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# Early Detection of the Acute Exacerbation of Interstitial Pneumonia after the Surgical Resection of Lung Cancer by Planned Chest Computed Tomography

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**Background:** To improve postoperative outcomes associated with interstitial pneumonia (IP) in patients with lung cancer, the management of the postoperative acute exacerbation of IP (PAEIP) was investigated. **Methods:** Patients with primary lung cancer were considered to be at risk for PAEIP (possible PAEIP) based on a preoperative evaluation. The early phase of this study was from January 2001 to December 2008, and the late phase was from January 2009 to December 2014. In the early phase, chest computed tomography (CT) was performed for patients for whom PAEIP was suspected based on their symptoms, whereas in the late phase, chest CT was routinely performed within a few days postoperatively. The numbers of possible PAEIP cases, actual PAEIP cases, and deaths within 90 days due to PAEIP were compared between both phases. **Results:** In the early and late phases, surgery was performed in 712 and 617 patients, 31 and 72 possible PAEIP cases were observed, nine and 12 actual PAEIP cases occurred, and the mean interval from the detection of PAEIP to starting treatment was 7.3±2.3 and 5.0±1.8 days, respectively. Five patients died in the early phase, and one patient died in the late phase. Significantly fewer PAEIP-related deaths were observed in the late phase ($p < 0.05$). **Conclusion:** Identifying patients at risk for PAEIP by routine postoperative CT examinations led to the early diagnosis and treatment of PAEIP, resulting in the reduction of PAEIP-related mortality.

*Key words:* 1. Interstitial lung diseases
2. Lung neoplasms
3. Lung surgery

## Introduction

Acute exacerbation (AE) of interstitial pneumonia (IP) is a major cause of early postoperative death after surgery for lung cancer [1-8]. Knowledge concerning the types of cases, operative techniques, and intraoperative management strategies associated with the postoperative AE (PAE) of IP (PAEIP) has been accumulated. For patients considered at risk of developing PAEIP (possible PAEIP), careful monitoring and postoperative management are important to ensure the early diagnosis and treatment of PAEIP [9-11].

A protocol for performing regular, scheduled computed tomography (CT) examinations after surgery

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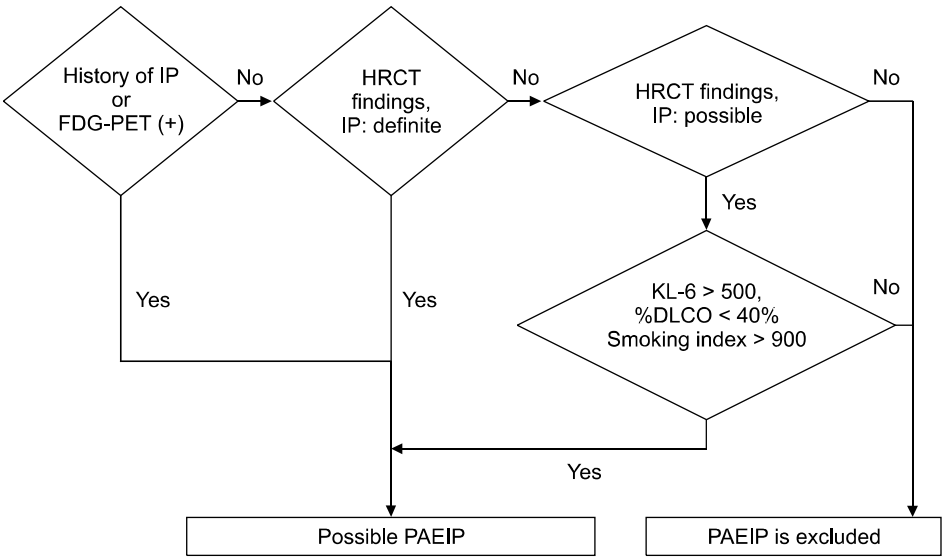


**Fig. 1.** Flow chart for confirming the PAE of IP with lung cancer. First, patients with IP, as indicated by a medical history of IP, including not only idiopathic pulmonary fibrosis but also all other forms of IP and positive findings on FDG-PET, which can show FDG uptake in areas of interstitial changes consistent with computed tomography findings, were identified. Second, the risk of PAEIP was identified by definite findings obtained from HRCT. In cases with possible IP findings on HRCT, other findings such as (1) the KL-6, (2) the DLCO, and (3) the smoking index, which is calculated by multiplying the average number of cigarettes smoked per day by the duration of smoking in years, were evaluated by the IP management team and comprehensively assessed to estimate the risk of PAEIP. The marker '+' means 'positive.' PAE, postoperative acute exacerbation; IP, interstitial pneumonia; FDG-PET, fluorodeoxyglucose-positron emission tomography; PAEIP, PAE of IP; HRCT, high-resolution computed tomography; KL-6, serum level of sialylated carbohydrate antigen; DLCO, diffusing capacity of the lungs for carbon monoxide.

for resecting lung cancer in patients with IP was implemented in our institution in January 2009. In this study, the cases treated before and after that time were grouped into the early and late phases, respectively.

In 2001, the authors' hospital created an interdisciplinary team including pulmonologists and surgeons for managing patients with IP. Patients at risk for PAEIP were subjected to close monitoring and management during the perioperative period. In January 2009, the authors began to use postoperative high-resolution CT (HRCT) of the chest routinely for detecting PAEIP. In this study, the effectiveness of this intervention was investigated by comparing the numbers of operations, possible cases of PAEIP, actual cases of PAEIP, the interval from the detection of PAEIP to the start of treatment, and the number of deaths during these periods.

## Methods

A total of 1,329 patients with primary lung cancer underwent surgery at the authors' hospital between January 2001 and December 2014. Based on the time when surgery was performed, the patients were divided into two groups, with 712 patients in the early phase (January 2001 to December 2008) and 617 patients in the late phase (January 2009 to December 2014).

A multidisciplinary team was organized to manage patients with IP in the hospital. From January 2001 to December 2014, possible PAEIP patients with confirmed or suspected primary lung cancer were selected according to the process shown in Fig. 1.

In order to reduce the risk of AE of IP during the perioperative period, the inspired oxygen concentration was kept as low as possible, and ulinastatin, a neutrophil-elastase inhibitor, was administered perioperatively. Ulinastatin at a dose of 300,000 units/day was started 2 days before surgery, and the dose was decreased to 100,000 units every 3 days postoperatively. Routine postoperative evaluations, including the measurement of peripheral oxygen saturation ($SpO_2$), blood tests (white blood cell count, lactate dehydrogenase [LDH], C-reactive protein [CRP], serum sialylated carbohydrate antigen KL-6 [KL-6], pul-

monary surfactant protein-D, and pulmonary surfactant protein-A), and chest radiography were performed.

In the early phase, patients with symptoms such as dyspnea, abnormal laboratory findings, or interstitial changes on chest radiography underwent further evaluation with chest HRCT. In the late phase, chest HRCT was routinely performed on postoperative days 4, 7, and 14. No patients, even those who exhibited a satisfactory postoperative course, were discharged from the hospital until at least postoperative day 8, and all were monitored as outpatients on day 14, when chest CT was performed.

In addition, throughout the early and late phases, $\beta$-D-glucan and brain natriuretic peptide levels were also measured in patients showing worsening interstitial changes on HRCT. Any patient in whom PAEIP could not be excluded received high doses of steroids (1,000 mg/day of methylprednisolone for 3 days, followed by gradual tapering) and sivelestat sodium hydrate (4.8 mg/kg/day for 14 days).

The numbers of operations for primary lung cancer, possible PAEIP cases, postoperative in-hospital deaths, deaths within 90 days, actual PAEIP cases, and PAEIP-related in-hospital deaths or deaths within 90 days (IP-related deaths) among the early phase patients were compared to the corresponding findings among the late phase patients.

Descriptive statistics of continuous variables are expressed as mean and standard deviation with the minimum and maximum values, while categorical variables are expressed as number and percentage. For statistical analysis, the chi-square test and the Fisher exact test were used to compare event frequencies between the two groups, and the t-test was used to compare mean values between groups. The level of statistical significance was set at less than 5%.

This study was approved by the ethics committee of Tokyo Women's Medical University (approval no. 1823). All patients received verbal and written explanations of the study and provided informed consent prior to enrollment.

## Results

A total of 103 patients (7.8%) were at risk for PAEIP, including 31 in the early phase and 72 in the late phase. No significant differences in serum KL-6, the diffusing capacity of the lungs for carbon monoxide (DLCO), and the smoking index, which is calculated by multiplying the average number of cigarettes smoked per day by the duration of smoking in years, were found between the patients in the early and late phases (Table 1).

Table 1. Clinical characteristics of patients at risk for postoperative acute exacerbation of interstitial pneumonia

| Characteristic | Early phase (Jan 2001–Dec 2008) | Late phase (Jan 2009–Dec 2014) | p-value |
|---|---|---|---|
| Age (yr) | 69.9±6.5 (range, 54–80) | 72.4±7.5 (range, 55–86) | 0.089[a] |
| Sex | | | 0.717[b] |
| Men | 27 (87.1) | 58 (80.6) | |
| Women | 4 (12.9) | 14 (19.4) | |
| Smoking index | 1,138.8±628.9 | 964.7±627.8 | 0.216[a] |
| Histological type | | | |
| Squamous cell ca. | 14 (45) | 31 (43) | |
| Adenocarcinoma | 11 (36) | 31 (43) | |
| Small cell ca. | 4 (13) | 5 (7) | |
| Adenosquamous ca. | 1 (3) | 3 (4) | |
| Other | 1 (3) | 2 (3) | |
| Pathological stage | | | |
| IA | 9 (29) | 29 (40) | |
| IB | 9 (29) | 14 (19) | |
| IIA | 2 (6.5) | 13 (18) | |
| IIB | 1 (3) | 9 (13) | |
| IIIA | 10 (32.5) | 6 (8.5) | |
| IV | 0 | 1 (1.5) | |
| Surgical procedure | | | |
| Pneumonectomy | 2 (6.5) | 0 | |
| Lobectomy | 22 (71) | 40 (56) | |
| Segmentectomy | 2 (6.5) | 16 (22) | |
| Wedge resection | 5 (16) | 16 (22) | |
| Operation time (min) | 205±74.2 | 174±67.7 | 0.051[a] |
| KL-6 (U/mL) | 814.8±536.7 | 608.6±488.8 | 0.059[a] |
| %DLCO (%) | 68.5±27.5 | 58.9±16.9 | 0.080[a] |
| Predicted %DLCO after operation (%) | 54.3±23.7 | 50.2±15.2 | 0.372[a] |

Values are presented as mean±standard deviation or number (%), unless otherwise stated. Smoking index is calculated by multiplying the average number of cigarettes smoked per day by the duration of smoking in years.
ca., carcinoma; KL-6, serum sialylated carbohydrate antigen KL-6; DLCO, diffusing capacity of the lungs for carbon monoxide.
[a]Calculated by the t-test. [b]Calculated by the chi-square test.

In terms of the distribution of pathological staging results, more stage IIIA patients were present in the early phase. Regarding surgical procedures, the late

Table 2. Comparison between early- and late-phase outcomes in cases of possible and actual PAEIP and the day of treatment initiation

| Variable | Early phase (Jan 2001–Dec 2008) | Late phase (Jan 2009–Dec 2014) | p-value |
|---|---|---|---|
| Possible PAE | 31 (4.4) | 72 (11.7) | |
| Actual PAE | 9 (1.2) | 12 (1.9) | |
| IP-related deaths within 90 days after surgery | 5 (0.70) | 1 (0.16) | 0.2249[a)] |
| Ratio of IP-related deaths in cases of possible PAE | (16.1) | (1.39) | 0.0091[a)] |
| Ratio of IP-related deaths in cases of actual PAE | (55.6) | (8.3) | 0.0464[a)] |
| Time of initiating treatment for PAE (day) | 7.3±2.3 (4–11) | 5.0±1.8 (4–8) | 0.0258[b)] |

Values are presented as number (% of all operations), (%), or mean±standard deviation (range).
PAE, postoperative acute exacerbation; IP, interstitial pneumonia; PAEIP, postoperative acute exacerbation of interstitial pneumonia.
[a)]Calculated by the Fisher exact test. [b)]Calculated by the t-test.

phase had no cases of pneumonectomy. Although no significant differences in the surgical procedures were found between the early and late phases, an increase in segmentectomy was noted in the late phase. No statistically significant differences between the early and late phases were found for other clinical characteristics (Table 1).

Nine and 12 patients had actual PAEIP in the early and late phases, respectively (Table 2). Five patients died in the early phase (three in-hospital deaths and two post-discharge deaths), corresponding to 0.7% of the total number of operations, 16.1% of the cases of possible PAEIP, and 55.6% of the cases of actual PAEIP. One patient died in the late phase (in-hospital death), corresponding to 0.16% of all operations, 1.39% of the cases of possible PAEIP, and 8.3% of the cases of actual PAEIP. The numbers of possible PAEIP-related deaths and actual PAEIP-related deaths were significantly lower in the late phase ($p < 0.05$). Although no significant difference between the numbers of deaths and operations was observed, a downward trend was observed for mortality in the late phase (Table 2).

In the early phase, PAEIP was suspected due to exertional dyspnea in five patients, decreased $SpO_2$ in two patients, and laboratory findings in two patients, and these PAEIP cases were confirmed by HRCT. In the late phase, all PAEIP cases were found by HRCT before the appearance of any symptoms or abnormal laboratory findings. In the late phase, abnormal HRCT findings were found in nine patients on postoperative day 4, three patients on day 7, and zero patients on day 14. Treatment was started within 1 day after these abnormal findings were noticed. The interval from the detection of PAEIP to the start of treatment was significantly shorter in the late phase than in the early phase ($p < 0.05$) (Table 2).

In the early and late phases, the average $SpO_2$ values after the onset of PAEIP decreased to 90% (range, 86% to 94%) and 92% (range, 86% to 95%), respectively.

Although the $SpO_2$ values were not significantly different between the early and late phases ($p = 0.3945$), the values in the early phase tended to be lower than that in the late phase. The average peak serum CRP values of PAEIP patients in the early and late phases were 18.38±6.4 mg/dL (range, 9.3 to 26.31 mg/dL) and 12.03±3.05 mg/dL (range, 6.33 to 15.66 mg/dL), respectively, and the CRP levels in the late phase were found to be lower than in the early phase ($p = 0.0204$).

In the actual PAEIP cases in this study, no clear clinical signs were found before the CT examinations in the late-phase cases, although in some cases, clear clinical signs were noticed at almost the same time as the CT examination.

Moreover, in both phases, all IP-related deaths after lung cancer surgery occurred among patients in whom PAEIP was suspected. Among the patients not at risk for PAEIP, 13 died in the hospital or within 90 days after discharge. The causes of death were bronchial stump fistula with infection in three patients, heart failure in three patients (ischemic heart failure, dilated cardiomyopathy, and severe arrhythmia), bronchopulmonary artery fistula, pyothorax, mediastinitis, pulmonary thromboembolism, acute myocardial infarction, acute aortic dissection, and acute superior mesenteric artery thrombosis, in one patient each. Death due to IP was not suspected in any of these patients.

## Discussion

Despite surgery, anti-cancer drugs, and radiotherapy for treating lung cancer associated with IP, complications such as AE of IP are often observed. Although surgery is the most effective treatment for operable cases, high rates of PAEIP and mortality have been reported after surgery for lung cancer associated with IP [1-8].

In this study, the rates of PAEIP-related deaths in possible and actual PAEIP cases in the late phase were found to have decreased significantly in comparison to the early phase (Table 1). No significant difference in the number of operations for lung cancer was found between the early and late phases, and this lack of a significant difference was speculated to be due to the small number of PAEIP-related deaths among the operations performed for lung cancer.

In a survey conducted by Miyamoto et al. [9] among 220 responding institutions of the 701 institutions certified by the Japan Association for Chest Surgery and Japanese Respiratory Society, the surgical mortality rate in patients with idiopathic IP (IIP), which corresponds to possible PAEIP in this study, from January 2003 to September 2007 was 3.5%, and the mortality rate in patients with actual PAEIP was 41.9%. In the authors' institution in the late phase, the mortality rates of patients with possible and actual PAEIP were 1.39% and 8.3%, respectively, which are better than those reported at other institutions.

The most important reason for the lower mortality rate in the late phase was probably the introduction of routine HRCT, which allowed PAEIP to be detected early, resulting in the earlier initiation of treatment.

It is possible that the number of subclinical IP cases was found to be lower in the early phase, and the diagnostic threshold of this study might be slightly higher than the threshold that is commonly employed, since the conventional mortality rate of patients with lung cancer associated with IP was additionally analyzed based on the presence of PAEIP. Even with the higher diagnostic threshold, the preoperative identification of patients at risk for AE of IP is believed to be important for reducing the mortality rate. Therefore, an important aspect of this study is that the mortality rate after the onset of AE of IP in the late phase was found to be lower than the mortality rate observed in the early phase.

Starting in the early phase, during anesthesia, the use of high-concentration oxygen was avoided as much as possible; the fraction of inspired oxygen was kept at less than 0.6, the $PaO_2$ was adjusted to be 80–100 mm Hg, and the tidal volume was reduced as much as possible. Since the postoperative care included the avoidance of high-concentration oxygen in all cases, no large bias affecting the results in this regard was present.

In the early phase, pneumonectomy was performed in two cases, whereas no pneumonectomy was performed in the late phase. However, more segmentectomy cases were present in the late phase than in the early phase, indicating that in the late phase, a tendency existed for more limited operations to be performed than in the early phase. In this study, the importance of periodic CT examinations was established for preventing mortality after the onset of PAEIP, as such examinations indicate the proper timing for the early initiation of treatment.

In the early phase, chest CT was performed based on a consideration of patients' clinical status, including symptoms, decrease in $SpO_2$, and laboratory findings such as increased serum KL-6. CT findings such as glass shadow, infiltrative shadow, and honeycomb lung were used to diagnose patients with AE of IP. In the late phase, HRCT was performed before the appearance of the clinical indications described above. Similar CT findings were used to diagnose patients with AE of IP, and the necessary treatments, including steroid therapy, were initiated as soon as possible. Certainly, upon the appearance of changes in HRCT, symptoms and signs such as respiratory distress, decreased $SpO_2$, and increased serum CRP values were observed, but only one fatal case occurred in the late period, suggesting that the early initiation of treatment could be important.

Sato et al. [10] reported that PAEIP was associated with the highest mortality rate after surgery for lung cancer and that a highly invasive surgical procedure was associated with the highest risk. This study was unable to exclude the possibility that the presence of fewer highly invasive surgical procedures (Table 1) in the late phase might have also contributed to the lower mortality rate. Moreover, the number of possible PAEIP patients was greater in the late phase.

This might relate to the more aggressive surgical treatment of lung cancer associated with IP, but the possibility that a group of measures taken regarding in-hospital PAEIP also resulted in a broader range of patients being considered as possible cases likewise could not be excluded.

Sugiura et al. [11] reported that the use of the typical honeycombing findings on preoperative CT to identify patients with usual IP is important in predicting the risk of postoperative AE. However, even in IIP cases, the rapid and accurate preoperative diagnosis of idiopathic pulmonary fibrosis (IPF) may be difficult. High CRP levels (＞2.0 mg/dL), high LDH levels (＞400 IU/L), high KL-6 biomarker levels, and low DLCO values are useful parameters for predicting PAEIP [1,2,5,7,12-16]. In a previous study to predict patients at risk for PAEIP, identifying such patients was reported to be more difficult [12].

Chida et al. [13] reported that among patients who develop acute respiratory distress syndrome after thoracic surgery, some had subclinical IPF that was undiagnosed preoperatively, with no clinical symptoms, normal results of pulmonary function testing, and only limited findings of IP on CT. In addition, 10% to 17% of patients who have undergone surgical resection for lung cancer associated with IPF are unable to be diagnosed with IPF before surgery [8,14]. However, among the 1,329 patients in this study, because the possible risk of PAE was comprehensively evaluated and recorded, a large number of such cases were found. Moreover, no IP-related deaths occurred among patients judged not to be at risk for PAEIP.

The effectiveness of neutrophil-elastase inhibitors such as ulinastatin in preventing the AE of IP has been investigated [17-19]. Bao et al. [17] reported that ulinastatin reduced the number of pulmonary injury events in rats. Although this study did not specifically investigate the efficacy of ulinastatin, ulinastatin is believed to enhance the therapeutic effects of early steroid therapy.

Since this study was a non-randomized study and compared clinical data obtained in different periods, several limitations must be considered when interpreting the findings. In addition, this study was exploratory in nature. Furthermore, the same group of doctors judged the possibility of postoperative AE in IP patients. Although judging the possibility of PAEIP in the early and late phases with the same standards may have been difficult, the ratio of patients predicted to be at risk of PAEIP among those undergoing lung cancer surgery tended to be higher in the late phase than in the early phase. However, no significant differences in preoperative KL-6, DLCO, the smoking index, or operative method between the early and late phases were observed.

This study used only limited clinical data from a single institution. No significant differences in the ratio of IP-related deaths after surgery were found between the early and late phases, although this was a long-term study. Because the criteria were very strict in this study, no deaths due to IP were suspected in any patients except those with possible PAEIP.

In this study, the criterion for identifying predicted cases of the onset of PAEIP could be considered weak. The main goal of this study was to focus on how to save the lives of patients suffering from PAEIP, which has a poor prognosis, after lung surgery, by promptly initiating adequate treatment. Indeed, in cases other than those identified to be at risk, no postoperative fatalities due to IP after lung surgery with concomitant pneumonia were found.

As a potential contributor to adverse events in this study, radiation exposure could be a problem. Frequent CT scans may also impose a significant financial burden on patients. However, since PAEIP can be fatal, its early detection by CT and the rapid initiation of treatment are important.

Under the present Japanese health care system, frequent CT examinations increase medical costs and place a financial burden on health care providers and patients. Moreover, frequent CT and HRCT examinations could increase the risk of radiation exposure, resulting in adverse effects in patients. Unfortunately, it was not possible as part of this study to assess the financial and radiation exposure issues because of the lack of suitable data.

This study showed that the use of HRCT was important in patients undergoing surgery for lung cancer associated with IP in order to accurately predict the risk of PAEIP. Whether further confirmation of patients possibly at risk of PAEIP is economically feasible remains an issue and requires further investigation. Approaches to reducing the possibility of postoperative AE among IP patients will be another important issue for further investigation.

In conclusion, among patients undergoing surgery for lung cancer associated with IP, the identification of patients at possible risk for PAEIP through routine postoperative CT examinations can lead to the early diagnosis and treatment of PAEIP and markedly reduce the risk of death related to PAEIP.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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