Title

Distribution of Interstitial Pneumonia Is a New Radiological Predictor of 90-day mortality after Resection of Lung Cancer

Running head

Predictor of pulmonary resection with IP

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ABSTRACT

Background: Surgery for lung cancer patients complicated with idiopathic interstitial pneumonia (IIP) is associated with a high rate of postoperative mortality. Preoperative predictors of postoperative exacerbation are needed to aid in the selection of suitable surgical candidates.

Methods: A retrospective study was performed on 1625 patients who underwent surgical resection of primary lung cancer between 2000 and 2012. Two hundred and three patients (12.5%) were found to be complicated with IIP. The following radiological findings were also evaluated: presence of honeycombing, distribution (diffuse or localized) and extension (central extension or peripheral localized) of honeycombing or infiltration. Clinical factors were also investigated. Multivariate analyses were conducted to identify predictors of surgical mortality.

Results: Thirty-day mortality was 0.5% in all of the patients and 1.6% among IIP patients. Ninety-day mortality was 1.4% among all patients and 6.4% among IIP patients. Multivariate analysis showed that the following parameters were significant predictors of 90-day mortality: preoperative pO2<70mmHg (HR 15.3), diffuse distribution and central extension of interstitial pneumonia on CT (HR 9.2), and blood loss during surgery (ml: HR 1.003).

Conclusions: Diffuse distribution and central extension of IIP was a significant predictor of 90-day mortality, as well as preoperative hypoxia and blood loss in surgery.

Keyword

Complications, Acute exacerbation, Surgery, Interstitial pneumonia

INTRODUCTION

While idiopathic interstitial pneumonia (IIP) is a well-known pathological lung condition that is frequently associated with lung cancer[1]. Surgery is one of the mainstay treatments for lung cancer, and postoperative mortality is generally quite low [2]. However surgical mortality after pulmonary resection with IIP is high because of lethal complication as the acute exacerbation of IIP. While most postoperative complications can be controlled, mortality due to the acute exacerbation of IIP has not been controlled. The prognosis of patients with resected lung cancer and IIP has been reported to be poor, and the indications for surgical resection should be carefully considered [3-5]. The surgical indications should be determined based on *preoperative* predictors and prognostic factors for patients with lung cancer and IIP. While several predictors of surgical mortality in pulmonary resection for patients with IIP have been reported, most papers have focused on patients with pathological pulmonary fibrosis or acute exacerbation of IIP, instead of radiological IIP [3-12]. Thus, such predictors cannot be applied in a preoperative setting. While several papers considered patients with IIP, which is diagnosed based on preoperative radiological findings, the number of patients has been insufficient [13, 14]. One large-scale study investigated radiologically diagnosed interstitial lung disease [15]. However, this was based on a retrospective questionnaire that could not allow us to evaluate the details of radiological factors.

Thus, we conducted a retrospective study on patients with lung cancer concomitant with IIP based on preoperative factors including radiological factors, and identified preoperative radiological factors that

were useful for predicting the short term mortality after lung surgery for lung cancer.

MATERIALS AND METHODS

This study was approved by the institutional review board of Juntendo University Hospital, which permitted us to perform this retrospective study.

Patients

A retrospective study was performed on 1625 patients who underwent pulmonary resection for clinical stage I-III primary lung cancer at our institute from January 2000 to March 2012. Preoperative high-resolution computed axial tomography (CAT) scans were available for *all* patients, and they were reviewed to identify patients with IIP by authors (M.F, K.S, T.M, K.T). All patients underwent preoperative thoracic CAT scan to evaluate the primary tumor and mediastinal nodes, and CAT was performed with a slice thickness of 3 mm or less using mediastinal (level of 40 Hounsfield units [HU], width of 400 HU), and lung (level of 600 HU, width of 1600 HU) window settings. The diagnosis of IIP was basically made according to reported criteria [16]. We diagnosed IIP based on the following criteria: 1. Exclusion of other known causes of interstitial lung disease, such as collagen disease or drug toxicity; 2. Findings of a usual interstitial pneumonia (UIP) pattern: characterized by the presence of basal-dominant reticular opacities and predominantly basal and subpleural distribution of honeycomb lesions, with

multiple equal-sized cystic lesions of 2 to 10 mm in diameter with a thick wall; 3. Findings of a non-UIP pattern: characterized by the presence of basal-predominant ground glass opacities and infiltrative shadows inconsistent with UIP patterns [15]. IIP was found in 203 (12.4%) patients and no surgical biopsy for the diagnosis of IIP was performed preoperatively. Preoperative work-up in surgical candidates consisted of a complete history, physical examination, laboratory findings, arterial blood gas analysis, plain chest roentgenogram, thoracic computed tomography (CT ; enhanced if possible), brain magnetic resonance imaging, positron emission tomography, respiratory function test, electrocardiogram, and echocardiogram in cases with abnormal electrocardiogram finding or a past history of heart disorder. Lung function test included functional vital capacity (FVC), forced expiratory volume in one second (FEV1.0), and diffusion capacity of the lung for carbon monoxide (DLCO). Conventional preoperative clinical factors included age, gender, smoking index, carcinoembryonic antigen (CEA), lactate dehydrogenase (LDH), KL-6, and arterial blood oxygen and carbon dioxide. The requirements for surgical resection in patients with lung cancer complicated with IIP were no distant metastasis, radiological resectable, no nodal involvement, and could tolerate surgery. Basically, the operative mode was supposed to be lobectomy or greater, except in compromised patients such as patients with poor lung function. Radiotherapy is, in principal, contraindicated for patients with IIP, due to a possible high rate of radiation pneumonitis. Therefore, for patients with lung cancer of clinical stage IIIA, induction chemotherapy followed by surgery is the first choice instead of definitive concurrent chemoradiotherapy

in cases with good risk. If a patient was diagnosed as poor risk, upfront surgery with or without adjuvant chemotherapy was a therapeutic option.

Radiological pattern investigated

The presence of infiltration or not was investigated on plain chest roentgenogram. The following radiological findings were evaluated by plain chest roentgenogram or thoracic CAT scan: presence of honeycombing with or without traction bronchiectasis, distribution of honeycombing or infiltration (diffuse vs localized), and extension of honeycombing or infiltration (central extension or peripheral localized). The distribution of IIP was considered to be diffuse when infiltration or honeycombing was located in more than one lobe. Central extension was diagnosed when infiltration or honeycombing extended up to the inner two-thirds on CAT scan.

Perioperative management

We did not adopt a preoperative medication for the prevention of postoperative acute exacerbation of IIP, except that five patients received a preoperative injection of 1g methyl-prednisolone. We have started a prospective randomized study on patients with IIP in which we examine whether or not preoperative sivelestat is useful for the prevention of acute exacerbation. Intraoperative infusion is relatively restricted [8], and the inhaled oxygen concentration is low. Postoperative management consists of the infusion of

approximately less than 1.5 times body weight in milliliters per hour. Our routine postoperative management includes intraoperative in over out balance of 5 ml/kg/hour of operative time, which is the volume of any material infused intraoperatively minus the total volume of any bleeding, drainage from a nasogastric tube, and urine output. We usually do not consider insensible vapor loss as a factor in the "out" element since little water is lost as vapor during thoracotomy.

For lung cancer, we routinely use video-assisted thoracotomy with a 7- to 15-cm incision of the skin, without cutting of the ribs. A double-lumen tracheal tube is used for single-lung ventilation, and extubation is performed in the operative theater just after the operation. A nasal cannula with 3 L oxygen or an oral mask at 5 L is used to maintain at least 95% saturation of hemoglobin. After a one-night stay in the intensive care unit, the patient is returned to their previous ward, and encouraged to walk around with inhaled oxygen. Food intake is allowed on the first day after surgery without any imitations, and includes approximately 2000 cc water. For patients who were considered to have poor cardiac function, such as patients 80 years or more in age, food intake is started on the second postoperative day, though water intake is not limited. Patients are monitored by electrocardiogram for at least two days. Extubation of the thoracic drain is decided based on a drainage volume of less than 300 cc per day and no air leakage. Chest roentgenogram is checked on the day of surgery, and on the first, third, and fifth days after surgery.

Acute exacerbation of IIP was defined follows: unexplained worsening or development of

dyspnea within 30 days; high-resolution CAT with new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycombing pattern consistent with a UIP pattern; decrease in arterial oxygen tension of more than 10 mm Hg under similar condition ; no evidence of pulmonary infection by endotracheal aspiration; and exclusion of alternative causes, including left heart failure, pulmonary embolism, or identified cause of acute lung injury [17]. All patients who were suspected to show acute exacerbation of IIP underwent immediate thoracic CAT scan, including a high-resolution view. The diagnosis was made by thoracic surgeons and doctors of pulmonary medicine clinically without any histological biopsy by thoracic surgeons. The treatment strategy for acute exacerbation of IIP is drip infusion of methyl-prednisolone at 500 to 1000 mg for three days, followed by oral prednisolone at 30 to 60 mg or no medication. In principal, consecutive CAT scans were evaluated on the first and third days after the onset of acute exacerbation of IIP.

Statistical analysis

Surgical mortality was defined as any death after surgery. The cause of death was investigated for all patients and determined on the day of death. The number of days was counted from the operation. The onset of acute exacerbation of IIP was determined based on clinical and radiological features (see above for details). Clinicopathological features associated with the presence and absence of IIP were investigated to clarify the characteristics of patients with lung cancer complicated with IIP. Surgical

mortality was evaluated in terms of the day of death. The details of patients who died from postoperative acute exacerbation of IIP were investigated. Predictors of 90-day mortality were determined by univariate and multivariate analyses. Continuous and categorical variables were compared with Student's t-test, and Fisher's exact test, respectively. Predictors of mortality were investigated by uni- and multivariate analyses using a logistic regression model. Statistical analyses were performed with SPSS 2.0 statistical software (SPSS, Inc, Chicago, IL). A *p* value of less than 0.05 was considered to be significant in this study.

RESULT

Patients with preoperative IIP were significantly older than those without ($p<0.01$, Table 1). The IIP group also included higher proportions of males and smokers ($p<0.01$). On the other hand, preoperative CEA, LDH, and preoperative arterial blood gas were similar in the two groups. The preoperative titer of KL-6 was significantly higher in the IIP group ($p<0.01$). With regard to the results of a lung function test, only %DLCO was significantly low in the IIP group ($p<0.01$). Advanced cases were more likely to be operated upon in the IIP group ($p<0.01$). Radiological findings in patients with IIP included 91 (44.8%) infiltration on plain chest x-ray, 70 (34.5%) honeycombing on CAT, 101 (49.8%) diffuse distribution, and 56 (27.6%) central extension (Table 2). With regard to surgical mortality, 30-, 60-, 90-, and 180-day mortality in patients with lung cancer complicated with IIP was 1.5%, 3.0%, 6.4%, and 7.9%, respectively

(Table 3). These mortality rates were significantly worse than those in patients without IIP ($p<0.05$). No postoperative acute exacerbation of IIP was found in patients with lung cancer without IIP. Five patients died from acute exacerbation of IIP, and all 5 were men aged 60 or more (Table 5, 6). Preoperative CAT scan showed either a UIP pattern or non-UIP pattern in all 5 (see above for details). The onset of postoperative acute exacerbation of IIP ranged from postoperative day 8 to 29. Abnormal LDH and KL-6 titer were seen in 4 (80%) and 2 (40%) patients, respectively. The interval between onset and death in patients with postoperative acute exacerbation of IIP ranged from 7 to 97 days, with a median of 21 days.

Among patients with preoperative IIP, the following predictors of 90-day mortality were determined based on a univariate analysis; age, preoperative arterial blood oxygen, %VC less than 80%, intraoperative blood loss, and radiological factors (Table 6). The significant radiological factors included distribution ($p=0.074$) and extension ($p=0.032$), while the presence of honeycombing was not significant. A multivariate analysis revealed that preoperative arterial blood gas less than 70 torr (HR 15.313, 95%CI 0.006-0.774), greater blood loss (ml, HR 1.003, 95%CI 1.001-1.004), and the presence of radiological findings of both diffuse distribution and central extension (HR 9.214, 95%CI 1.244-68.279) were predictors of 90-day mortality (Table 7).

DISCUSSION

Several papers have addressed the feasibility of surgery for patients with lung cancer and interstitial pneumonia [3-15]. Those papers concluded that pulmonary resection for lung cancer complicated with IIP carries an extremely high risk and poor prognosis, and the indication for such surgery should be decided upon considering prognostic factors. While most of these authors considered patients with pathological pulmonary fibrosis or acute exacerbation of IIP [3-12], a few considered preoperatively diagnosed IIP [13-15]. The latter reports either included relatively small numbers of patients [13, 14] or were based on just a questionnaire [15]. Therefore, we conducted a retrospective study on patients with IIP which diagnosed with preoperative CT findings and identified radiological findings that predicted 90-day mortality.

In this study, while the 90-day mortality was 4 times greater than the 30-day mortality (6.4% vs 1.5%) in patients with IIP, both the 30-day and 90-day mortality were less than 1% in patients without IIP (Table 2). Two previous reports have used 90-day mortality as a primary endpoint for evaluating the short-term outcome of lung cancer surgery in patients with IIP [4, 5]. Saito et al. reported that 30-day mortality was 0% in all patients and 90-day mortality was 3.6% in patients with IP and 0.3% in those without IP [4]. Watanabe et al. reported that the 90-day surgical mortality in patients with stage I lung cancer complicated with IIP was 7.1% [5]. However, none of those reports discussed predictors of 90-day mortality. We used 90-day mortality as a primary endpoint for investigating patients with lung cancer and IIP because patients with IIP should frequently die more than 30 days and less than 90 days after surgery. Thirty-day mortality could lead to the underestimation of postoperative death, and we adopted 90-day

mortality as a primary endpoint in this study. Thus, we concluded that 90-day mortality should be the primary endpoint for evaluating the short-term outcome in patients with IIP.

The Japanese Association for Chest Surgery conducted a large-scale, multi-institutional retrospective study on lung cancer patients with IIP [15]. This study was the largest study on patients with lung cancer and IIP, and included 1763 cases. Our institution participated in this study, which was based on the use of a questionnaire. This study identified the following seven predictors of acute exacerbation within 30 days after surgery; surgical procedure, male sex, history of exacerbation, preoperative steroid use, serum KL-6 levels, usual interstitial pneumonia appearance on CAT scan, and reduced percent predicted vital capacity. In this study, 30-day mortality was 2.6% and the mortality rate was 43.9% after acute exacerbation of IIP. At our institute, 30-day mortality was 1.5% and the mortality rate after acute exacerbation was similar to that in this study. In the large-scale study, the number of days from acute exacerbation to death ranged from 1 to 82, with a median of 20, and therefore they should have used 90-day mortality as a primary endpoint, as we indicated in our study. Their evaluation based on 30-day mortality could have resulted in an underestimation.

With regard to the surgical procedure, a lesser pulmonary resection was recommended to minimize the frequency of acute exacerbation of IIP [15], which is not consistent with our data. It is difficult to evaluate the extension of lung cancer in the field of IIP. Thus, for most patients with lung cancer complicated with IIP, lesser resection, especially wide wedge resection, is not suitable. Based on

our result, there were no differences between lobectomy and lesser resection including segmentectomy and wide wedge resection. This discrepancy between large-scale data and our data may be associated with operative time or blood loss, which means that both our operative time and blood loss were quite low. Based on our policy, for patients with lung cancer and IIP, an experienced attending surgeon (KT, SO, KS) can perform pulmonary resection to minimize operative time and blood loss. The time for single-lung ventilation should be minimized to reduce stress in the dependent lung caused by pressure and the duration of a high concentration of oxygen should be maximized [18]. The perioperative volume of infusion is also related to stress, as we reported previously [8]. Therefore, we do not hesitate to perform lobectomy or more for patients with lung cancer with IIP to maintain a sufficient surgical margin. Since patients with IIP cannot tolerate radiotherapy, surgical resection should be performed as a last resort for such patients. This study is limited by its single-center basis and its retrospective nature. The indications and the details of the operative procedures may vary between institutes. Thus, it is not clear whether or not our data can be generalized. We are planning to perform a prospective multi-institutional study on the feasibility of our radiological factors for predicting 90-day mortality for lung cancer complicated with IIP. Another limitation involves the radiological evaluation. There was some controversy between observers in the radiological evaluation of distribution or extension, and objective methods of evaluation should be investigated in the future.

Despite these limitations, we conclude that 90-day mortality should be considered a primary endpoint for

the evaluation of lung cancer complicated with IIP, and a new radiological predictor of 90-day mortality was identified, which should be considered when selecting patients who may benefit from surgery for lung cancer from among patients with IIP.

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Conflicts of interest

There is no conflict of interest to disclose.

Table 1 Patient characteristics

Variables	IIP (N=203)	without IIP (N=1422)	p-value[a]
Age [b]	69.5±0.6	65.2 ±0.3	<0.001
Male	173 (85.2%)	834 (58.6%)	<0.001
Smoking history [b] (pack years)	51.6 ±31.9	29.8 ±35.4	<0.001
CEA [b] (ng/ml)	9.46 ±1.3	7.26±0.8	0.313
LDH [b] (IU/L)	244.85±7.1	228.9±2.6	0.035
KL-6 [b] (U/mL)	672.8±40.7	362.0±36.3	<0.001
Preoperative PaO_2 [b] (mm Hg)	87.4±11.3	88.3±13.1	0.413
FVC [b] (L)	3.00±0.05	3.47±0.2	0.050
%VC (%)	94.4±17.7	97.3±15.9	0.028
$FEV_{1.0}$% [b] (%)	74.8%±0.7	74.9±0.3	0.88
%DLCO [b] (%)	48.2±1.2	64.5±0.5	<0.001
Procedure			
Lobectomy or grater	165 (81.3%)	1089 (76.5%)	0.132
Lesser resection	32 (15.7%)	299 (21.0%)	0.514
Clinical stage (I / II / III)			
I	138(68.0%)	1122(80.9%)	<0.001
II	30(14.7%)	117(8.4%)	
III	35(17.2%)	147(10.6%)	
Operative time [b]	184.8±84.3	189.1±86.5	0.5121
Blood loss [b]	170.4±299.8	154.1±287.5	0.4571
Pathological stage (I / II / III)			

I	94(50.5%)	874(66.7%)	<0.001
II	35(18.8%)	176(13.4%)	
III	51(27.4%)	249(19%)	
IV	6(3.2%)	11(0.8%)	

[a] p value in Fisher's exact test or student t-test. [b] Continuous variable, [c] Lobectomy or grater which includes pneumonectomy. [d] segmentectomy and wide included.

IIP=idiopathic interstitial pneumonia, CEA=carcinoembryonic antigen, LDH=lactate dehydrogenase, KL-6= sialylated carbohydrate antigen KL-6, FVC=functional vital capacity; FEV1.0=forced expiratory volume in one second; %DLCO=percentage of diffusing capacity of the lung for carbon monoxide. Values are presented as mean ± SD (range) unless specified otherwise.

Table 2 Radiological characteristics in patients with IIP

Radiological findings	present	absent
Infiltration on plain chest x-ray	91 (44.8%)	101 (49.8%)
Honeycombing on CAT	70 (34.5%)	65 (32.0%)
Distribution, diffuse	101 (49.8%)	92 (45.3%)
Extension, central	56 (27.6%)	137 (67.5%)

Table 3 Postoperative mortality by postoperative period

	IIP n=203	without IIP n=1422	HR	p-value[a]
30-day mortality	3 (1.5%)	5 (0.4%)	4.37	0.045
60-day mortality	6 (3.0%)	8 (0.6%)	5.83	0.001
90-day mortality	13 (6.4%)	10 (0.7%)	6.06	<0.001
180-day mortality	16 (7.9%)	25 (1.8%)	5.81	<0.001

[a] p-value in logistic regression analysis. IPF=idiopathic interstitialpneumonia, HR=hazard ratio

Table 4 Cases of death after surgery exclude lung cancer

IP (n=203)				
Age	c-Stage	Surgery	Cause of death	date of occurrence / date of death
45M	IIIA	Lt.pneumonectomy	Acute respiratory failure	3POD/ 3POD
71M	IIIA	RUL+SVC replacement	Pneumonia	1POD/ 12POD
63M	IB	RUL	Exacerbation of IP	12POD/ 24POD
69M	IA	RUL	Exacerbation of IP	10POD/ 31POD
65M	IIIA	RUML	Exacerbation of IP	29POD/ 36POD
67M	IIIA	RLL	Exacerbation of IP	14POD/ 62POD
66M	IIIA	Rt. Sleeve pneumopnectomy +SVC replacement	Bronchopleural fistura	9POD/ 67POD
75M	IA	Lt. WWR	Exacerbation of IP	8POD/ 105POD
78M	IA	RUL	Unknown	-/ 113POD

Non-IP (n=1422)				
Age	c-Stage	Surgery	Cause of death	date of occurrence / date of death
71F	IB	LUL	Cerebral infarction	2POD/ 2POD
68M	IIB	Rt. Sleeve Pneumonectomy	Heamorrhage	18POD/ 18POD
74M	IIB	Rt. Sleeve Upper Lobectomy	Heamorrhage	19POD/ 19POD
66M	IA	RUL	Unknown	- / 29POD
68M	IIB	RUL	Choking	- / 33POD
51M	IIIA	Rt.S6 segmentectomy	Pneumonia undergoing chemotherapy	- / 118POD

44M	IIIA	Rt.WWR	Pneumonia undergoing chemotherapy	- / 151POD
74M	IB	LUL	debilitate	- / 168POD

POD: post-operative day, RUL: right upper lobectomy, RUML: right upper and middle lobectomy, RLL: right lower lobectomy, SVC: superior vena cava, LUL: left upper lobectomy, LLL: left lower lobectomy, WWR: wide wedge resection.

Table 5 Characteristics of patient who died from acute exacerbation of IIP

Age/ gender	Procedure	Pathology of IP	blood loss	operative time	Onset	LDH [a]	KL-6 [b]	Outcome
63/ man	lobectomy	Unknown	30 cc	160 minutes	12POD	elevated	elevated	died in 24POD
69/ man	lobectomy	fibrotic NSIP	210 cc	169 minutes	10POD	normal	normal	died in 31POD
65/ man	lobectomy	UIP	65 cc	168 minutes	29POD	elevated	elevated	died in 36POD
67/ man	lobectomy	UIP	32 cc	187 minutes	14POD	elevated	normal	died in 62POD
75/ man	wedge	UIP	700 cc	233 minutes	8POD	elevated	normal	died in 105POD

[a] LDH at onset of acute exacerbation of IIP, [b] KL-6 at onset of acute exacerbation of IIP,

IIP=idiopathic interstitial pneumonia, POD=post-operative day, NSIP=nonspecific interstitial pneumonia, UIP=usual interstitial pneumonia

Table 6 Univariate analysis to identify predictors of 90-day mortality among patients with IIP

Variables	Hazard ratio	95% CI	P-value[a]
Age[b]	0.920	0.848-0.998	0.046
Preoperative pO2<70mmHg	14.10	2.713-73.276	0.002
Preoperative KL-6≥500 (U/mL)	0.614	0.074-5.077	0.650
Preoperative LDH≥222 (IU/L)	1.972	0.453-8.595	0.366
Smoking history (PYS>40)	2.469	0.289-21.131	0.409
%VC <80 (%)	4.167	1.043-16.652	0.043
$FEV_{1.0}$% <70 (%)	1.156	0.277-4.826	0.843
%DLco<40 (%)	1.500	0.322-6.991	0.606
Infiltration on plain chest x-ray	4.837	0.991-23.613	0.051
Honeycombing on CAT	1.336	0.564-3.264	0.495
Distribution (diffuse vs localized)	4.238	0.869-20.677	0.074
Extension (Central vs peripheral)	4.250	1.134-15.925	0.032
Distribution and extension (Central and diffuse vs others)			
	6.461	1.700-24.557	0.006
Procedure (limited vs lobectomy)	0.614	0.074-5.077	0.650
Operative time[b]	1.006	1.000-1.011	0.052
Blood loss[b]	1.002	1.001-1.004	0.001

[a] P-value in logistic regression analysis, [b] Continuous variable

IIPF=idiopathic interstitial pneumonia, CI= confidence interval, KL-6=sialylated carbohydrate antigen KL-6, LDH=lactate dehydrogenase, PYS=pack-year smoking, FVC=functional vital capacity; FEV1.0=forced expiratory volume in one second; %DLCO=percentage of diffusing capacity of the lung for carbon monoxide, CAT=computerized axial tomography

Table 7 Multivariate analysis to identify predictors of 90-day mortality in IPF patients

Variables	Hazard ratio	95% CI	P-value[a]
Preoperative arterial blood gas			
PaO2 less than 70 torr	15.313	0.006-0.774	0.031
Blood loss[b] (ml)			
	1.003	1.001-1.004	0.002
Radiological findings on CAT scan			
Diffuse and central[c]	9.214	1.244-68.279	0.030

[a] P-value in logistic regression analysis, [b] Continuous variable, [c] Definition of diffuse distribution and central extension was detailed in the text.

IPF=idiopathic pulmonary fibrosis, CI= confidence interval, CAT=computerized axial tomography

Figure legends

Figure 1A. Thoracic computed axial tomography which shows localized distribution in the lower lobe, and this patient was categorized in localized as to distribution.

Figure 1B. Thoracic computed axial tomography which shows diffuse distribution, which mean infiltration is located in more than one lobe.

Figure 2A. Thoracic computed axial tomography which shows peripheral extension of infiltration.

Figure 2B. Thoracic computed axial tomography which shows central extension of infiltration or honeycombing, which means radiological findings of IPF extend up to inner two third of lung field.

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