Clinical impact of SUV$_{max}$ of interstitial lesions in lung cancer patients with interstitial lung disease who underwent pulmonary resection

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Background: Acute exacerbation of interstitial lung disease often causes fatal respiratory deterioration in lung cancer patients with interstitial lung disease. Here, we examined whether the maximum standardized uptake value of a contralateral interstitial lesion was a predictive factor of acute exacerbation of interstitial lung disease within 30 days postoperatively in lung cancer patients with interstitial lung disease who underwent pulmonary resection.

Methods: Overall, 117 consecutive lung cancer patients with interstitial lung disease who underwent pulmonary resection between August 2010 and April 2019 at the Kumamoto University Hospital were retrospectively analysed for the association between the maximum standardized uptake value of the contralateral interstitial lesions and interstitial lung disease parameters.

Results: The median maximum standardized uptake value of contralateral interstitial lesions was 1.61, which was regarded as the cut-off point predictive of the incidence of acute exacerbation of interstitial lung disease. Eight patients developed postoperative acute exacerbation of interstitial lung disease. There was no significant association between the maximum standardized uptake value of the contralateral interstitial lesions and postoperative acute exacerbation of interstitial lung disease. The maximum standardized uptake value was weakly but significantly associated with lactate dehydrogenase levels (r=0.211, P=0.022), Krebs von den Lungen-6 (r=0.208, P=0.028), and % diffusing capacity for carbon monoxide (r=-0.290, P=0.002). Moreover, seven patients developed acute exacerbation of the interstitial lung disease during the clinical course after 30 postoperative days, and the incidence rate of acute exacerbation of interstitial lung disease was significantly higher in the high maximum standardized uptake value group (≥1.61) than in the low maximum standardised uptake value group (<1.61) (12.7% *vs.* 0%, P=0.002, Gray's test).

Conclusions: Maximum standardized uptake value was not a predictor of postoperative acute exacerbation of interstitial lung disease in lung cancer patients with interstitial lung disease after pulmonary resection, but could be a predictive tool of an association with interstitial lung disease severity and activity markers.

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Introduction

Lung cancer (LC) is a common complication in patients with interstitial lung disease (ILD), with an incidence ranging from 13% to 20.4% (1-3). Early-stage LC patients with existing ILD may undergo pulmonary resection in case of preserved pulmonary function. Acute exacerbation of ILD (AE-ILD) can often lead to acute respiratory failure, resulting in a life-threatening complication in LC patients with ILD who underwent surgery. In previous studies, the incidence and mortality rate of postoperative AE-ILD (pAE-ILD) are reported as 7.4–22.9% and 33.3–100%, respectively (4-6). Thus, the prediction of pAE-ILD is important in LC patients with ILD undergoing pulmonary resection to guide the surgical management and avoid this complication.

Numerous studies have reported the predictive factors for pAE-ILD, such as elevated lactate dehydrogenase (LDH) level, elevated Krebs von den Lungen-6 (KL-6), decreased % vital capacity (VC), and fibrosis grade on high-resolution computed tomography in LC patients with ILD (5,7,8). Recently, Sato *et al.* reported a risk scoring system for the prediction of pAE-ILD in LC patients with ILD who underwent surgery, which consists of seven clinical factors: AE history, surgical procedure, usual interstitial pneumonia (UIP) pattern on CT, male sex, use of corticosteroid prior to surgery, serum KL-6 level, and %VC (4,9). Moreover, in a previous study, we found that the maximum standardized uptake value (SUV$_{max}$) of contralateral interstitial lesions on fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) images was a significant predictive factor for the development of AE-ILD in LC patients with ILD who received chemotherapy (10). However, it is unclear whether the SUV$_{max}$ of contralateral interstitial lesions predicts pAE-ILD in LC patients with ILD who underwent pulmonary resection, as research is limited in this area.

Herein, we examined the correlation between SUV$_{max}$ of the contralateral interstitial lesions and ILD parameters to clarify whether SUV$_{max}$ was a predictive factor for pAE-ILD in LC patients with ILD who underwent pulmonary resection. We present the following article in accordance with the STARD reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-604/rc).

Methods

Patients

We recruited 123 LC consecutive patients with ILD who underwent ^{18}F-FDG PET/CT prior to surgery and surgical pulmonary resection at our institute between August 2010 and April 2019. We excluded one patient who underwent salvage surgery and five patients in whom we were unable to estimate the SUV$_{max}$ since the ^{18}F-FDG PET/CT examination was performed at another institution. The remaining 117 patients were enrolled in this retrospective study which was designed by investigator-initiation (Figure S1). Their baseline demographic and clinical parameters before lung resection were obtained from medical records, and the following parameters being included: age, sex, Eastern Cooperative Oncology Group (ECOG) performance Status (PS) (11), smoking status, medical history of ILD, histology, pathological stage, laboratory test results, pulmonary function, and surgical procedure type. The ILD-Gender-Age-Physiology (GAP) score was calculated based on the following five variables: ILD pattern, sex, age, forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLco) (12). The pathological stage was classified using the eighth edition of the TNM classification. The risk score for predicting the occurrence of AE-ILD after pulmonary resection was calculated based on seven variables: AE history, surgical procedures, UIP pattern on CT finding, male sex, use of corticosteroid prior to surgery, serum KL-6 level, and %VC (9). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional review board of Kumamoto University Hospital (IRB number: 2399) approved this research. The requirement of written informed consent from all patients
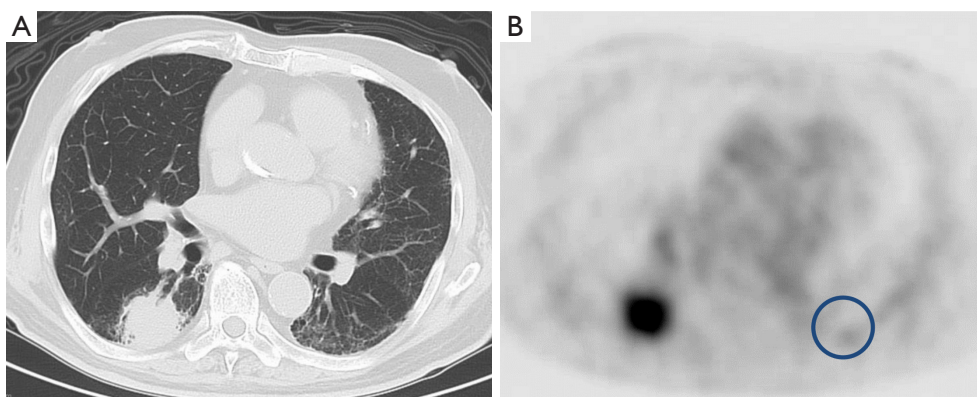
Figure 1 Representative images of CT (A), and matched ^{18}F-FDG PET image (B). Manual placement of a region of interest with a fixed size of approximately 30 mm in diameter in the background lung field of the PET image (solid line) for measurement of SUV$_{max}$ of the contralateral interstitial lesion. CT, computed tomography; ^{18}F-FDG PET, fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography; SUV$_{max}$, maximum standardized uptake value.

was waived due to the retrospective nature of the study.

Diagnosis of ILD and AE-ILD

ILD was diagnosed based on evidence of diffuse parenchymal and interstitial lung abnormalities on chest CT and classified into two groups based on the UIP pattern using the international consensus criteria of the American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association. UIP was identified as the presence of the following CT findings: opacities with honeycombing with/without traction bronchiectasis with subpleural and basal predominance as well as in a heterogeneous distribution (13). AE-ILD was diagnosed, using the consensus statement of the same organizations above when the following clinical criteria were identified: subjective development of dyspnoea within 30 days, progressive hypoxemia due to impaired pulmonary gas exchange, new bilateral alveolar infiltrates regardless of the extent of the segment on CT findings, and the absence of the following conditions: infection, pneumothorax, pulmonary embolism, congestive heart failure, or worsening of lung tumours (14). pAE-ILD was diagnosed when the development of AE-ILD was identified within 30 days postoperatively. ILD and AE-ILD on all CT scans was evaluated by two independent experienced pulmonologists (KA and KS). CT findings were considered concordant when both pulmonologists reached the same result. When they reached different results, CT scans were re-examined, and the final findings were agreed upon by

consensus between the two pulmonologists.

Acquisition and data analysis of ^{18}F-FDG PET/CT imaging

The SUV$_{max}$ of interstitial lesions was measured as explained in our previous study protocol (10). In brief, after fasting for at least 5 h, a whole-body ^{18}F-FDG PET/CT scan was performed in the patients, 60 min after receiving injections of approximately 185–296 MBq of ^{18}F-FDG, using PET/CT scanners (Gemini-GXL or Gemini-TF, Philips Healthcare, Cleveland, OH, USA; Discovery-IQ, GE Healthcare, Milwaukee, WI, USA). The highest ^{18}F-FDG uptake was measured by a circular region-of-interest with a fixed diameter of approximately 30 mm on PET images corresponding to the interstitial lesion region on CT and defined as SUV$_{max}$ (*Figure 1*).

Statistical analysis

The clinical values were compared using Chi-square or Fisher's exact tests and Mann-Whitney U tests. Quantitative variables were described as medians. Pearson's correlation test was used to evaluate the correlation between the two values. The cumulative incidences of pAE-ILD and AE-ILD after 30 postoperative days were calculated using Gray's test to consider the competing risks which prevented the occurrence of death in cases of AE-ILD by other causes, such as cancer-specific death. Two-tailed P value of less than 0.05 was considered statistically significant. Statistical

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Table 1 Patient characteristics

Characteristics	Value (N=117)
Median age, years, (range)	71 (39–86)
Sex (male/female), N (%)	103/14 (88.0/12.0)
ECOG PS (0–1/2), N (%)	114/3 (97.4/2.6)
Smoking status (yes/no), N (%)	112/5 (95.7/4.3)
Histology (Ad/Sq/Sm/other), N (%)	49/47/9/12 (41.9/40.2/7.7/10.3)
PStage (0/I/II/III/IV), N (%)	4/73/17/21/2 (3.4/62.4/14.5/17.9/1.7)
ILD pattern (UIP/non-UIP), N (%)	27/90 (23.1/76.9)
Median LDH, U/L (range)	202.5 (132–350)
Median KL-6[†], U/mL (range)	487.0 (149–717)
Median %FVC, % (range)	95.1 (55.2–136.3)
Median %DLco[‡], % (range)	64.8 (40.6–98.6)
Median ILD-GAP, score[‡] (range)	1.0 (–2–5)
Surgical procedure (lobectomy/segmentectomy/partial resection), N (%)	96/2/19 (82.1/1.7/16.2)
Preoperative steroid use (yes/no), N (%)	9 /108 (7.7/92.3)
Preoperative pirfenidone use (yes/no), N (%)	21/96 (17.9/82.1)
History of AE (yes/no), N (%)	0/117 (0.0/100.0)
Median RS for predicting AE after pulmonary resection[†] (range)	7.0 (0–14)
Median SUV$_{max}$ of contralateral interstitial lesion (range)	1.61 (0.82–3.70)

[†], six patients were not evaluated for KL-6 and RS for predicting AE after pulmonary resection were not evaluated in six patients; [‡], nine patients were not evaluated for %DLco and ILD-GAP score. ECOG PS, Eastern Cooperative Oncology Group Performance Status; Ad, adenocarcinoma; Sq, squamous cell carcinoma; Sm, small cell carcinoma; pStage, pathological stage; ILD, interstitial lung disease; UIP, usual interstitial pneumonia; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; %FVC, percent predicted forced vital capacity; %DLco, percent predicted diffusing capacity for carbon monoxide; GAP, Gender-Age-Physiology; AE, acute exacerbation; RS, risk score; SUV$_{max}$, maximum standard uptake value.

analyses were performed using SPSS (version 27.0; IBM, Armonk, NY, USA) and R statistical software (R Foundation for Statistical Computing, version. 4.0.2).

Results

Patient characteristics

The characteristics of the 117 patients who underwent ^{18}F-FDG PET/CT scans prior to the surgery and lung resection are shown in *Table 1*. The median age of the patients was 71 (range, 39–86) years, and 103 (88.0%) patients were males. The ECOG PS was 0–1 in 114 patients (97.4%) and 112 (95.7%) patients were smokers. In the histological type, adenocarcinoma, squamous cell carcinoma, and small cell carcinoma accounted for 49

(41.9%), 47 (40.2%), and 9 (7.7%) patients, respectively. Most patients (115, 98.3%) were diagnosed with stage 0–III LC. UIP patterns in CT findings were observed in 27 (23.1%), while non-UIP patterns were seen in 90 (76.9%) patients. The median serum LDH and KL-6 levels, %FVC, %DLco, ILD-GAP score, and risk score for predicting AE after pulmonary resection were 202.5 U/L, 487.0 U/mL, 95.1%, 64.8%, 1.0, and 7.0, respectively. Lobectomy type of surgical resection was performed in 96 (82.1%) patients. Among patients with a preoperative history of ILD, by 9 (7.7%) and 21 (17.9%) patients used steroids and pirfenidone, respectively. The median SUV$_{max}$ of the contralateral interstitial lesions was 1.61 (range, 0.82–3.70). The median follow-up time since the lung surgery was 786 days (range, 9–3,315 days).

Table 2 Comparison of clinicopathological factors between the pAE-ILD and non-pAE-ILD groups

Characteristics	Non-pAE-ILD (N=109)	pAE-ILD (N=8)	P value
Median age, years, (range)	71.0 (39–86)	77.5 (66–84)	0.014
Sex (male/female), N (%)	95/14 (87.2/12.8)	8/0 (100.0/0.0)	0.349
ECOG PS (0–1/2), N (%)	106/3 (97.2/2.8)	8/0 (100.0/0.0)	0.807
Smoking status (yes/no), N (%)	104/5 (95.4/4.6)	8/0 (100.0/0.0)	0.697
Histology (NSCLC/SCLC), N (%)	100/9 (91.7/8.3)	8/0 (100.0/0.0)	0.516
pStage (0–II/III–IV), N (%)	89/20 (81.7/18.3)	5/3 (62.5/37.5)	0.189
ILD (UIP/non-UIP), N (%)	22/87 (20.2/79.8)	5/3 (62.5/37.5)	0.016
Median LDH, U/L (range)	203.0 (132–350)	151.0 (149–228)	0.059
Median KL-6[†], U/mL (range)	461.0 (149–1,855)	680.5 (409–2,019)	0.080
Median %FVC, % (range)	96.2 (55.2–136.3)	90.1 (72.9–125.2)	0.315
Median %DLco[‡], % (range)	64.8 (40.6–98.6)	75.8 (48.0–104.1)	0.897
ILD-GAP score[‡] (<1/≥1), N (%)	19/81 (19.0/81.0)	0/8 (0.0/100.0)	0.201
Surgical producer (lobectomy/limited surgery), N (%)	88/21 (80.7/19.3)	8/0 (100.0/0.0)	0.194
Preoperative steroid use (yes/no), N (%)	9/100 (8.3/91.7)	0/8 (0.0/100.0)	0.516
Preoperative pirfenidone use (yes/no), N (%)	19/90 (17.4/82.6)	2/6 (25.0/75.0)	0.438
RS for predicting AE after pulmonary resection[†] (0–10/11–14), N (%)	85/18 (82.5/17.5)	3/5 (37.5/62.5)	0.009
Median SUV_{max} of contralateral interstitial lesion (range)	1.61 (0.82–3.70)	1.62 (1.40–2.05)	0.944

[‡], nine patients were not evaluated for %DLco and ILD-GAP score; [†], six patients were not evaluated for KL-6 and RS for predicting AE after pulmonary resection. AE, acute exacerbation; ILD, interstitial lung disease; LDH, lactate dehydrogenase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; pStage, pathological stage; UIP, usual interstitial pneumonia; LDH, lactate dehydrogenase; KL-6, Krebs von den Lungen-6; %FVC, percent predicted forced vital capacity; %DLco, percent predicted diffusing capacity for carbon monoxide; GAP, Gender-Age-Physiology; RS, risk score; SUV_{max}, maximum standard uptake value.

Correlation between the SUVmax of contralateral interstitial lesions and pAE-ILD

The pAE-ILD occurred in eight patients, among whom four patients died. The incidence and mortality rate of pAE-ILD were 6.8% and 50%, respectively.

Table 2 shows the absence of a significant association between SUV_{max} of contralateral interstitial lesions and pAE-ILD, while the proportion of UIP pattern, high level of KL-6, and high-risk score for predicting AE-ILD after pulmonary resection in the AE-ILD group were significantly higher than those in the non-AE-ILD group. Additionally, there was no significant association between the SUV_{max} of ipsilateral interstitial lesions and pAE-ILD (Figure S2).

We defined the median SUV_{max} of contralateral interstitial lesions (1.61) as the cut-off value and divided the patients into high SUV_{max} (≥1.61) and low SUV_{max} (<1.61)

groups. No significant differences in the incidence of pAE-ILD were observed between those two groups (6.8 *vs.* 6.9%; P=0.978, Gray's test; *Figure 2*).

Correlation between SUVmax of contralateral interstitial lesions and severity and activity of ILD

There were significant positive correlations between SUV_{max} of contralateral interstitial lesions and LDH (r=0.211, P=0.022), KL-6 (r=0.208, P=0.028), and negative correlation between SUV_{max} and %DLco (r=−0.290, P=0.002), except for %FVC (*Figure 3*). The median SUV_{max} in the UIP pattern group was significantly higher than that in the non-UIP pattern group (1.740 *vs.* 1.520, P=0.018; Figure S3).

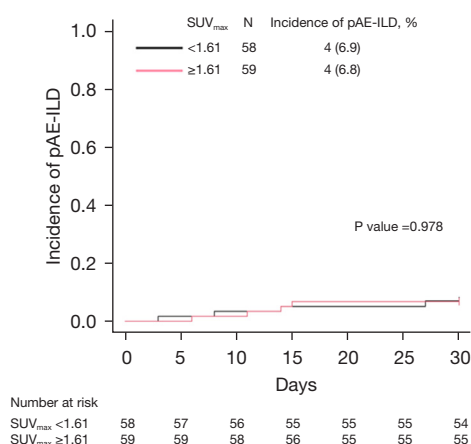Moreover, we followed up with the patients without pAE-ILD within 30 days postoperatively and identified seven

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Figure 2 Cumulative incidence curve of pAE-ILD in low (<1.61) and high (≥1.61) SUV$_{max}$ groups. pAE-ILD, postoperative acute exacerbation of interstitial lung disease; SUV$_{max}$, maximum standardized uptake value.
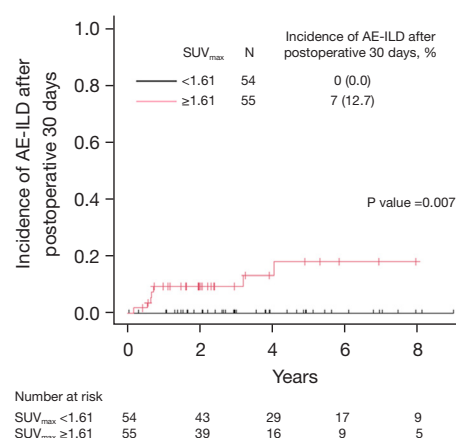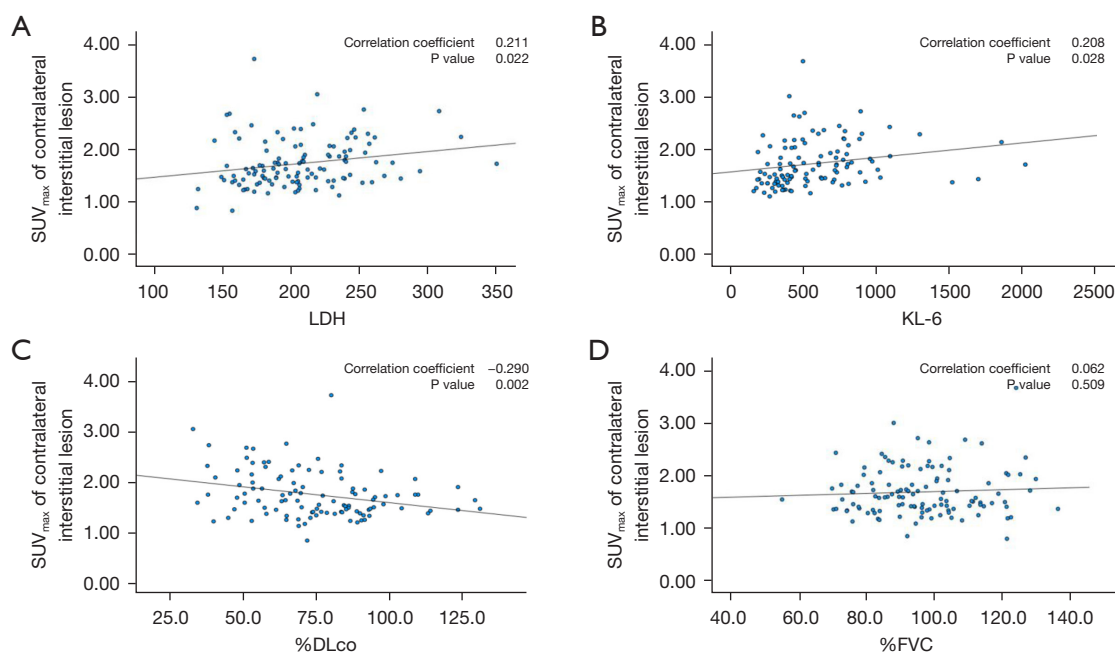
Figure 4 Cumulative incidence curve of AE-ILD during the clinical course after 30 days postoperatively in low (<1.61) and high (≥1.61) SUV$_{max}$ groups. AE-ILD, acute exacerbation of interstitial lung disease; SUV$_{max}$, maximum standardized uptake value.

Figure 3 Pearson's correlation coefficients between SUV$_{max}$ of contralateral interstitial lesions and (A) LDH, (B) KL-6, (C) %DLco, and (D) %FVC. SUV$_{max}$, maximum standardized uptake value; LDH, lactate dehydrogenase; KL-6, sialylated glycoprotein Krebs von den Lungen-6; FVC, forced vital capacity; %DLco, diffusing capacity of the lung for carbon monoxide.

additional patients who developed AE-ILD. There was a significantly higher incidence of AE-ILD after 30 days postoperatively in the high SUV$_{max}$ group than that in the low SUV$_{max}$ group (incidence rate; 12.7% *vs.* 0.0%; P=0.007,

Figure 4). Additionally, the median SUV$_{max}$ of contralateral interstitial lesions in the AE-ILD group after 30 days postoperatively was significantly higher than that in the non-AE-ILD group (2.210 *vs.* 1.575, P=0.006; Figure S4).

Discussion

This study aimed to examine whether SUV_{max} (calculated from the ^{18}F-FDG PET/CT images) of contralateral interstitial lesions was a predictive factor for pAE-ILD in LC patients with ILD who underwent pulmonary resection. Our results revealed that the SUV_{max} of contralateral interstitial lesions was not associated with the occurrence of pAE-ILD in these patients. Further analysis of the results for disease indicators of ILD revealed that SUV_{max} was significantly correlated with the UIP pattern, elevation of LDH and KL-6, decrease in %DLco, and a higher incidence of AE-ILD after 30 days postoperatively in LC patients with ILD. This result suggests that SUV_{max} of contralateral interstitial lesions may be a marker of the severity and activity of ILD, and supports the decision to perform surgery for LC in those patients, considering the risk of developing AE-ILD in the future.

The current study showed that the incidence and 90-day mortality of pAE-ILD in LC patients with ILD who underwent lung surgery was 6.8% and 50%, respectively, which is consistent with previous reports (4-6). pAE-ILD is a life-threatening complication; therefore, the prevention and management of pAE-ILD is crucial in LC patients with ILD undergoing pulmonary resection. Recently, the perioperative administration of an antifibrotic agent, pirfenidone, for LC surgery was reported to reduce the frequency of pAE-ILD in LC patients with idiopathic pulmonary fibrosis (IPF) (15-17), however, this study did not demonstrate the efficacy of pirfenidone in preventing pAE-ILD. The preventive effect of pirfenidone is currently being evaluated in a randomized phase III trial of pirfenidone *vs.* placebo (PIII-PEOPLE study, UMIN000029411) in LC patients with IPF. Although our study did not determine a significant difference, Sato *et al.* reported that limited surgery was associated with a lower frequency of pAE-ILD (4). In LC patients with ILD, limited surgery could be a useful method of preventing pAE-ILD.

There is limited evidence on the clinical significance of ^{18}F-FDG uptake in interstitial lesions in PET/CT images in patients with ILD. Several previous reports demonstrated that the accumulation of ^{18}F-FDG uptake on interstitial pneumonia lesions in ILD patients was negatively correlated with DLco and positively correlated with KL-6 (18,19). These factors are indicators of disease progression for interstitial pneumonia in ILD patients (20-22). Our results also showed a correlation between SUV_{max} of contralateral interstitial lesions and disease progression markers of ILD. Moreover, patients with ILDs, especially IPF, experience AE-ILD in the natural course of disease progression, and its incidence is approximately 4–20% of cases annually (14,23). Notably, the high accumulation of ^{18}F-FDG uptake in interstitial lesions was significantly correlated with the incidence of AE-ILD after 30 days postoperatively in LC patients with ILD who received pulmonary surgery. Hence, the SUV_{max} of contralateral interstitial lesions might demonstrate disease severity and activity of ILD in LC patients with ILD.

The current study displayed a significant association between pAE-ILD and the UIP pattern, elevation of KL-6, and a high score in the risk score system for predicting AE after surgery proposed by Sato et al, which is consistent with previous studies (4,6,7,9). However, there were no significant differences in the correlation between the SUV_{max} of contralateral interstitial lesions and pAE-ILD, in contrast to previous similar reports (24,25), and our previous study on LC patients with ILD treated with chemotherapy (10). The reason for the discrepancy between our result and other similar previous reports is believed to be the higher ^{18}F-FDG accumulation in interstitial lesions of ILD patients with the UIP pattern with honeycomb cysts than in ILD patients with the non-UIP pattern, as reported by Umeda *et al.* (26). Compared to previous reports, our study may have included more mild cases with fewer UIP patterns on chest CT and fewer instances of low pulmonary function such as higher %DLco. Additionally, two possible reasons may explain the discrepancy between our current and previous results: the different types of triggers for AE-ILD and the duration of observation. First, lung damage due to hyperoxia, single-lung ventilation, and hyperextension of the contralateral lung have been considered as contributors to the development of surgical procedure-related AE-ILD. Conversely, it has been proposed that chemotherapy-related AE-ILD is caused by direct cytotoxic lung injury and an immune-mediated mechanism (27,28). Additionally, the effect of these AE-ILD triggers occurs only once in case of surgery, but repetitively in case of chemotherapy. Thus, the various causes of AE-ILD triggers and the number of lung attacks by these triggers might have caused the differences in our two reports. Second, pAE-ILD in this study was detected during a short duration of observation (within 30 days after surgery), while in our previous study on LC patients with ILD treated with chemotherapy, AE-ILD was detected in long-follow-up periods (the occurrence of AE-ILD from the first administration of chemotherapy to

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the time of death regardless of the cause or the last follow-up). As mentioned above, patients with a high SUV$_{max}$ of contralateral interstitial lesions more frequently experienced AE-ILD after 30 days postoperatively. Thus, the SUV$_{max}$ of contralateral interstitial lesions might be useful for the prediction of AE-ILD in the natural disease course in patients with ILD.

The mechanism of ^{18}F-FDG accumulation in interstitial lesions may involve fibroblast cells stimulated by transforming growth factor-β (TGF-β). Previous reports had demonstrated that the TGF-β-stimulated fibroblast cells have increased glucose transporter-1 at the cell membrane and active metabolism (29), which leads to increased ^{18}F-FDG uptake in interstitial lesions on PET image (30,31). Additionally, TGF-β-stimulated fibroblast cells not only produce excessive collagen type-1, which contributes to the progression of pulmonary fibrosis (32), but also release cytokines, such as IL-6, and produce inflammatory changes in the lung microenvironment (33). Thus, the ^{18}F-FDG accumulation in interstitial lesions might represent an increase in TGF-β-stimulated fibroblast cells, which might reflect a pulmonary microenvironment with increased fibrosis and inflammation.

This study had several limitations. First, this study was retrospectively conducted at a single institution among the Japanese population only. Moreover, there was a risk of bias because of the nature of the retrospective study. Second, the surgical procedure of lobectomy or limited surgery was decided by each surgeon while considering the patient's pulmonary function and comorbidity, which may have affected our results. Third, several clinical variables such as LDH and KL-6 were elevated because of the activity of interstitial pneumonia and cancer progression (34-36). Therefore, the study results should be interpreted with caution, and large-scale, multi-centre, prospective studies are required to analyse these findings.

In conclusion, SUV$_{max}$ of contralateral interstitial lesions was not a predictive factor for pAE-ILD. However, it was an indicator of disease severity and activity of ILD in LC patients with ILD who underwent pulmonary resection. Further studies are needed to evaluate the relationship between ^{18}F-FDG accumulation in interstitial lesions and the pathophysiology of ILD.

Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-604/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-604/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-604/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-604/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the institutional review board of Kumamoto University Hospital (IRB number: 2399) and the requirement for individual consent for this retrospective analysis was waived.

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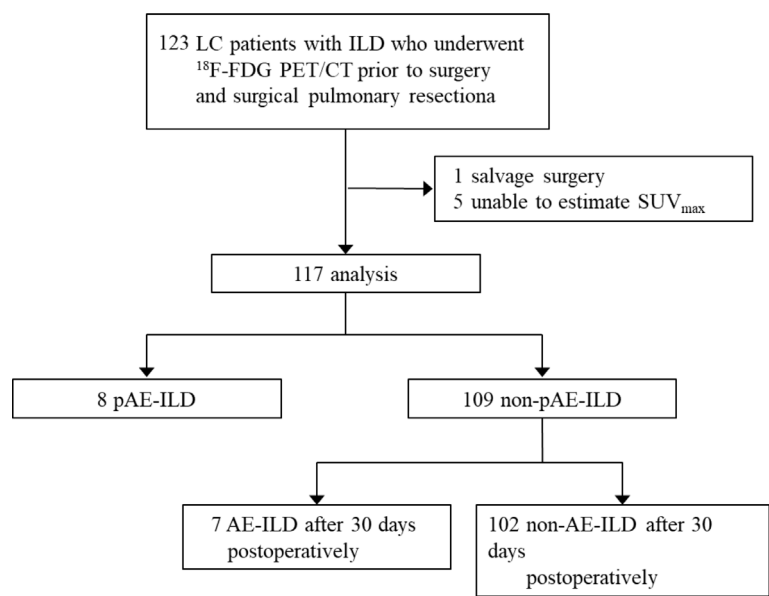
Figure S1 Patient flow. *, pAE-ILD: AE-ILD occurring within 30 days postoperatively. LC, lung cancer; ILD, interstitial lung disease; ^{18}F-FDG PET/CT, fluorine-18 2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography; SUV_{max}, maximum standardized uptake value; AE-ILD, acute exacerbation of ILD; pAE-ILD, postoperative AE-ILD.
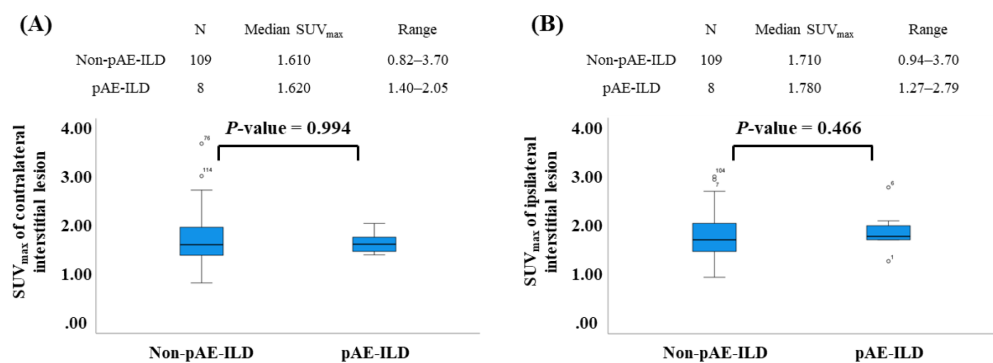

Figure S2 Correlation between the incidence of pAE-ILD and SUV_{max} of (A) contralateral and (B) ipsilateral interstitial lesions. ILD, interstitial lung disease; SUV_{max}, maximum standardized uptake value.
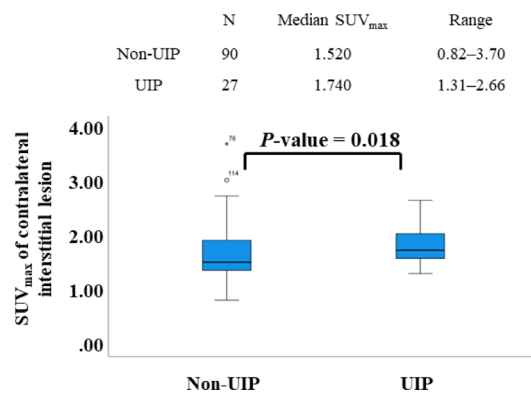
	N	Median SUV$_{max}$	Range
Non-UIP	90	1.520	0.82–3.70
UIP	27	1.740	1.31–2.66

Figure S3 Correlation between SUV$_{max}$ of contralateral interstitial lesions and ILD pattern. ILD, interstitial lung disease; SUV$_{max}$, maximum standardized uptake value.
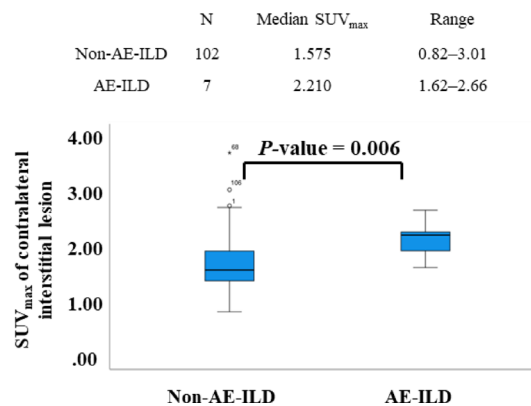

	N	Median SUV$_{max}$	Range
Non-AE-ILD	102	1.575	0.82–3.01
AE-ILD	7	2.210	1.62–2.66

Figure S4 Correlation between SUV$_{max}$ of contralateral interstitial lesions and the incidence of AE-ILD after 30 days postoperatively. SUV$_{max}$, maximum standardized uptake value; AE-ILD, acute exacerbation of interstitial lung disease.