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# Pneumonectomy for Non-Small Cell Lung Cancer Impacts Survival：A Comparative Analysis of Skip Metastasis and Visceral Pleural Involvement

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**Abstract**：Objective：This study retrospectively analyzed the influence of skip mediastinal lymph node metastases and visceral pleural involvement on survival in patients undergoing a pneumonectomy. Methods：From July 1993 to July 2003, 937 consecutive patients with a diagnosis of non-small cell lung cancer underwent surgical resection. Among them, 61 patients (6.5%) underwent a pneumonectomy with lymph node dissection. There were 51 men (83.6%) and 10 women (16.4%) with a mean age of 63.7±9.0 years (range, 39-79 years). Especially, in this study, for the pathological N2 stage patients, some patients were found to have no metastatic involvement of their hilar lymph nodes on histopathological examination, these N2 metastases were called skip metastases. The survival probabilities were calculated by the Kaplan-Meier method, and differences in survival were determined by the log-rank analysis. Results：Squamous cell carcinoma was the most common cell type, and it was present in 33 of 61 patients (54.1%). Other cell types were adenocarcinoma in 15 patients (24.6%) and other types in 13 patients (21.3%). The overall 5-year survival rate of the 61 patients was 18.3%. Survival in the patients without pathologic lymph node metastasis was significantly higher than in the patients with pathologic lymph node metastasis ($P$=0.0165). For pathological N2 stage patients, survival in the patients without pathologic hilar lymph node (#7) metastasis was significantly higher than in the patients with pathologic hilar lymph node (#7) metastasis ($P$=0.0026), and survival in the patients without pathologic visceral pleural involvement was significantly higher than in the patients with pathologic pleural involvement ($P$=0.0165). Conclusion：Our results suggest that preoperative evaluations, such as age, performance status, spirometry, cardiac function, etc, should thus be done in patients with non-small cell lung cancer who need to undergo a pneumonectomy, and that it is necessary to select pneumonectomy patients carefully. In addition, by performing a complete mediastinal lymph node dissection with hilar lymph node (#7) sites, a pneumonectomy can achieve survival results similar to those of other surgical modalities.

**Key words：Pneumonectomy, Skip metastasis, Visceral pleural involvement**

## Introduction

Carcinoma of the lung is the most common cause of cancer deaths in Japan. During the past two decades, there has been increased experience using parenchyma-sparing techniques such as a sleeve lobectomy in the surgical management of lung cancer. The indications for such procedures are not well defined but include anatomically appropriate lesions in patients with or without sufficient pulmonary compromise, in whom the use of a pneumonectomy is contraindicated. The rates of complication and mortality for a sleeve lobectomy are

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similar to those of a pneumonectomy.[1] The long-term survival is similar for the two procedures, and it has been demonstrated that the preserved lung parenchyma with a sleeve lobectomy contributes to overall respiratory function, thus decreasing the perioperative loss of the respiratory function.[2)3)] Previously, several studies have examined the impact of various factors such as skip mediastinal lymph node metastases and visceral pleural involvement in lung resections for non-small cell lung cancer.[4)-7)] For pathological N2 stage patients, some patients were found to have no metastatic involvement of their hilar lymph nodes on histopathological examination, and such N2 metastases were called as skip metastasis. In this study, we retrospectively analyzed the influence of the skip mediastinal lymph node metastases and pleural involvement on the survival of patients undergoing a pneumonectomy.

## Patient and Methods

From July 1993 to July 2003, 937 consecutive patients with a clinical diagnosis of non-small cell lung cancer underwent surgical resections at the Department of 2nd Surgery, Fukuoka University Hospital, Japan. Among them, 61 patients (6.5%) underwent a pneumonectomy with lymph node dissection. Eight patients with small cell carcinoma, 5 patients with stage Ⅳ non-small cell lung cancer, and 15 patients with an incomplete resection were excluded from the analysis. A pneumonectomy was performed only for lesions that could not be removed with a less invasive resection. A preoperative evaluation consisted of a physical examination, hematological and biochemical investigations, chest X-ray, electrocardiogram, and computed tomography of the chest and abdomen. Additional investigations such as liver ultrasound, bone scan, and computed tomography of the head were performed if required based on the clinical findings and/or laboratory parameters (eg, abnormal liver enzymes or serum calcium, skeletal symptoms, hepatomegaly, splenomegaly, lymphadenopathy, abnormal neurological examination, etc.). All patients underwent spirometry and arterial blood gas measurements.

The patients were considered for a lung resection if there was no evidence of mediastinal involvement by the tumor or distant metastatic disease and they were deemed to have an adequate cardiac reserve and a predicted postoperative forced expiratory volume in 1 second of at least 0.8 L, as assessed by preoperative spirometry. The operative approach consisted of a standard pneumonectomy with block dissection of the hilar nodes and mediastinal lymph nodes as appropriate. Prior to the closure of the thoracotomy, the stump/anastomosis was checked with inflation pressures of 30 cm $H_2O$. A single intracostal drain was used. Postoperative fiberoptic bronchoscopy was not used to assess the anastomosis. Patients were routinely extubated in the operating room and transferred to the recovery room. Operative mortality was defined as death during hospitalization for pneumonectomy or any death within 30 days of surgery.

A histopathological analysis was carried out and the tumors were staged using the international Tumor, Node, Metastasis (TNM) staging system for lung cancer.

**Statistical analysis：**

The survival probabilities were calculated by the Kaplan-Meier method, and differences in survival were determined by the log-rank analysis. Statistical significance was defined as a P value of less than 0.05.

## Results

Patient characteristics are presented in Table 1. There were 51 men (83.6%) and 10 women (16.4%)；the mean age of patients was 63.7±9.0 years (range, 39－79 years). The mean body mass index was 21.6±3.4 (range, 14.9－31.7). The mean serum CEA (carcinoembryonic antigen) was 15.2±30.2 ng/dl (range, 0.7－141.6 ng/dl). The mean serum SCC (Squamous cell carcinoma) was 3.7±5.2 ng/dl (range, 0.0－19.0 ng/dl). The mean FEV 1.0 (Forced expiratory volume in 1 second) was 2,076 ±607 ml (range, 1,170-4,730 ml). The mean operating time was 309.49±111.81 minutes (range, 170-630 minutes), and the mean blood loss was 869±1,328 ml (range 180-3,517 ml). The histology and pathological staging are presented in Table 2. Squa-

mous cell carcinoma was the most common cell type and was present in 33 of 61 patients (54.1%). Other cell types were adenocarcinoma in 15 patients (24.6%) and other types in 13 patients (21.3%). Operative mortality was 6.6% (4 of 61 patients). The cause of death was pneumonia in two patients, empyema in one patient, and intraoperative acute heart failure in one patient. A total of 13 of 61 patients(21.3%)experienced early postoperative complications. There were respiratory complications in 6 (9.8%), cardiovascular complications in 2 (3.3%), and other complications in 5 patients (8.2%).

**Survival analysis：**

The overall 5-year survival rate of the 61 patients was 18.3% (Figure 1). The 5-year survival rates without pathologic lymph node metastasis and with pathologic lymph node metastasis were 32.8% and 5.6%, respectively. Survival in the patients without pathologic lymph node metastasis was significantly higher than in patients with pathologic lymph node metastasis (Figure 2, $P=0.0165$). For pathological N2 stage patients, the 5-year survival rate without pathologic hilar lymph node (#7) metastasis and with pathologic hilar lymph node (#7) metastasis were 25.9% and 0%, respectively. Survival in patients without pathologic lymph node #7 metastasis was significantly higher than in patients with pathologic lymph

**Table 1.** Patient characteristics

| Characteristics | No. of Patients (%) |
|---|---|
| Age (y) | 63.7±9.0 |
| Sex | |
| Male | 51 (83.6) |
| Female | 10 (16.4) |
| Body Mass Index | 21.6±3.4 |
| Pack-year | 47.9±37.0 |
| Serum CEA (ng/dl) | 15.2±30.2 |
| Serum SCC (ng/dl) | 3.7±5.2 |
| Serum albmin (mg/dl) | 3.5±0.7 |
| Serum hemoglobin (mg/dl) | 12.4±1.9 |
| PO2 (mmHg) | 80.8±10.6 |
| PCO2 (mmHg) | 41.3±4.3 |
| FVC (L) | 3,056±874 |
| FVC% (%) | 94±21 |
| FEV1.0 (L) | 2,076±607 |
| FEV1.0 % (%) | 69±10 |
| Operation time (min) | 309.49±111.81 |
| Blood loss (ml) | 869±1,328 |

CEA：carcinoembryonic antigen, SCC：Squamous cell carcinoma, FEV 1.0：forced expiratory volume in 1 second, FEV 1.0%：FEV 1.0/FVC×100, FVC：forced vital capacity

**Table 2.** Histologic type and the pathologic staging of the patients

| | | No. of Patients (%) |
|---|---|---|
| Side of operation | | |
| Right | | 22 (36.1) |
| Left | | 39 (63.9) |
| Histology | | |
| Adenocarcinoma | | |
| Squamous | | 15 (24.6) |
| cell carcinoma | | 33 (54.1) |
| Other | | 13 (21.3) |
| Tumor differentiation | | |
| Well | | 12 (19.7) |
| Moderate | | 7 (11.5) |
| Poor | | 20 (32.8) |
| T stage | | |
| | 1 | 0 (0) |
| | 2 | 27 (44.3) |
| | 3 | 18 (29.5) |
| | 4 | 16 (26.2) |
| N stage | | |
| | 0 | 22 (36.1) |
| | 1 | 9 (14.8) |
| | 2 | 27 (44.3) |
| | 3 | 3 (4.8) |
| Pleural involvment | | |
| | p0 | 20 (32.8) |
| | p1 | 12 (19.7) |
| | p2 | 7 (11.4) |
| | p3 | 22 (36.1) |
| Stage | | |
| | Ⅰ | 9 (14.8) |
| | Ⅱ | 11 (18.0) |
| | Ⅲ | 41 (67.2) |

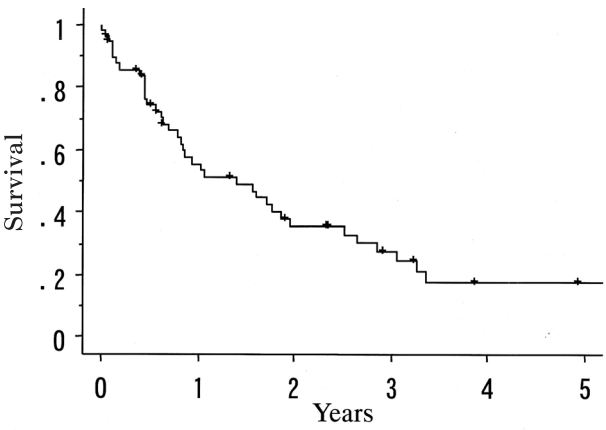


**Fig. 1.** Overall Kaplan-Meier survival curve of patients who underwent a pneumonectomy.

node #7 metastasis (Fig 3, $P=0.0026$), and survival in patients without pathologic pleural involvement was significantly higher than in patients with pathologic pleural involvement (Fig 4, $P=0.0165$). The effects on survival of age, sex, packs per year, tumor differentiation, pathological T stage, tumor location, and histology were not significant (data not shown). The 5-year survival rate of the normal group (FEV 1.0% is greater than or equal to 70%) and obstructive disorder group (FEV 1.0% is less than 70%) were 24.5% and 10.5%, respectively. FEV 1.0% did not significantly affect the outcome (Fig 5). However, patients with obstructive disorder (FEV 1.0% is less than 70%) were more likely to have a poor prognosis than patients with normal FEV 1.0% (FEV 1.0% is greater than or equal to 70%), although the differences were not statistically significant ($P=0.0607$).

## Discussion

A pneumonectomy carries a greater operative risk than a lobectomy and provides no benefit in terms of local recurrence and survival; however, this procedure may be unavoidable for anatomical and technical reasons.[8] The reasons for performing a pneumonectomy in this series were a central location of the tumor, tumor crossing the fissures,

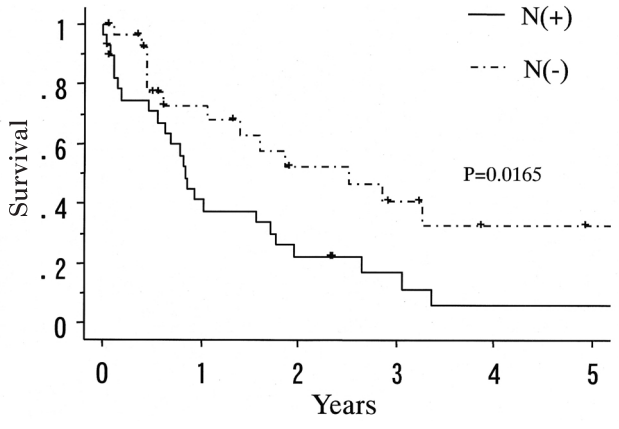


Fig. 2. Kaplan–Meier survival curves of patients with and without pathologic lymph node metastasis.

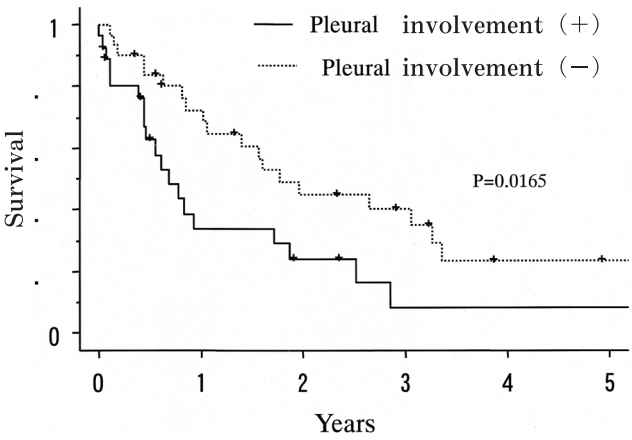


Fig. 4. Kaplan–Meier survival curves of the patients with and without pathological pleural involvement.

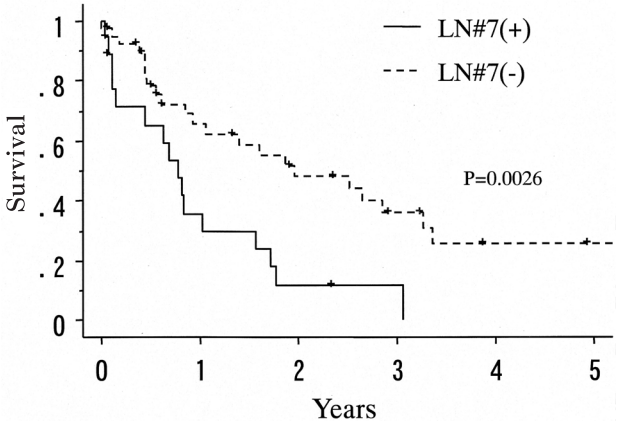


Fig. 3. Kaplan–Meier survival curves of patients with and without pathological lymph node #7 metastasis.

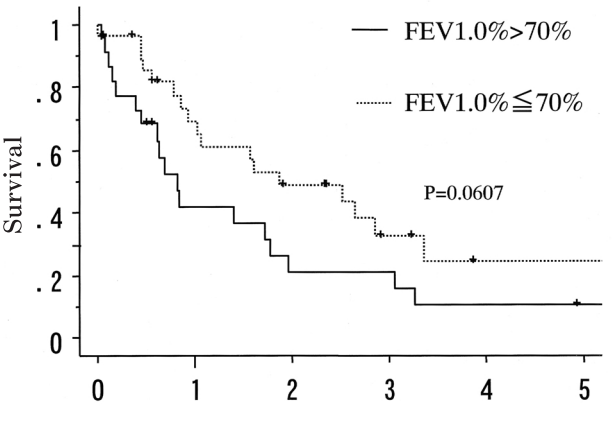


Fig. 5. Kaplan–Meier survival curves of patients according to the obstructive disorder group (FEV 1.0% is less than 70%) and the normal group (FEV 1.0% is greater than or equal to 70%).

the presence of large lymph nodes or a cancerous mass in close proximity to the pulmonary artery branches, thus preventing their safe dissection, and intraoperative problems in which a pneumonectomy was undertaken as a bail-out procedure. The long-term consequences of pneumonectomy on cardiorespiratory function and quality of life are well described.[9] Predictors of outcome after the removal of one lung have also been described, but whether pneumonectomy per se influences the overall survival remains controversial.[10] In our study, the overall 5-year survival of 18.3% among the patients was acceptable, and it was similar to the overall 5-year survival of 17.8% to 35.0% reported from other institutions.[9-12] In regard to the postoperative prognosis of skip metastases patients, in our study, survival in patients without pathologic lymph node #7 metastasis was significantly higher than in patients with pathologic lymph node #7 metastasis for pathological N2 stage patients. Some studies have also shown that pathological N2 patients with skip metastases had a more favorable prognosis in comparison to pathological N2 patients with continuous N2 metastases.[4-6] The mechanism for the development of skip metastases may be the existence of lymphatic channels going directly to the mediastinum. Riquet and colleagues reported that subpleural lymphatics had direct passages to the mediastinal lymph nodes in 22% of segments in the right lung and in 25% of segments in the left lung.[4-6] On the other hand, Rouviere described the subcarinal nodes as a crossroad where lymphatic vessels from the various organs in the thorax meet directly or by means of lymphoid relays, and communications are present between the subcarinal nodes and all lobes of the lung.[13] In our study, among the pathological N2 patients with pneumonectomy, the presence of skip metastases was an independent factor of survival. Therefore, we suggest that preoperative evaluations including, positron emission tomography, be done whether the mediastinal lymph nodes contain metastases or not. In addition, if there is any doubt, we recommend that neoadjuvant therapy be done, and during the surgical procedure, a mediastinal lymph node dissection should be performed.

In this study, survival in patients without pathologic pleural involvement was significantly higher than in patients with pathologic pleural involvement ($P=0.0165$). For pleural involvement, Osaki and colleagues reported that among the patients with pathologic T1 and T2 stage non-small cell cancer, the prognosis of patients with pleural involvement was significantly poorer than in patients without pleural involvement, and pleural involvement was a potentially a significant and independent prognostic factor, along with lymph node involvement.[7] We think that in any patient who undergoes a pneumonectomy, regardless of the pathologic T stage, the prognosis for those without pathologic pleural involvement is better than for those with pathologic pleural involvement.

The finding that preoperative spirometry is a predictor of long-term survival after major resection such as pneumonectomy for lung cancer has not yet been widely reported. The factor that survival is unfavorably influenced at the low extremes of spirometric measurements in populations with chronic obstructive pulmonary disease is well known.[15] Our results provide further evidence regarding the relationship between a spirometry and long-term survival to include patients with less marked impairments in airflow. The effect of spirometry on long-term survival is relatively small compared with the effects of the pathologic stage and age. Nevertheless, further investigations of this relationship are needed. Our results suggest that preoperative evaluations such as spirometry must be done in patients with non-small cell lung cancer who must undergo a pneumonectomy; in addition, it is necessary to choose which patients undergo pneumonectomy carefully. Furthermore, with a complete mediastinal lymph node dissection, a pneumonectomy can achieve similar survival outcomes to other surgical techniques. However, the population of this study was small, and therefore larger studies are needed. Moreover, despite adjusting for observed covariates, the effects of patient selection and other potential confounding factors limit the conclusions that can be drawn from this retrospective study. Randomized prospective trials therefore need to be performed in the future.

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