLC, video-assisted thoracoscopic surgery (VATS) was shown to reduce surgical stress. Unfortunately, no patient received VATS in the present study. Whether VATS is useful for lung cancer patients with pneumoconiosis is debatable, given the severe adhesion caused by pneumoconiosis. A comparison of thoracotomy with VATS is underway.

We conclude that the possibility that pneumoconiosis may be a carcinogenic cause for SCC of the lung is highly likely. However, if enough consideration is done to the hemorrhage, pneumoconiosis does not increase the risk of an operation or the malignancy of tumors in patients with NSCLC.

#### **Acknowledgment**

We are indebted to all the clinical staff at Iwamizawa Rosai Hospital (Iwamizawa, Hokkaido, Japan) for access to their patients.

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## Figure legends

### Fig. 1

Preoperative pulmonary function of patients with and without pneumoconiosis who underwent surgery. (Limits of the box plot are the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the data sets, and the error bars indicate the 10<sup>th</sup> and 90<sup>th</sup> percentiles. The bar within the box represents the median for data set.)

### Fig. 2

Operative findings and postoperative course. (Limits of the box plot are the 25<sup>th</sup> and 75<sup>th</sup> percentiles of the data sets, and the error bars indicate the 10<sup>th</sup> and 90<sup>th</sup> percentiles. The bar within the box represents the median for data set.)

### Fig. 3

Kaplan-Meier analysis of the overall survival of patients with and without pneumoconiosis (log-rank test,  $p=0.9424$ )

**Table 1.** Clinical features of patients with and without pneumoconiosis who underwent surgery.

<b>Variables</b>	<b>Pneumoconiosis (+)</b>	<b>Pneumoconiosis (-)</b>	<b>P value</b>
No. of patients	34 (27.9%)	88 (72.1%)	
Gender			0.0070 <sup>a</sup>
Males	34	64	
Females	0	24	
Mean age (range)	69.1 (56-77)	65.1 (43-84)	0.0070 <sup>b</sup>
Histological stage			0.5339 <sup>a</sup>
I	19	40	
II	6	14	
III	6	27	
IV	3	7	
pT classification			0.0951 <sup>a</sup>
T <sub>1</sub>	11	39	
T <sub>2</sub>	20	32	
T <sub>3</sub>	3	11	
T <sub>4</sub>	0	6	
pN classification			0.1158 <sup>a</sup>
N <sub>0</sub>	22	43	
N <sub>1</sub>	7	13	
N <sub>2</sub>	5	32	
Histological type			0.0072 <sup>a</sup>
Squamous cell carcinoma	24	35	
Adenocarcinoma	10	49	
Large cell carcinoma	0	4	
Type of operation			0.4514 <sup>a</sup>
Pneumonectomy	5	9	
Lobectomy	29	76	
Segmentectomy	0	3	
Operation related death			0.5367 <sup>a</sup>
Yes.	2	3	
No.	32	85	
<sup>a</sup> $\chi^2$ test	<sup>b</sup> Mann- Whitney U test		

**Table 2.** Incidence of postoperative complications

<b>Complications</b>	<b>Pneumoconiosis (+)</b> (n= 34)	<b>Pneumoconiosis (-)</b> (n= 88)	<b>P value<sup>a</sup></b>
Bacterial pneumonia			0.1837
Yes	6	8	
No	28	80	
Acute respiratory failure			0.0542
Yes	5	4	
No	29	84	
Prolong air leak, bronchopleural fistula			0.7668
Yes	8	23	
No	26	65	
Pneumothorax			0.7595
Yes	2	4	
No	32	84	
Postoperative hemorrhage			0.0022
Yes	10	7	
No	24	81	
Cardiovascular			0.8515
Yes	2	6	
No	32	82	

<sup>a</sup> $\chi^2$  test





