World Journal of Surgery and Surgical Research

Case Series
Published: 14 Sep, 2021

Fluorodeoxyglucose-Positron Emission Tomography Signal Predicts Acute Exacerbation of Interstitial Pneumonia after Lung Cancer Surgery

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Abstract

Background: In this study, we evaluated the activity of IPF on preoperative PET in patients who underwent lung cancer surgery and attempted to identify high-risk patients who might develop postoperative Acute Exacerbation (AE) of IPF.

Methods: The pulmonary uptake of Fluorodeoxyglucose (^{18}F-FDG) was quantified at six sites (left and right sides of the upper, middle, and lower lobes), and AE of IPF after lung cancer surgery was examined.

Results: UIP patients had a significantly higher FDG distribution in the right upper lobe than other IPs ($p<0.05$). Seven patients who were all UIP developed AE after lung resection, their FDG accumulation was high in bilateral upper lobe ($p<0.05$), in UIPs.

Conclusion: The widely distributed pulmonary uptake of ^{18}F-FDG on preoperative PET might be an etiologic factor predicting postoperative AE in UIP patients with lung cancer.

Keywords: Interstitial pneumonia; Positron emission tomography; FDG distribution; Postoperative acute exacerbation

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Received Date: *09 Aug 2021*
Accepted Date: *09 Sep 2021*
Published Date: *14 Sep 2021*

Citation:
Yasuda M, Yoshikai T, Koga H, Chikaishi Y, Iwanami T, Osaki T. Fluorodeoxyglucose-Positron Emission Tomography Signal Predicts Acute Exacerbation of Interstitial Pneumonia after Lung Cancer Surgery. World J Surg Surgical Res. 2021; 4: 1339.

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Introduction

It has been reported that the incidence of primary lung cancer is increased in patients with Idiopathic Pulmonary Fibrosis (IPF), ranging from 7.5% to 17.8% [1,2]. Postoperative Acute Exacerbation (AE) of IPF is associated with a high mortality rate after pulmonary resection; of all postoperative complications, AE is the most likely to be fatal [3,4]. Although some authors have attempted to identify predictors of postoperative AE in IPF patients [3-5], none have been established.

Recently, there have been many reports on the use of Positron Emission Tomography (PET) in IPF. These signal changes have been related to regions of lung parenchymal changes on High-Resolution Computed Tomography (HRCT) [6-9]. In preclinical studies, the Fluorodeoxyglucose (^{18}F-FDG) uptake was found to reflect the migration of inflammatory cells [10]. However, few studies have addressed predictors on PET scans for postoperative AE in IPF patients [11,12].

In this study, we evaluated the ^{18}F-FDG signal on preoperative PET in IPF patients who underwent lung cancer surgery and attempted to identify high-risk patients who might develop postoperative AE of IPF.

Case Series

Patients

From 2013 to 2018, 63 patients who had been histopathologically diagnosed with Interstitial Pneumonia (IP) underwent lung resection for lung cancer at the Department of Chest Surgery, Iizuka Hospital, Iizuka, Japan. This work was approved by the Internal Review Board of the institution (R-17174), and written informed consent was obtained from all patients. The clinical data of the patients were retrospectively reviewed (Table 1).

Table 1: Patients' characteristics.

	UIP (n=49)	non-UIP (n=14)
Gender, M/F	45/4	7/7
Median age, year (range)	74 (59-85)	69 (48-78)
Smoking history, ex/never	46/3	9/3
Pack years	67.04 ± 27.04	46 ± 14.39
Vital capacity (% predicted)	97.43 ± 17.77	99.7 ± 17.6
FEV 1.0 (% predicted)	74.52 ± 13.32	77.01 ± 8.38
KL-6 (U/ml)	574.61 ± 305.91	538.5 ± 327.14
Surgical procedure		
Bi-Lobectomy	5	0
Lobectomy	26	6
Segmentectomy	3	1
Wedge resection	15	7
Pathological type		
Adenocarcinoma	15	5
Squamous cell carcinoma	20	6
Adeno-squamous cell carcinoma	3	0
Small-cell carcinoma	6	1
Other	5	2
Pathological Stage		
I/II	42	13
III/IV	7	1

FEV1.0: Forced Expiratory Volume in one second

Table 2: UIP patients' characteristics.

	AE (n=7)	non-AE (n=42)
Gender, M/F	7/0	38/4
Median age, year (range)	75 (68-85)	74 (59-85)
Smoking history, ex/never	7/0	39/3
Pack years	50±31.53	53±21.85
Vital capacity (% predicted)	90.3±16.89	96.35±17.53
FEV 1.0 (% predicted)	72.16±10.34	76.23±9.71
KL-6 (U/ml)	459±99.67	520.5±327.78
Surgical procedure		
Bi-Lobectomy	2	4
Lobectomy	4	21
Segmentectomy	1	2
Wedge resection	0	15
Pathological type		
Adenocarcinoma	4	11
Squamous cell carcinoma	2	18
Adeno-squamous cell carcinoma	1	2
Small-cell carcinoma	0	6
Other	0	5
Pathological Stage		
I/II	4	38
III/IV	3	4

FEV1.0: Forced Expiratory Volume in one second

Preoperative PET

Before surgery, all patients underwent PET. FDG-PET was performed using a Discovery ST PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). All patients fasted for at least 6 h, and the blood glucose concentration of each patient was monitored prior to the intravenous injection of ^{18}F-FDG. The injection dose of radioactive tracer was calculated as 0.11 to 0.13 millicuries per kilogram of body weight. FDG-PET/CT was conducted according to the standard protocol. A whole body scans from mid-thigh to vertex commenced at approximately 60 min after injection. Non contrast enhanced CT was conducted with a current of 120 mA to 170 mA, a voltage of 120 kV, a section thickness of 5 mm or 3.75 mm, and a reconstruction interval of 5 mm or 3.75 mm. The attenuation corrected PET image was scanned at 2 min per frame and reconstructed using CT data with iterative algorithms.

Image interpretation

Morphological, metabolic and fused PET/CT images were inspected in axial, coronal, and sagittal views using the Xeleris software program from GE Healthcare. Three senior nuclear medicine physicians independently interpreted the PET/CT images (based on clinical pathological data, location, shape, CT attenuation, and the ^{18}F-FDG uptake), and then the maximum ^{18}F-FDG uptake was calculated for six sites (right and left upper, middle [lingular], and lower lobes). The maximum ^{18}F-FDG uptake data were compared using a non-parametric test (Wilcoxon's signed-rank test). A p-value <0.05 was considered significant.

The preoperative FDG uptake in IPF patients with lung cancer

We performed thoracic surgery for lung cancer patients with IP (Table 1). Among UIP patients, 92% were male (45/49), 94% were smokers (46/49), and 69% underwent segmentectomy or lobectomy (34/49). In contrast, among other IP patients, 50% were male (7/14), 75% were smokers (9/12), and 50% underwent segmentectomy or lobectomy (7/14). These results suggested that UIP patients tended to be male smokers and required wide resection for their lung cancer.

In all cases, the areas of ground glass changes on HRCT showed an ^{18}F-FDG uptake, with the area concentrated in the bilateral lower lobe (Figure 1). Furthermore, UIP patients showed higher FDG accumulation in the upper lobe than other IPs, especially the right upper lobe ($p<0.05$), which was not significantly different from the left upper lobe ($p=0.0736$) (Figure 1). Based on these findings, UIP patients had a wider distribution of the ^{18}F-FDG uptake in the upper lobe on PET than other IPs.

Postoperative AE in IPF patients with lung cancer

Seven patients (all UIP) developed AE after lung resection (Table 2). All AE patients were male smokers and underwent segmentectomy or lobectomy. These patients showed that the areas of postoperative enhanced ground glass changes were almost the same areas that had demonstrated a preoperative FDG uptake. However, in the upper lobe, the areas of postoperative enhanced ground glass changes were normal lung parenchyma on HRCT (Figure 2). These results suggested that PET scan might be more useful for detecting early inflammatory changes in lung parenchyma than HRCT.

In addition, cases with postoperative AE showed significantly more widespread preoperative FDG distribution in the bilateral upper lobe than non-AE cases ($p<0.05$) (Figure 3). These results suggest that a wide distribution of the preoperative ^{18}F-FDG uptake through the upper lobe might be a predictor for postoperative AE in UIP patients

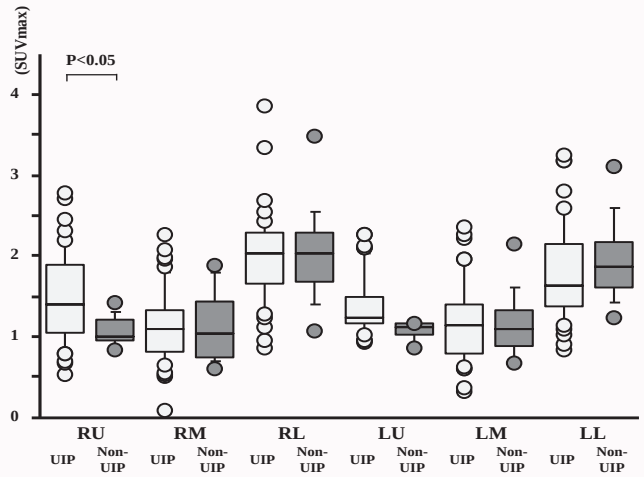

Figure 1: In 63 IP patients (49 UIP, 14 non-UIP) with lung cancer, the preoperative FDG uptake was examined at 6sites in the lung (right- or left-side upper/middle/lower lobes). The data show the maximum ^{18}F-FDG uptake. Lines indicate median values, boxes indicate the values between the upper and the lower quartile, whiskers indicate 95% confidence interval, and dots indicate outliners.

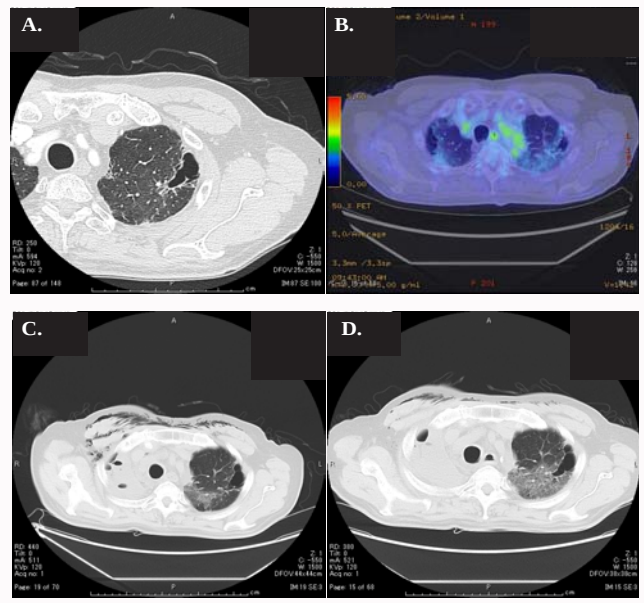

Figure 2: Representative image of a postoperative AE case. Right upper lobectomy was performed for lung cancer. No ground glass changes were seen on preoperative HRCT (A), but an FDG uptake was seen in the left upper lobe on preoperative PET (B). Postoperative AE of UIP occurred at postoperative day 10.Ground glass changes in the left upper lobe were seen on CT at postoperative day 10 (C), with gradual enhancement noted at postoperative day14 (D).

with lung cancer.

Discussion

Lung cancer patients with Interstitial Lung Diseases (ILDs) who have undergone pulmonary resection often develop AE of IP in the postoperative period [3,4]. To identify patients at particularly high risk of AE, we evaluated the preoperative ^{18}F-FDG uptake area on PET. The major findings of our present report are as follows: (i) UIP patients with lung cancer showed a widespread ^{18}F-FDG uptake throughout the upper lobe; (ii) in postoperative AE cases, the areas that demonstrated a preoperative FDG uptake, enhanced ground

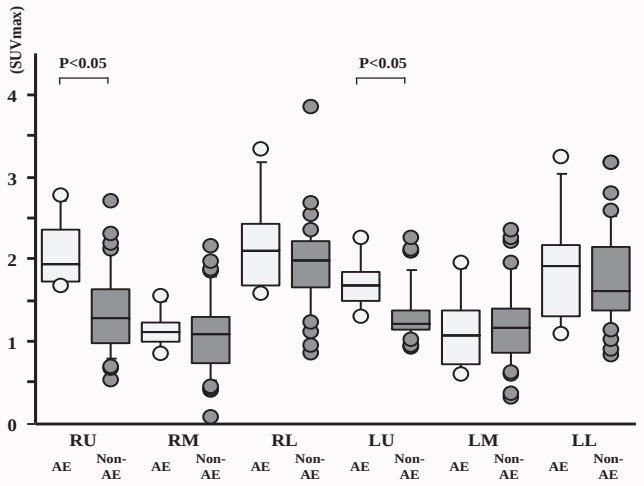

Figure 3: In 49 UIP patients (7 AE, 42 non-AE) with lung cancer, the preoperative FDG uptake was examined at 6 sites in the lung (right or left side of upper/middle/lower lobes). The data show the maximum ^{18}F-FDG uptake. Lines indicate median values, boxes indicate the values between the upper and the lower quartile, whiskers indicate 95% confidence interval, and dots indicate outliners.

glass changes, and (iii) the cases showed significantly widespread preoperative FDG distribution in the bilateral upper lobe. These results suggested that the wide distribution of the FDG uptake on preoperative PET was an important factor predicting postoperative AE in UIP patients with lung cancer.

PET using ^{18}F-FDG is useful for diagnostic purposes to detect the metabolic activity of tissues in several lung diseases, including lung cancer [7,13,14]. Recently, PET has also been used to evaluate interstitial lung diseases, such as pulmonary fibrosis [6-9]. Interstitial lung disease shows an ^{18}F-FDG uptake because of the involvement of Glucose transporter-1 (Glut-1), the predominant glucose transporter in the lung that is responsible for the ^{18}F-FDG uptake [7]. Chemaly et al. [10] reported that Glut-1 is usually expressed on the surface of erythrocytes in normal lung. However, in IPF patients, inflammatory cells, such as neutrophils and macrophages, showed the upregulation of Glut-1. These results suggested that the enhanced ^{18}F-FDG uptake on PET in IPF is a result of an increase in the populations of inflammatory cells. Win et al. [6] reported that IPF is accompanied by the increased pulmonary uptake of ^{18}F-FDG on PET, even in those areas with a normal morphological appearance of the lung parenchyma on HRCT. In our UIP patients, the FDG accumulation tended to be distributed more widely throughout the upper lobe than in other IP patients (Figure 1). Furthermore, in our postoperative AE case, the preoperative uptake of ^{18}F-FDG on PET in the upper lobe, even in those areas with a normal morphological appearance of the lung parenchyma on HRCT, showed enhanced ground glass changes in postoperative AE (Figure 2). These results also suggested that PET may be sensitive for detecting early inflammatory changes in UIP patients with lung cancer and may play an important role in the early disease detection in cases of postoperative AE.

Previous studies have shown that interstitial lung diseases were associated with a higher incidence of lung cancer than the general population, with a relative risk of 7.3 to 14.1, and the prevalence of lung cancer among ILD patients ranged from 5% to 15% [1,2]. For patients with interstitial lung diseases, surgical insult, even if small, can trigger the acute deterioration of interstitial lung diseases, also

known as AE [3,4]. Sato et al. [15] reported that the incidence of AE after pulmonary resection was 9.3% in lung cancer patients with ILDs. Therefore, the prediction of postoperative AE has been long desired, as this would enable to stratification of ILD patients and elucidate each patient's individual risk for AE. Sato et al. [16] also reported a simple scoring system using the following seven parameters to identify individuals at high risk of AE: history of AE, surgical procedures, UIP appearance on CT, gender, preoperative steroid use, serum sialylated carbohydrate antigen levels, and vital capacity. Recently, several reports have investigated predictors on PET scans for AE in IPF patients [11,12,17]. Those authors found that a high FDG accumulation was a predictor for AE. In the present study, seven patients (all UIP) actually developed postoperative AE. The cases showed significantly more widespread preoperative FDG distribution in the bilateral upper lobe than non-AE cases (Figure 3). Our results suggested that the distribution of the FDG uptake might be a predictor for AE in IPF patients.

Curative therapy for IPF is still lacking. Several trials have shown that pirfenidon and nintedanib can be efficient in preventing the decline in the lung function in IPF patients [18,19]. Pirfinidon has also been shown to be effective in improving the mortality of IPF patients [20]. Recently, Iwata et al reported that perioperative pirfenidon treatment is effective for reducing the risk of postoperative AE in IPF patients with lung cancer [21]. However, further clinical research is needed.

Several limitations associated with the present study warrant mention. First, the number of patients was small. In our institution, not all patients who had resected lung cancer underwent preoperative PET. In addition, a pathological diagnosis of UIP was not always obtained using a resected specimen in the patients who showed ground glass changes on preoperative HRCT. These patients may represent a small population of UIP with lung cancer. Second, regarding the method of evaluating the FDG uptake on preoperative PET, in our study, the maximum ^{18}F-FDG uptake was evaluated in six sites of the lung. We did not account for the influence of lung cancer.

In conclusion, our findings suggest that the distribution of ^{18}F-FDG in upper lobe on PET may be an etiologic factor predicting postoperative AE in UIP patients with lung cancer. Further accumulation of clinical experience and the establishment of treatment strategies for postoperative AE are needed.

Ethical Statement

This work was approved by the Internal Review Board of the institution (R-17174), and written informed consent was obtained from all patients.

Financial Support

This study was partially funded by the grant funding for clinical research of Iizuka Hospital.

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