Association between F-18 fluorodeoxyglucose uptake of noncancerous lung area and acute exacerbation of interstitial pneumonia in patients with lung cancer after resection

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ABSTRACT

Background: Idiopathic pulmonary fibrosis is defined as a specific form of progressive fibrosing interstitial pneumonia. Postoperative acute exacerbation is considered a lethal comorbidity for patients with lung cancer, particularly when it is accompanied with idiopathic pulmonary fibrosis. Thus, pretherapeutic risk stratification for acute exacerbation has been anticipated. In this study, we aimed to investigate whether the maximum standardized uptake value of F-18 fluorodeoxyglucose is useful for assessing the postoperative risk of acute exacerbation and severe respiratory adverse events in patients with lung cancer after surgical resection.

Methods: A total of 822 patients with lung cancer who underwent preoperative high-resolution computed tomography, fluorodeoxyglucose-positron emission tomography/computed tomography, and pulmonary resection between July 2012 and July 2018 were assessed. Maximum standardized uptake value of the main tumor and that of the noncancerous lung area were measured using a 3-dimensional workstation. Multivariable analyses for acute exacerbation and severe respiratory adverse events were performed using the logistic regression model.

Results: Among all patients, 120 (14.6%) had idiopathic pulmonary fibrosis findings on high-resolution computed tomography whereas severe respiratory adverse events were observed in 35 (4.2%) patients, including those with acute exacerbation ($n = 15$, 1.8%). Maximum standardized uptake value of the main tumor and that of the noncancerous lung area were independently associated with both acute exacerbation and severe respiratory adverse events on multivariable analysis, both in all patients and in the 120 patients with idiopathic pulmonary fibrosis. Risk stratification analysis showed that 19.0% and 30.2% of patients who were positive for idiopathic pulmonary fibrosis on high-resolution computed tomography and with a maximum standardized uptake value of the main tumor and that of the noncancerous lung area 1.69 or greater (the optimal cutoff value relevant to acute exacerbation) experienced acute exacerbation and severe respiratory adverse events, respectively.

Conclusions: Maximum standardized uptake value of the main tumor and that of the noncancerous lung area were independently associated with the incidence of postoperative acute exacerbation and severe respiratory adverse events in patients with lung cancer. (J Thorac Cardiovasc Surg 2020;159:1111-8)

Measurement of the SUVmax of noncancerous lung area using a 3-dimensional workstation.

Central Message

Maximum standardized uptake value of noncancerous lung area is significantly associated with the incidence of AE of interstitial pneumonia in patients after lung cancer surgery.

Perspective

This study aims to investigate whether SUVmax of F-18 FDG can be used to assess the risk of postoperative AE of IP in patients with lung cancer after surgical resection. Clinico-surgical variables, including metabolic metrics on FDG-PET, are expected to be useful for the determination of appropriate treatment strategies for patients with lung cancer with IP.

See Commentary on page 1119.

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Abbreviations and Acronyms

AE	= acute exacerbation
CT	= computed tomography
FDG	= fluorodeoxyglucose
IP	= interstitial pneumonia
IPF	= idiopathic pulmonary fibrosis
NCA	= noncancerous lung area
PET	= positron emission tomography
ROC	= receiver operating characteristic
SRAE	= severe respiratory adverse event
SUVmax	= maximum standardized uptake value
UIP	= usual interstitial pneumonitis
%VC	= percentage vital capacity

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The incidence of lung cancer in patients with interstitial pneumonia (IP), most of which is idiopathic pulmonary fibrosis (IPF), is higher than in the general population, and relative risks were reported to be between 7% and 14%.¹ In patients with IPF with lung cancer, postoperative acute exacerbation (AE) is considered a lethal comorbidity with a high mortality rate of 30% to 100%.^{1,2} A recent report of a multicenter cohort study in Japan demonstrated that postoperative AE occurred in 0.5% of all surgical cases of lung cancer.³ In addition, the prevalence of IPF has been found to increase considerably with age.⁴ Therefore, it is important to assess the postoperative risk of AE; however, there is little consensus about which criteria are the most appropriate to identify patients at high risk of AE after surgical resection for lung cancer.

Recent studies identified a metabolic shift in patients with IPF, with increased glycolysis, particularly in their fibroblasts.⁵⁻⁷ The cellular mechanism underlying increased F-18 fluorodeoxyglucose (FDG) accumulation in malignant tumors is associated with a higher rate of glucose transport across the cell membrane.⁸ FDG-positron emission tomography (FDG-PET) contributes to the staging, qualitative diagnosis, and assessment of the therapeutic effects of treatments for lung cancer management.^{9,10} FDG-PET signals were also found to be consistently increased and measurable in some patients with IPF.¹¹ PET signals were increased in the area of honeycombing, in which these fibrosis regions may be

active.¹² Nobashi and colleagues¹¹ showed that increased F-18 FDG uptake in the lung parenchyma was associated with poor survival in patients with IP. Flechsig and colleagues¹³ also showed that F-18 FDG-PET/computed tomography (CT) was able to detect patients at high risk for progressive IPs. These findings suggest that F-18 FDG uptake is likely to be associated with the severity of the fibrotic process, and there are common molecular mechanisms that causes DNA damage in both cancer and IPF.^{14,15} We speculated that the incidence of postoperative AE may be relevant to preoperative FDG-PET signals in the noncancerous lung areas of patients with lung cancer, particularly in those with accompanying IPF. Therefore, in this study we aimed to investigate whether FDG-PET/CT can be used to assess the risk of postoperative AE and severe respiratory adverse events (SRAEs) in patients who underwent surgical resection for primary lung cancer (Video 1 and Figure 1).

PATIENTS AND METHODS**Patients**

We identified 822 patients with lung cancer who underwent preoperative FDG-PET/CT in a designated facility for this study and underwent subsequent pulmonary resection between July 2012 and July 2018 (Figure 2). We reviewed the patients' clinical records, including age, sex, smoking history, CT and FDG-PET/CT imaging findings, results of pulmonary function tests, surgical records, and postoperative adverse events. Postoperative adverse events were evaluated on the basis of the Clavian-Dindo classification.¹⁶ IPF was diagnosed in accordance with the American Thoracic Society/European Respiratory Society/The Japanese Respiratory Society/Latin American Thoracic Association IPF criteria on high-resolution CT (HRCT).¹⁷ Radiologic findings (1: usual interstitial pneumonitis [UIP]; 2: probable UIP; 3: non-UIP, including

VIDEO 1. Flow chart of the current study for the purpose of identifying factors associated with acute exacerbation (AE) of interstitial pneumonia after lung cancer surgery and the way of measuring both Tumor-SUVmax and NCA-SUVmax. PET, Positron emission tomography; CT, computed tomography; DICOM, digital imaging and communications in medicine; 3D, 3-dimensional; SUVmax, maximum standardized uptake value; IPF, idiopathic pulmonary fibrosis; NCA, noncancerous lung area; Post-op, postoperative. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)31659-9/fulltext](https://www.jtcvs.org/article/S0022-5223(19)31659-9/fulltext).

FIGURE 1. Overview of the current study for the purpose of identifying factors associated with AE of interstitial pneumonia after lung cancer surgery. PET, Positron emission tomography; CT, computed tomography; DICOM, digital imaging and communications in medicine; 3D, 3-dimensional; SUVmax, maximum standardized uptake value; IPF, idiopathic pulmonary fibrosis; NCA, noncancerous lung area; Post-op, postoperative.

indeterminate for UIP and cases without any IP findings) were confirmed by 2 respiratory physicians (S.A. and A.Y.), and a radiologist (R.M.). Patients were excluded if (1) preoperative FDG-PET/CT was not performed; (2) preoperative FDG-PET/CT was performed in other facilities; or (3) the maximum standardized uptake value (SUVmax) was not measurable on a 3-dimensional workstation (Figure 2). Data collection and analyses were approved, and the need to obtain written informed consent from each patient was waived by the Institutional Review Board of Tokyo Medical University.

Definition of Acute Exacerbation and Severe Respiratory Adverse Events

AE is defined by the following clinical characteristics: (1) unexplained worsening or development of dyspnea within 30 days; (2) intensified dyspnea; (3) increase in the interstitial shadow on chest radiography and chest CT; (4) decrease in arterial oxygen tension of more than 10 mm Hg under similar conditions; (5) no evidence of pulmonary infection; and (6) exclusion of alternative causes, such as cardiac failure, pulmonary embolism, or other identifiable causes of lung injury.^{17,18} SRAEs are defined as grade IIIa or more in the respiratory complications on the Clavian-Dindo classification and represent comprehensive and severe postoperative respiratory

adverse events, including AEs, bacterial pneumonia, empyema, and bronchial fistula.¹⁶

Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Assessment

All FDG-PET/CT data obtained from the designated facility were used in this study. Patients with blood glucose values of more than 150 mg/dL during PET/CT image acquisition were excluded. All patients were assessed using a Biograph PET/CT scanner (Siemens Healthcare, Erlangen, Germany). Unenhanced CT images of sections 2 to 4 mm thick that matched the PET images were acquired from the head to the pelvic floor of each patient using a standard protocol. Immediately after CT, PET covering the identical axial field of view for 2 to 4 minutes per table position depending on the condition of the patient and the scanner performance was conducted. The SUVmax was established by drawing regions of interests (ROIs) around the primary tumor on attenuation-corrected FDG-PET images and calculated using the software integrated within the PET/CT scanner based on the following formula: $SUV_{max} = C(MBq/kg) / [ID(MBq) / (w(kg))]$ in which C is defined as the maximal activity at a single pixel within the tissue designated by the ROI, and ID is defined as the injected dose/kg of body weight (w).

FIGURE 2. Flow chart of the selection of patients analyzed in this study. *FDG*, Fluorodeoxyglucose; *PET*, positron emission tomography; *CT*, computed tomography; *SUVmax*, maximum standardized uptake value; *3D*, 3-dimensional.

Measurement of Maximum Standardized Uptake Value of the Main Tumor and Noncancerous Lung Area

The preoperative FDG-PET/CT images of each patient were transferred to the Synapse Vincent 3D workstation (Fujifilm Corporation, Tokyo, Japan). In every case, both SUVmax of the main tumor (Tumor-SUVmax) and the noncancerous lung area (NCA-SUVmax) were measured. ROIs were drawn, and maximum FDG uptake in the noncancerous lung area was confirmed on HRCT and measured as NCA-SUVmax. ROIs were also measured at least 1 cm away from the tumor and other organs, such as the ribs, heart, liver, and chest wall. Uptake from the liver and mediastinum was manually excluded. [Figure 3](#) shows representative cases of UIP, probable UIP, and non-UIP.

Statistical Analysis

Univariable and multivariable logistic regression analyses were performed to identify predictors for AE and SRAEs using the following factors: sex, age, smoking index, tumor size, degree of lymph node dissection (mediastinal vs hilar or none), number of resected lung segments (wedge resection was calculated as 0.5), % vital capacity (%VC), Tumor-SUVmax, NCA-SUVmax, and IPF on CT (yes vs no). A backward stepwise selection method was used to build logistic regression models. The receiver operating characteristic (ROC) area under the curve of significant factors associated with AE and SRAEs was measured, and each cutoff level on the ROC curves for significant parameters associated with AE and SRAEs represents a sensitivity/specificity pair corresponding to a particular decision threshold. Categorical comparison was performed using the Pearson chi-square test for discrete data and the Mann-Whitney *U* test or 1-way analysis of variance for continuous data. All tests were 2-sided. The SPSS statistical software package (version 25.0; DDR3 RDIMM, SPSS Inc, Chicago, Ill) was used for statistical analyses.

RESULTS

The characteristics of the patients are listed in [Table 1](#). The cohort in this study consisted of 460 men and 362 women (mean age, 67.9 ± 10.1 years; range, 23-87 years). Of these, 120 (14.6%) had IPF findings on HRCT. SRAEs were observed in 35 patients (4.2%), including those with AE ($n = 15$, 1.8%). The detailed characteristics of patients with AE are summarized in [Table E1](#).

Univariable and multivariable analyses were performed to identify clinico-surgical factors associated with the incidence of AE and SRAEs. Age, sex, %VC, NCA-SUVmax, smoking index, and IPF on CT were associated with AE on univariable analysis (data not shown), whereas NCA-SUVmax ($P = .002$) and the presence of IPF ($P = .002$) were independent factors on multivariable analysis for AE ([Table 2](#)). Sex, age, tumor size, %VC, Tumor-SUVmax, NCA-SUVmax, smoking index, the number of resected segments, and the presence of IPF were significantly associated with SRAEs on univariable analysis (data not shown), whereas multivariable analysis demonstrated that age ($P = .022$), Tumor-SUVmax ($P = .033$), NCA-SUVmax ($P = .005$), the number of resected segments ($P = .046$), and the presence of IPF ($P = .002$) were independent significant factors for SRAEs ([Table 2](#)). We performed univariable and multivariable analyses to investigate factors associated with the incidence of AE and SRAEs, particularly in the 120 patients with IPF. Only NCA-SUVmax was associated with both AE and SRAEs on univariable analysis (data not shown), whereas NCA-SUVmax was also found to be an independent factor on multivariable analysis for both AE ($P = .004$) and SRAEs ($P = .002$) on multivariable analysis ([Table 3](#)).

Quantitative analyses of Tumor-SUVmax and NCA-SUVmax are shown in [Figure 4](#). In terms of Tumor-SUVmax, patients with IPF demonstrated higher values than non-IPF patients ($P < .001$; [Figure 4, A](#)). No statistical difference was observed between patients with UIP and those with probable UIP, whereas values of patients with probable UIP were higher than those of patients with non-UIP ($P < .001$; [Figure 4, B](#)). Values of patients presenting AE were higher than those of patients without AE ($P < .001$; [Figure 4, C](#)), whereas values of patients who developed SRAE were higher than those of patients without SRAEs ($P < .001$; [Figure 4, D](#)). NCA-SUVmax values of

FIGURE 3. Representative images of the evaluation results of SUVs in noncancerous lung areas obtained using a 3-dimensional workstation. A, UIP. B, Probable UIP. C, Non-UIP. SUV, Standardized uptake value.

patients with IPF were higher than those of patients with non-IPF ($P < .001$; Figure 4, E). Values of patients with UIP were higher than those of patients with probable UIP ($P < .001$; Figure 4, F). NCA-SUVmax values of patients who developed AE were higher than those of patients without AE ($P < .001$; Figure 4, G), whereas values of patients who developed SRAE were higher than those of patients without SRAEs ($P < .001$; Figure 4, H).

To investigate the effect of NCA-SUVmax on the incidence of AE and SRAEs, we calculated the ROC curves for AE and SRAEs. The area under the curve and the optimal cutoff value relevant to AE were 0.90 and 1.69, respectively (Figure E1, A), and those relevant to SRAEs were 0.77 and 1.55, respectively (Figure E1, B). Table 4 shows a summary of the risk stratification to identify patients presenting AE and SRAEs according to NCA-SUVmax and chest CT findings. The list shows that 19.0% and 30.2% of patients with positive IPF and NCA-SUV max 1.69 or greater developed AE and SRAEs, respectively.

DISCUSSION

The 30-day mortality rate after pulmonary resection for patients with lung cancer was reported to be 0.33% in a Japanese large-scale database.^{1,19,20} AE is characterized by diffuse and rapid alveolar damage superimposed on a background of IP and is the most frequent cause of death of these patients, accounting for 43.9% of cases of 30-day mortality.² In the present study, the in-hospital mortality rate for patients with AE of IP after surgery was 60% (9/15 patients). A pretherapeutic risk stratification system for AE has long been anticipated. Sato and colleagues² reported

a predictive score of AE with IP after pulmonary surgery for lung cancer that was established using 7 predictors, namely, history of AE, surgical procedures (wedge resection or more extensive procedures), CT findings, preoperative steroid use, sex, serum KL-6 level, and %VC, based on a total of 1763 Japanese patients with lung cancer and concomitant interstitial lung disease, and the high-risk group demonstrated that the predicted probability of the incidence of AE was more than 25%. Kumar and colleagues²¹ reported that surgical procedure, lower preoperative diffusion capacity for carbon monoxide (DL_{CO}), and a higher preoperative composite physiologic index calculated with $FEV_{1.0}$, forced VC, and DL_{CO} were associated with postoperative acute respiratory distress syndrome in patients with lung cancer and IPF. Nevertheless, the underlying pathophysiology leading to the acceleration of the onset of AE remains unclear. Given that there were patients without UIP findings on HRCT who presented with postoperative AE in the current series and published reports, other supplementary or alternative imaging modalities associated with the incidence of AE are warranted.

F-18 FDG-PET/CT is the standard assessment modality for patients with lung cancer and has a large impact on patient management, initial staging, therapeutic response assessment, and prediction of survival outcomes.^{10,22} Recently, it has been reported that the role of PET/CT extends beyond its clinical use and can be used not only for oncologic assessment but also for evaluation of severity of IP.²³ In animal studies using a bleomycin-induced pulmonary fibrotic murine model, F-18 FDG uptake was associated with the fibrotic process.^{24,25} Bondue and colleagues²⁴ reported that F-18 FDG uptake increased

TABLE 1. Patient background

Variable	n = 822 (%)
Age (mean ± SD)	67.9 ± 10.1
Sex	
Men	460 (56.0)
Women	362 (44.0)
Smoking	
Yes	506 (61.6)
No	316 (38.4)
Brinkmann Index (mean ± SD)	578.4 ± 707.4
FEV _{1.0} %	
≥70	545 (66.3)
<70	277 (33.7)
%VC	
≥80	804 (97.8)
<80	18 (2.2)
Tumor-SUVmax (mean ± SD)	9.75 ± 9.20
IPF on CT	120 (14.6)
NCA-SUVmax (mean ± SD)	1.25 ± 0.53
Tumor location	
Right upper lobe	266 (32.4)
Right middle lobe	51 (6.2)
Right lower lobe	177 (21.5)
Left upper lobe	197 (24.0)
Left lower lobe	131 (15.9)
Procedure	
Wedge resection	39 (4.7)
Segmentectomy	45 (5.5)
Lobectomy	727 (88.5)
Pneumonectomy	11 (1.3)
Lymph node dissection	
None	45 (5.5)
Hilar	94 (11.4)
Mediastinal	683 (83.1)
Lung cancer histology	
Adenocarcinoma	641 (78.0)
Squamous cell carcinoma	108 (13.1)
Others	73 (8.9)
Duration of surgery, min (mean ± SD)	211.5 ± 68.1
Bleeding, mL (mean ± SD)	109.3 ± 359.4
Pathological stage	
0	9 (1.1)
I	545 (66.3)
II	143 (17.4)
III	118 (14.4)
IV	7 (0.8)
SRAE	
AE	15 (1.8)
Severe pneumonia	9 (1.1)
Empyema	7 (0.8)
Bronchopleural fistula	4 (0.5)

SD, Standard deviation; FEV, forced expiratory volume; VC, vital capacity; IPF, idiopathic pulmonary fibrosis; CT, computed tomography; NCA, noncancerous lung area; SUV, standardized uptake value; SRAE, severe respiratory adverse event; AE, acute exacerbation.

TABLE 2. Multivariable analysis for factors associated with acute exacerbation and severe respiratory adverse events after surgery (n = 822)

Variables	HR (95% CI)	P value
Multivariable analysis for AE		
NCA-SUVmax	2.301 (1.365-3.879)	.002
IPF on CT (yes/no)	8.982 (2.543-35.97)	.002
Multivariable analysis for SRAEs		
Age	1.065 (1.009-1.124)	.022
Tumor-SUVmax	1.045 (1.004-1.089)	.033
NCA-SUVmax	1.926 (1.262-2.942)	.005
No. of resected segments	1.258 (1.004-1.576)	.046
IPF on CT (yes/no)	3.710 (1.592-8.643)	.002

HR, Hazard ratio; CI, confidence interval; AE, acute exacerbation; NCA, noncancerous lung area; SUV, standardized uptake value; IPF, idiopathic pulmonary fibrosis; CT, computed tomography; SRAE, severe respiratory adverse event.

together with the early recruitment of leukocytes during the inflammatory phase and then persisted in the later fibrotic phase in their murine model of lung fibrosis. Recent clinical studies reported that high uptake values of F-18 FDG in the lung parenchyma of patients with IPF were associated with high mortality.^{13,23} In the present study, multivariable analysis of the entire population and the 120 patients with IPF demonstrated that NCA-SUVmax was independently associated with postoperative AE, and the incidences of AE and SRAEs were 19.0% and 30.2%, respectively, for patients with IPF and NCA-SUVmax 1.69 or greater. All 12 patients with UIP who developed postoperative AE showed increased NCA-SUVmax values of greater than 1.69, whereas IPF categorization on CT showed a stronger association with NCA-SUVmax than Tumor-SUVmax. These results suggest that lung cancers arising from metabolically active fibrotic parenchyma have the potential of high-grade malignancy, and that these patients need to be considered as being at high risk for life-threatening complications. The integration of CT evaluation of UIP and NCA-SUVmax with PET/CT is more helpful in estimating the risk of postoperative AE than the individual use of either modality and may enable patients with UIP and increased NCA-SUVmax to receive perioperative

TABLE 3. Multivariable analysis for factors associated with acute exacerbation and severe respiratory adverse events after surgery in patients with idiopathic pulmonary fibrosis (n = 120)

Variables	HR (95% CI)	P value
Multivariable analysis for AE		
NCA-SUVmax	2.952 (1.406-6.197)	.004
Multivariable analysis for SRAEs		
NCA-SUVmax	2.643 (1.335-5.234)	.002

HR, Hazard ratio; CI, confidence interval; AE, acute exacerbation; NCA, noncancerous lung area; SUV, standardized uptake value; SRAE, severe respiratory adverse event.

FIGURE 4. Comparison of maximum standardized uptake values between lung tumors (*Tumor-SUVmax*) and noncancerous lung areas (*NCA-SUVmax*). A, Patients with IPF demonstrated significantly higher *Tumor-SUVmax* values than those in patients without IPF. B, There was a significant difference in *Tumor-SUVmax* values between patients with probable UIP and those without UIP, but no difference between patients with UIP and those with probable UIP. C, *Tumor-SUVmax* values of patients presenting AE was higher than those of patients without AE. D, *Tumor-SUVmax* values of patients presenting SRAEs were higher than those of patients without SRAEs. E, *NCA-SUVmax* values of patients with IPF were higher than those of patients without IPF. F, *NCA-SUVmax* values in patients with UIP were significantly higher than those in patients with probable UIP. G, *NCA-SUVmax* values of patients presenting AE were higher than those of patients without AE. H, *NCA-SUVmax* values of patients presenting SRAE were higher than those of patients without SRAEs. *IPF*, Idiopathic pulmonary fibrosis; *UIP*, usual interstitial pneumonitis; *AE*, acute exacerbation; *SRAE*, severe respiratory adverse event.

prophylactic treatments, such as corticosteroids, sivelestat, nintedanib, and pirfenidone, or alternative treatments according to the comorbidity status of the patient. Recently, much attention has been focused on pretherapeutic identification for immune therapy-induced lung injury and

radiation-induced pneumonitis before its physiologic manifestation. Of the 3 patients with IPF who underwent radiotherapy in our hospital in 2018, 2 patients with increased *NCA-SUVmax* values of greater than 2 developed AE (data not shown). On the other hand, the 2

TABLE 4. Risk stratification to identify acute exacerbations and severe respiratory adverse events after surgery

Variables	No. of patients	No. of AEs	Proportion of AEs (%)	No. of SRAEs	Proportion of SRAEs (%)
All patients	822	15	1.8	35	4.3
Patients with IPF	120	12	10.0	21	17.5
Patient with <i>NCA-SUVmax</i> ≥ 1.55	129	12	9.3	22	17.1
Patient with <i>NCA-SUVmax</i> ≥ 1.69	83	12	14.5	19	22.9
Patients with IPF + <i>NCA-SUV max</i> ≥ 1.55	80	12	15.0	20	25.0
Patients with IPF + <i>NCA-SUV max</i> ≥ 1.69	63	12	19.0	19	30.2

AE, Acute exacerbation; SRAE, severe respiratory adverse events; IPF, idiopathic pulmonary fibrosis; NCA, noncancerous lung area; SUV, standardized uptake value.

patients with NCA-SUVmax values below the cutoff who received programmed death-1 inhibitors did not develop AE (data not shown). The importance of measuring Tumor-SUVmax and NCA-SUVmax separately needs to be confirmed by a larger prospective study for the potential practical use of these parameters.

Study Limitations

This study has several limitations. First, the optimal cutoff value of SUVmax that dichotomized the 2 groups is only valid in the present population because of its variability by the number of patients, plasma glucose concentration, and type of scanner. To partly overcome this problem, an anthropomorphic body phantom study to adjust quantitative SUVs should be performed when a multi-institutional observational study is performed. Second, whereas AE-IPF is clinically important, its rareness makes it difficult to study in a large number of patients, causing inadequate statistical power that might not ensure a realistic chance of obtaining significant results. It is also occasionally difficult to accurately diagnose this condition from CT findings in the presence of an AE. Third, the diagnostic approach for IPF in this study is based only on HRCT features. We did not always perform lung cancer surgery together with surgical lung biopsy of different lobes with the intention to diagnosing IPF.

CONCLUSIONS

NCA-SUVmax was independently associated with the incidence of AE and SRAEs on multivariable analysis in the entire population and in patients with IPF. FDG-PET/CT imaging of patients with lung cancer contributes to daily clinical practice not only for the assessment of malignant tumor grade but also for the identification of individuals at high risk of postoperative AE and will assist in complex clinical decision-making.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: acute exacerbation, idiopathic pulmonary fibrosis, lung cancer, SUVmax

FIGURE E1. The receiver operating characteristic areas under the curves for maximum standardized uptake values (*SUVmax*) in noncancerous lung area used to identify the probability of AE (A) and severe respiratory adverse events (B) after surgery. *AUC*, Area under the curve.

TABLE E1. Background of patients with acute exacerbation of idiopathic pulmonary fibrosis

Patient	Sex	Age (y)	Administration of preoperative PSL	Classification of IP	KL-6 level (U/mL)	NCA-SUV max	Tumor-SUVmax	%VC (%)	FEV _{1.0} (%)	Surgical procedure (degree of lymph node dissection)	Histology	Pathological stage	Outcome*
1	F	81	No	Probable UIP	—	2.07	4.80	108.1	75.2	Lobectomy (Mediastinal)	Adenocarcinoma	IIA	Alive
2	M	65	No	UIP	4783	2.95	19.1	83.4	81.3	Wedge resection (None)	Adenocarcinoma	IB	Alive
3	M	79	No	Probable UIP	929	2.90	21.8	108.2	60.0	Lobectomy (Hilar)	Squamous	IB	Deceased
4	M	72	Yes	Probable UIP	—	2.94	22.8	113.3	76.8	Lobectomy (Mediastinal)	Adenocarcinoma	IIIA	Alive
5	M	71	No	Non-UIP	—	1.25	16.3	109.5	60.9	Pneumonectomy (Mediastinal)	Squamous	IIIB	Deceased
6	M	78	No	UIP	965	3.09	22.8	87.9	70.7	Lobectomy (Mediastinal)	Pleomorphic	IIB	Deceased
7	M	66	No	UIP	351	1.90	9.40	97.7	43.0	Wedge resection (None)	Adenocarcinoma	IIA	Alive
8	M	73	No	UIP	1281	3.28	15.7	60.1	93.0	Lobectomy (Mediastinal)	Squamous	IIIA	Deceased
9	M	60	No	UIP	4636	2.65	15.1	97.3	79.1	Lobectomy (Hilar)	Squamous	IA	Deceased
10	M	76	No	Probable UIP	—	1.86	15.0	127.6	74.6	Lobectomy (Mediastinal)	Squamous	IIA	Deceased
11	M	73	No	Non-UIP	—	1.24	20.7	109.9	78.0	Lobectomy (Mediastinal)	Pleomorphic	IIA	Deceased
12	M	79	No	UIP	681	1.70	7.56	65.1	73.6	Lobectomy (Mediastinal)	Squamous	IIA	Deceased
13	M	74	Yes	UIP	934	2.92	6.45	84.4	69.0	Lobectomy (Mediastinal)	SCLC	IIIA	Alive
14	M	74	No	Non-UIP	—	1.23	9.87	100	76.9	Lobectomy (Mediastinal)	Adenocarcinoma	IB	Alive
15	M	78	No	Probable UIP	612	2.02	6.79	110.7	72.0	Lobectomy (Mediastinal)	Adenosquamous	IB	Deceased

PSL, Prednisolone; IP, interstitial pneumonia; KL-6, sialylated carbohydrate antigen Krebs von den Lungen-6; NCA, noncancerous lung area; SUVmax, maximum standardized uptake value; VC, vital capacity; FEV, forced expiratory volume; UIP, usual interstitial pneumonitis; SCLC, small cell lung cancer. *Cause of death described as due to acute exacerbation.