



The maximum dimension of the inferior vena cava is a significant predictor of postoperative mortality in lung cancer patients with idiopathic interstitial pneumonia

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Abstract

Purpose Several vascular measurements in computed tomography (CT) were reported to be indicators of pulmonary hypertension in chronic obstructive pulmonary disease (COPD) patients. We evaluated the usefulness of these parameters as predictors of postoperative mortality in lung cancer patients with IIP.

Methods This retrospective study was performed on 1888 patients. The following CT findings were evaluated: diameter of the main pulmonary artery, ascending aorta, and the short axis of the inferior vena cava (IVC). Univariate and multivariate analyses were conducted to determine predictors of surgical mortality.

Results In the IIP patients, the 90-day mortality was 0.8%, and the 2-year mortality was 5.8%. Regarding the 90-day mortality in patients with IIP, a multivariate analysis revealed a short axis of IVC > 21 mm [odds ratio (OR) 6.4, $p < 0.01$] and the risk score reported by Japanese Association for Chest Surgery (JACS) (OR 1.4, $p = 0.01$) as independent predictors. Regarding the 2-year mortality in patients with IIP, a multivariate analysis revealed IVC > 21 mm (OR 2.3, $p < 0.04$), %VC < 80% (OR 2.4, $p = 0.02$), and pathological cancer stages II and III vs. I (OR 7.2, $p < 0.001$) as independent predictors.

Conclusions Enlargement of the IVC as measured by CT was a significant predictor of mortality after surgery for lung cancer with IIP patients.

Keywords Inferior vena cava · Idiopathic interstitial pneumonia · Lung cancer · Surgical mortality

Introduction

The prognosis of lung cancer patients with idiopathic interstitial pneumonia (IIP) has been reported to be poor, and the indications for surgical resection should be carefully considered [1–3]. Furthermore, such indications should be

determined based on cancer progression and the state of IIP. Regarding the state of IIP, the risk of acute exacerbation after surgery as well as the prognosis and severity of IIP per se influence decision-making.

Pulmonary hypertension (PH) is reported to be associated with an increased risk of mortality in patients with pulmonary fibrosis [4, 5]. However, it is unusual to evaluate PH and the right heart function by echocardiogram or catheterization of the heart before surgery. Regarding the evaluation of PH, several papers have described the usefulness of measuring diameter of the main pulmonary artery (MPAD) or MPAD/aorta ratio (PA–Ao ratio) on computed tomography (CT) in chronic obstructive pulmonary disease (COPD) patients [6, 7]. However, there are no data concerning the relationship between those vascular measurements on CT with IIP. Furthermore, there are no reports on the dimension of the inferior vena cava (IVC), despite its importance in echo diagnoses. In trauma patients, the diameter of the IVC on CT rather than an echogram was reported to be useful

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for evaluating hypovolemia [8, 9]. The measurement of the MPA and IVC may be able to be applied for the preoperative assessment of right heart load in patients with IIP and to predict the prognosis of lung cancer patients with IIP.

We therefore conducted a retrospective study of patients with lung cancer concomitant with IIP based on preoperative factors, including several vascular measurements on CT, and found that the preoperative radiological vascular dimensions were useful for predicting surgical mortality after pulmonary resection for lung cancer with IIP.

Methods

Study population

A retrospective study was performed on 1888 patients with clinical stage I–III lung cancer who underwent pulmonary resection between January 2009 and December 2015 at our institute. All patients underwent a preoperative thoracic CT scan performed with a slice thickness of ≤ 2 mm using mediastinal [level of 40 Hounsfield units (HU), width of 400 HU] and lung (level of 600 HU, width of 1600 HU) window settings. All CT findings were reviewed anew by the authors (two radiologists: Kazuhiro Suzuki and Akihiro Hotta; one pulmonary medicine physician: Kazuhiro Ando; two thoracic surgeons: Mariko Fukui and Kazuya Takamochi). We diagnosed IIP based on the reported criteria [10–12] and classified patients into three groups: usual interstitial pneumonia (UIP) pattern, possible UIP pattern, and inconsistent with UIP pattern based on the official the American Thoracic Society (ATS)/the European Respiratory Society (ERS)/the Japanese Respiratory Society (JRS)/the Latin American Thoracic Association (ALAT) statement [4]. Patients with a reticular shadow, which may be attributed to a displaced lung by osteophytes or self-weight consolidation, were excluded from the IIP groups. The presence of emphysema was also evaluated, and a positive diagnosis was made when the emphysema area accounted for more than 10% of the lungs. We excluded patients for whom pulmonary resection was cancelled due to dissemination ($n = 37$) and those who received chemotherapy or radiotherapy ($n = 83$) to exclude interstitial lung disease from known causes (Fig. 1).

The preoperative evaluation included a complete history, physical examination, laboratory findings, arterial blood gas analysis, chest X-ray, and pulmonary function tests, as well as CT of the chest and abdomen, electrocardiogram, and echocardiogram for patients with an abnormal electrocardiogram (ECG) or a history of heart disorder. We also used a scoring system (JACS score) for predicting acute exacerbation of IIP after pulmonary resection in lung cancer patients [13].

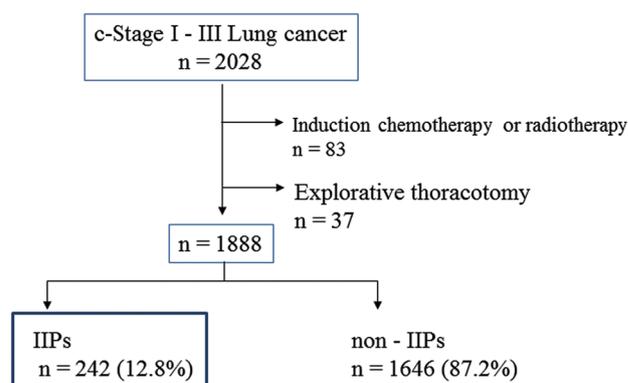


Fig. 1 The demographics of the patients in the present study

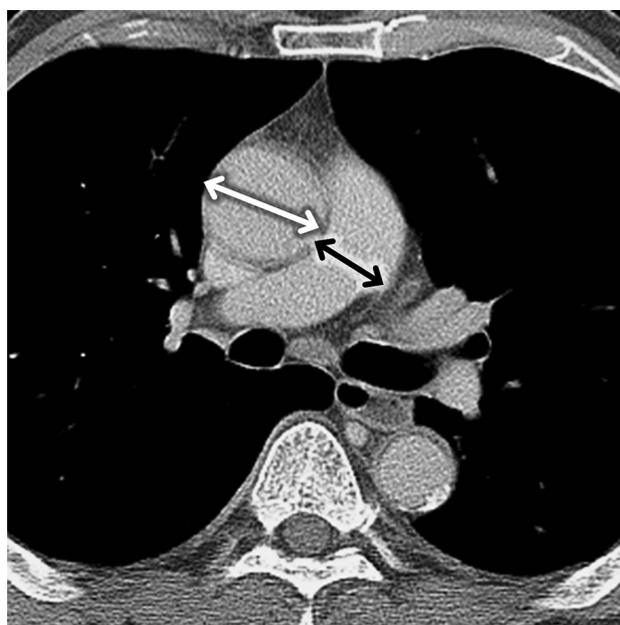


Fig. 2 The diameter of the main pulmonary artery at the level of its bifurcation (black line) was evaluated. The ascending aorta in the same image (white line) was used for measuring the diameter of the aorta (Ao)

In the present study, the same surgical team performed all of the surgeries and coordinated the perioperative management for all patients. Details of our management have been reported previously [14].

The radiological measurement of the vascular diameter

The factors we used as indices of the right-side cardiac pressure were the main pulmonary artery diameter (MPAD), which is measured as the diameter of the main pulmonary artery at the level of its bifurcation (Fig. 2); the ratio of the

MPAD to the diameter of the aorta at the same level of the MPAD (PA–Ao ratio); and the maximum dimension of the IVC, which is measured as the short axis of the IVC between the left atrium and hepatic vein (Fig. 3).

Definition of surgical outcomes

Operative mortality was defined as death within 30 and 90 days of resection. Postoperative complications were defined to include hypoxia requiring home oxygen therapy, acute lung injury (ALI), pneumonia, intractable air leakage requiring adhesion therapy or additional drainage, bronchopleural fistula proven by bronchoscope or operative findings of leakage, empyema, arrhythmias, and acute exacerbation of IIP (defined as worsening of dyspnea and hypoxia from baseline within 30 days, including new ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycombing pattern). Findings with alternative causes, such as left heart failure, aspiration pneumonia, pulmonary embolism, or identified causes of acute lung injury, were excluded from acute exacerbation of IIP. Respiratory morbidity in this study was defined as acute exacerbation of IIP, hypoxia, ALI, and pneumonia.

Statistical analyses

Predictors of the 90-day mortality were determined by univariate and multivariate analyses using a logistic regression model. Survival curves were estimated using the Kaplan–Meier method. Predictors of the 2-year survival

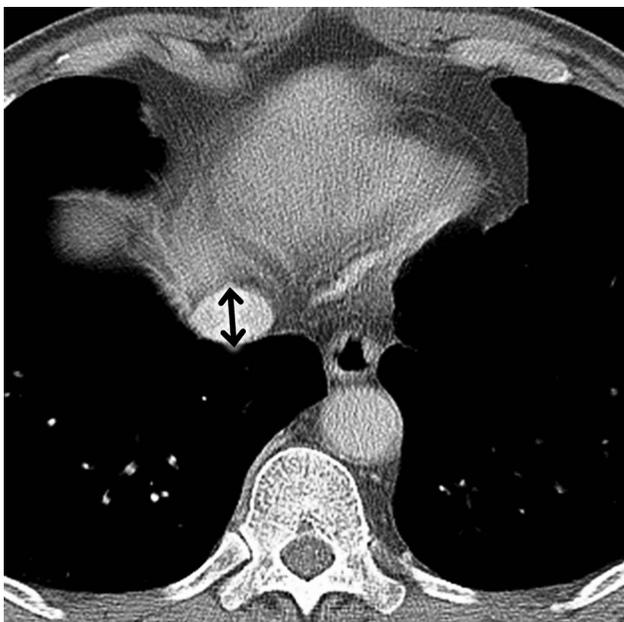


Fig. 3 The short axis of the inferior vena cava (IVC) between the left atrium and hepatic vein was measured as the short axis of the IVC

were investigated by univariate and multivariate analyses using Cox's proportional hazard model.

All of the statistical analyses were performed using the SPSS 24.0 software program (SPSS Inc., Chicago, IL, USA). *P* values of <0.05 were considered to indicate statistical significance.

This study was approved by the ethics committee at our institute (2015015).

Results

The clinical characteristics of the IIP patients are shown in Table 1. Men and severe smokers were dominant, and the average percentage of diffusing capacity of the lung for carbon monoxide (%DLCO) was $44.2\% \pm 15.8\%$. Emphysema was a complication in 52.5% patients with IIP. Regarding the surgical procedure, lobectomy or more centered on complete resection was performed in 82.6% of cases.

Table 2 shows the dimensions of MPA, IVC, and Ao on CT. These average values are roughly the same as previously reported (MPA in COPD: 28.7 mm, MPA in non-COPD: 25.3 mm) [7]. Forty-five patients (18.6%) underwent echocardiography, including 8 patients with an IVC of >21 mm on CT and 1 who was diagnosed with PH by echocardiography. Among the patients with an IVC dimension of ≤ 21 mm, none had PH.

Morbidities within 30 days and mortality after surgery were reviewed and are presented in Table 3. Acute exacerbation of IIP occurred in 11 patients (4.5%). The 90-day mortality was 5.8%. Causes of death within 90 days were acute exacerbation of IIP ($n=4$), respiratory failure ($n=2$), pneumonia ($n=1$), sudden death of unknown cause ($n=2$) and cancer ($n=5$).

The 2-year overall survival was 68.0%, and the 2-year cancer-specific survival was 81.0%. The survival and cancer-specific survival of patients with larger IVCs (>21 mm) was not significantly different from those of patients with normal IVCs (≤ 21 mm) (log-rank test, $p=0.0518$ and $p=0.4677$). The 2-year survival rates of patients with larger and normal IVCs were 55.6% and 71.5%, respectively.

Among patients with IIP, the following predictors of 90-day mortality were identified based on a univariate analysis: JACS score, diffuse and central extension of IIP, preoperative arterial blood gas <70 mmHg, %VC <80%, clinical cancer stage (I vs. II and III), and dimension of MPAD >29 mm, and IVC >21 mm. A multivariate analysis revealed that the JACS score [odds ratio (OR) 1.401, 95% confidence interval (CI) 1.082–1.813] and IVC >21 mm (OR 6.896, 95% CI 1.969–24.154) were predictors of 90-day mortality (Table 4). Regarding the 2-year mortality in patients with IIP, a multivariate analysis revealed IVC >21 mm (OR 2.333, 95% CI 1.283–4.242), %VC <80%

Table 1 Baseline characteristics of the patients

Variables		(%)
Number of patients	242	
Age (years)	71.9 ± 7.3	
Age > 75 years (<i>n</i>)	93	(38.4)
Gender: male (<i>n</i>)	196	(81.0)
Smoking history (pack-years)	51.3 ± 36.5	
CEA (ng/mL)	10.1 ± 25.5	
Preoperative LDH (IU/L)	208.8 ± 51.3	
Preoperative KL-6 (U/mL)	574.0 ± 373.9	
FVC (L)	3.13 ± 0.77	
%VC	96.3 ± 17.8	
%VC < 80%	44	(18.2)
FEV1.0/FVC (L)	2.13 ± 0.51	
FEV1.0/FVC < 0.7	89	(36.8)
%DLCO	44.2 ± 15.8	
%DLCO < 40%	85	(35.1)
pO ₂ (mmHg)	83.8 ± 10.5	
pO ₂ < 70 mmHg	20	(8.3)
Radiological type of IIP		
UIP pattern/possible UIP	90	(37.2)
Inconsistent with UIP	152	(64.8)
Emphysema (CPFE)	127	(52.5)
Distribution (diffuse)	95	(39.3)
Diffuse and central extension of IP	36	(14.9)
JACS score	7.3 ± 3.0	
0–10	163	(67.4)
11–14	64	(26.4)
≥ 15	0	
No data	14	
Clinical stage		
Stage I	168	(69.4)
Stage II or III	74	(30.6)
Pathological stage		
Stage I	124	(51.3)
Stage II or III	116	(47.9)
Histology of lung cancer		
Squamous cell carcinoma	105	(43.4)
Non-squamous cell carcinoma	137	(56.6)
Procedure		
Lobectomy or more	200	(82.6)
Limited resection	42	(17.4)

CEA carcinoembryonic antigen, LDH lactate dehydrogenase, KL-6 sialylated carbohydrate antigen, VC vital capacity, FEV1.0 Forced expiratory volume in one second, %DLCO percentage of diffusing capacity of the lung for carbon monoxide, JACS Japanese Association for Chest Surgery

^a*p* value in the *t* test

^b*p* value in Chi-square test

Table 2 Measurement of dilatation MPA, IVC, Ao on computed tomography

Variables	
Number of patients	242
IVC > 21 mm	37 (15.5%)
IVC > 25 mm	4 (1.6%)
MPAD > 29 mm	40 (16.5%)
MPAD/Ao > 1.0	16 (6.6%)
Average value	
MPAD	26.0 ± 3.6
Ao	34.5 ± 3.8
IVC	18.0 ± 3.5
MPAD/Ao	0.76 ± 0.12
IVC/Ao	0.52 ± 0.14

MPAD main pulmonary artery diameter at the level of its bifurcation, Ao diameter of the ascending aorta is at the same level of MPAD, IVC maximum diameter of the inferior vena cava between the hepatic vein and left atria

Table 3 Morbidities within 30 days and mortalities after surgery

Variables	Total
Number of patients	242
Morbidities	
Acute exacerbation of IIP	11 (4.5%)
Hypoxia that required home oxygen therapy	51 (21.1%)
Pneumonia	11 (4.5%)
Intractable air leakage	19 (7.9%)
Bronchopleural fistula	7 (2.8%)
Empyema	4 (1.7%)
Arrhythmias	31 (12.8%)
30-day mortality	2 (0.8%)
90-day mortality	14 (5.8%)
2-year mortality	68 (28.1%)

^a*p* value in the Chi-square test

^bRespiratory morbidity: acute exacerbation of idiopathic interstitial pneumonia (IIP), hypoxia, acute lung injury (ALI) and pneumonia

(OR 1.916, 95% CI 1.099–3.341), diffuse and central extension of IIP (OR 2.012, 95% CI 1.077–3.760), and pathological cancer stage II and III vs. I (OR 6.206, 95% CI 3.302–11.664) as independent predictors (Table 5).

Table 6 shows the clinicopathological characteristics classified by the IVC diameter. The two IVC groups were similar in their age, rate of emphysema, clinical and pathological stage of lung cancer, and JACS score. The percentages of patients with hypoxia (pO₂ < 70 mmHg) in the IVC > 21 mm and ≤ 21 mm groups were 17.8% and 6.3%, respectively (*p* = 0.013). The percentages of patients with restrictive lung disease (%VC < 80%) in the IVC > 21 mm and ≤ 21 mm groups were 33.3% and 14.1%, respectively (*p* = 0.003).

Table 4 Results of univariate and multivariate analyses to identify the 90-day mortality in IIP patients

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	<i>p</i> value ^a	Odds ratio	95% CI	<i>p</i> value
Age > 75 years	0.712	0.217–2.343	0.712			
Gender: male	499.021	0.000	0.997			
JACS score	1.367	1.076–1.736	0.011	1.401	1.082–1.813	0.010
UIP pattern	1.241	0.945–1.631	0.121			
Diffuse and central extension of IIP	3.403	1.072–10.804	0.038			
KL-6 ≥ 1000 IU/L	2.653	0.502–14.028	0.251			
pO ₂ < 70 mmHg	3.369	1.857–13.244	0.042			
%VC < 80%	4.286	1.364–13.464	0.013			
FEV1.0/FVC < 0.7	0.492	0.132–1.837	0.291			
%DLCO < 40%	3.247	0.946–11.145	0.061			
Surgical procedure	1.063	0.724–1.560	0.755			
Cancer stages c-II and III vs. I	3.273	1.093–9.768	0.034			
MPAD > 29 mm	4.279	1.397–13.109	0.011			
MPAD/Ao ratio > 1.0	2.548	0.519–12.513	0.249			
IVC > 21 mm	6.400	2.096–19.538	0.001	6.896	1.969–24.154	0.003

JACS Japanese Association for Chest Surgery, UIP usual interstitial pneumonia, KL-6 sialylated carbohydrate antigen, VC vital capacity, FEV1.0 Forced expiratory volume in one second, %DLCO percentage of diffusing capacity of the lung for carbon monoxide, MPAD main pulmonary artery diameter at the level of its bifurcation, Ao diameter of the ascending aorta is at the same level of MPAD, IVC maximum diameter of the inferior vena cava between the hepatic vein and left atria

^a*p* value in the logistic regression test

Table 5 Results of univariate and multivariate analyses to identify the two-year mortality in IIP patients

Variables	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	<i>p</i> value ^a	Odds ratio	95% CI	<i>p</i> value
Age > 75 years	0.883	0.531–1.467	0.631			
Gender: male	1.346	1.037–1.747	0.026			
UIP pattern	1.173	1.042–1.322	0.008			
Diffuse and central extension of IIP	1.847	1.041–3.277	0.036	2.012	1.077–3.760	0.028
KL-6 ≥ 1000 IU/L	1.867	0.832–4.193	0.136			
pO ₂ < 70 mmHg	1.099	0.404–2.989	0.853			
%VC < 80%	2.629	1.567–4/4-0	<0.001	1.916	1.099–3.341	0.022
FEV1.0/FVC < 0.7	0.602	0.350–1.035	0.602			
%DLCO < 40%	1.369	0.820–2.286	0.229			
Surgical procedure	1.210	0.619–2.368	0.577			
Cancer stages p-II and III vs. I	4.376	2.493–7.681	<0.001	6.206	3.302–11.664	<0.001
MPAD > 29 mm	1.458	0.832–2.553	0.203			
MPAD/Ao ratio > 1.0	0.924	0.336–2.537	0.878			
IVC > 21 mm	1.968	1.143–3.390	0.015	2.333	1.283–4.242	0.005

UIP usual interstitial pneumonia, KL-6 sialylated carbohydrate antigen, VC vital capacity, FEV1.0 Forced expiratory volume in one second, %DLCO percentage of diffusing capacity of the lung for carbon monoxide, MPAD main pulmonary artery diameter at the level of its bifurcation, Ao diameter of the ascending aorta is at the same level of MPAD, IVC maximum diameter of the inferior vena cava between the hepatic vein and left atria

^a*p* value in the logistic regression test

Table 6 A comparison of characteristics between patients with IVC > 21 and ≤ 21 mm

Variables	IVC ≤ 21 mm	IVC > 21 mm	<i>p</i>
Number of patients	191 (%)	45 (%)	
Age (years)	71.7 ± 7.5	71.8 ± 6.9	0.935
Age > 75 years (<i>n</i>)	64 (33.5)	18 (40.0)	0.411
Gender: male (<i>n</i>)	152 (79.6)	40 (88.9)	0.149
Smoking history (pack-years)	45.6 ± 39.9	48.0 ± 41.5	0.723
CEA (ng/mL)	10.6 ± 28.0	8.9 ± 12.7	0.708
Preoperative LDH (IU/L)	207.1 ± 43.4	216.3 ± 79.1	0.347
Preoperative KL-6 (U/mL)	576.8 ± 389.8	580 ± 348.9	0.960
FVC (L)	3.16 ± 0.75	3.14 ± 0.82	0.912
%VC	97.2 ± 16.9	93.4 ± 17.5	0.189
%VC < 80%	27 (14.1)	15 (33.3)	0.003
FEV1.0/FVC (L)	2.17 ± 0.49	2.02 ± 0.53	0.059
FEV1.0/FVC < 0.7	69 (36.1)	19 (42.2)	0.396
%DLCO	45.2 ± 15.8	40.3 ± 16.1	0.088
%DLCO < 40%	60 (31.4)	20 (44.4)	0.093
pO ₂ (mmHg)	84.6 ± 10.5	80.3 ± 9.9	0.012
pO ₂ < 70 mmHg	12 (6.3)	8 (17.8)	0.013
Radiological type of IIPs			0.033
UIP pattern/possible UIP	65 (34.0)	23 (51.1)	
Inconsistent with UIP	126 (66.0)	22 (48.9)	
Emphysema (CPFE)	97 (50.8)	29 (64.4)	0.098
Diffuse and central extension of IP	26 (13.6)	7 (15.6)	0.735
JACS score	7.5 ± 2.9	8.0 ± 2.8	0.315
Clinical stage			0.698
Stage I	133 (69.6)	30 (66.7)	
Stage II or III	58 (30.4)	15 (33.3)	
Pathological stage			0.350
Stage I	94 (49.2)	25 (55.6)	
Stage II or III	93 (48.7)	18 (40.0)	
Histology of lung cancer			0.012
Squamous cell carcinoma	116 (60.7)	18 (40.0)	
Non-squamous cell carcinoma	75 (39.3)	27 (60.0)	

CEA carcinoembryonic antigen, LDH lactate dehydrogenase, KL-6 sialylated carbohydrate antigen, VC vital capacity, FEV1.0 Forced expiratory volume in one second, %DLCO percentage of diffusing capacity of the lung for carbon monoxide, JACS Japanese Association for Chest Surgery

^a*p* value in the *t* test

^b*p* value in Chi-square test

Discussion

Several previous reports have concluded that pulmonary resection for lung cancer complicated with IIP carries an extremely high risk and a poor prognosis [10, 15].

In the short term, the coexistence of IIP increases the risk of postoperative morbidity, such as acute exacerbation

(AE) of IIP, pneumonia, bronchopleural fistula, and respiratory failure [1–3, 10]. The largest study of the surgical outcome of patients with lung cancer and IIP was conducted by the Japanese Association for Chest Surgery [10]. This study, which included 1763 patients, reported a 30-day mortality of 2.6% and an AE rate of 9.3%. The following seven predictors of AE were reported within 30 days after surgery: surgical procedure, gender, history of exacerbation, preoperative steroid use, serum KL-6 levels, IP pattern on CT, and percent predicted vital capacity. Sato reported a simple risk score (JACS score) [13] using these data. In our study, the JACS score was useful for predicting the short-term mortality after surgery. Although many useful reports have been published, the investigable factors depend on the preoperative examination of lung cancer. The factors that are not common as preoperative examination are not usually evaluated even if it was reported to be important factor on the estimation severity of IIPs. As such, the information including desaturation on exercise, %DLCO, and PH evaluated by echocardiography tend to be missing.

In the long term, the predictors of the prognosis of lung cancer patients with IIP are the cancer stage and natural history of IIP. Features associated with an increased risk of mortality in idiopathic pulmonary fibrosis are a %DLCO < 40% of the predicted value, desaturation of < 88% during 6-minute walk test, extent of honeycombing on high-resolution CT, and PH [4]. PH is the most important factor that has been detected in many reports [16, 17], but it is rarely evaluated before lung cancer surgery. Detecting the effect PH by CT would be very meaningful, as CT in the inspiration phase is required before lung cancer surgery.

The dimensions of MPA and the PA–Ao ratio on CT were reported to be predictors of the outcome in COPD patients [6, 7, 18, 19]. However, in the present study, the MPAD and PA–A ratio was not significant predictors among IIP patients in a multivariate analysis. IIP patients are reported to have 1.5- to twofold greater risk of complication by arteriosclerosis than non-IIP patients [20, 21], and the MPAD and PA–Ao ratio may differ substantially among individuals. In our study, the IVC diameter may have indicated the severity of pulmonary fibrosis. However, the IVC dimension is a relatively new factor, it could easily be measured during inspiration on CT. And it is likely less affected by other complications such as arteriosclerosis. The cut-off value in this study was > 21 mm, which was also used in the assessment by echocardiogram [22, 23]. This indicator closely reflected the prognosis after surgery in lung cancer patients with IIP.

This study is limited by its single-center design and retrospective nature. As such, the details of the operative procedures may vary between institutes, and this limits the generalizability of our findings. Another limitation involves the radiological evaluation, as there was some controversy

between the observers in the radiological evaluation of the type of IIP and the vascular dimensions.

However, despite these limitations, we conclude that enlargement of the IVC was a significant predictor of the 90-day and 2-year mortality among IIP patients. Measuring the IVC by CT is expected to be simple and useful for these patients.

Compliance with ethical standards

Conflict of interest None declared.

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