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**Research Article**

# Is 18F-fluorodeoxyglucose PET recommended for small lung nodules? CT findings of 18F-fluorodeoxyglucose non-avid lung cancer

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## Abstract

**Objectives:** To determine the image characteristics associated with low 18F-FDG (18F-fluorodeoxyglucose) avidity among 8-15 mm solid lung cancer.

**Methods:** Patients satisfying the following criteria were included: underwent surgery between January 2014 and December 2019 for lung cancer, presented 8-15 mm nodule without measurable ground glass component on preoperative CT, and underwent 18F-FDG PET before resection. Image characteristics, including air bronchogram, concave shape, pleural attachment, and background emphysema, were evaluated by two board-certified radiologists. The Mann-Whitney U test was used to compare maximum standardized uptake (SUVmax) values from 18F-FDG PET images.

**Results:** The analysis included 235 patients. The SUVmax values of lesions with air bronchogram and concave shape were significantly lower than the SUVmax values of lesions without these features (median: 1.55 vs 2.56 and 1.66 vs 2.45, both $P < .001$), whereas lesions arising from emphysematous lungs had significantly higher SUVmax values than lesions arising from non-emphysematous lungs (2.90 vs 1.69, $P < .001$). No significant differences were detected between lesions attached and not attached to pleura. The interobserver agreement was almost perfect for air bronchograms and background emphysema ($\kappa = 0.882$ and 0.927, respectively), and 89.7% of lesions with air bronchograms and arising from non-emphysematous lungs showed SUVmax values below 2.5.

**Conclusions:** Among 8-15 mm solid lung cancer, the presence of air bronchograms and concave shape and the absence of background emphysema were associated with low 18F-FDG accumulation.

**Advances in knowledge:** 18F-FDG PET can be misleading in differentiating certain type of small solid lung cancer.

**Keywords:** pulmonary emphysema; lung neoplasms; tomography; X-ray computed; fluorodeoxyglucose F18.

## Introduction

Lung cancer is one of the leading causes of cancer-related mortality worldwide.[1] Therapeutic intervention at an early stage leads to favourable prognoses[2]; thus, early diagnosis of lung cancer based on image examinations is vitally important. In this context, low-dose CT (LDCT) is the most widely used imaging modality for the early diagnosis of lung cancer worldwide and contributes to the reduction in lung cancer mortality.[3] Several guidelines have been released to predict the malignancy of nodules detected on lung cancer screening by CT.[4,5] These guidelines suggest that the risk of malignancy increases with the size of the nodule, and a shorter follow-up interval or further investigation is recommended for nodules larger than 8 mm.

Pulmonary nodules detected on CT can be differentiated using 18F-fluorodeoxyglucose (18F-FDG) PET. As 18F-FDG reflects glucose metabolism, more 18F-FDG accumulates in malignant tumours than in benign lesions.[6,7] The commonly used maximum standardized uptake value (SUVmax) threshold between malignancy and benignancy is 2.5.[7,8] As biopsies are technically challenging for small nodules, 18F-FDG PET is particularly useful for relatively small nodules.[9,10] As a matter of fact, Lung-Rads® 2022 recommends a 3-month follow-up on LDCT or 18F-FDG PET for 8-15 mm nodules detected on LDCT.[4]

Despite its usefulness, 18F-FDG PET has limitations. Some lung cancers have low glucose metabolism and therefore are detected as false negatives on 18F-FDG PET. In addition, smaller lung cancers tend to accumulate less 18F-FDG[11]; therefore, small pulmonary nodules are less likely to be detected using 18F-FDG PET. Previous studies using 18F-FDG PET to detect lung cancer usually focus on nodules that are >15 mm,[12,13] and thereby the extent of false-negative detection of lung cancers with nodules between 8 and 15 mm is unclear.

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If the nodule is larger than 8 mm, the imaging features can be identified to some extent on CT images. If the imaging features of undetected lung cancers (false negatives) with 18F-FDG PET are elucidated, then unnecessary 18F-FDG PET can be avoided, as 18F-FDG PET will not be diagnostically useful for nodules with these imaging features. Thus, the purpose of this study was to identify CT imaging characteristics associated with low 18F-FDG PET accumulation in solid lung cancers between 8 and 15 mm in size.

## Methods

### Patient population

This retrospective study was approved by the institutional review board (approval number, 2022-72), and the need for written informed consent was waived due to its retrospective nature.

From January 2014 to December 2019, 3043 patients underwent surgery for lung tumours. Patients meeting the following criteria were retrospectively screened: (1) tumour diameter (average of long and short axes on the axial image) was ≥8 and <15 mm, (2) no measurable ground glass opacity (GGO) components were identified on preoperative CT, and (3) underwent 18F-FDG PET before surgery. Criteria (1) and (2) were evaluated based on preoperative CT reports provided by board-certified diagnostic radiologists during routine clinical practice. Whilst 246 patients met the inclusion criteria, 11 patients were excluded for the following reasons: $n = 1$, treatment with preoperative chemotherapy; $n = 5$, pathologically diagnosed with a recurrent or metastatic tumour; and $n = 5$, thin slice images were not available. Thus, 235 patients were included in this study. Figure 1 shows the flowchart of patient inclusion.

### CT data acquisition

CT scans were performed with 16-detector row scanners (Aquilion PRIME, Cannon Medical Systems, Otawara, Japan) or 160-detector row scanners (Aquilion Precision, Cannon Medical Systems). CT scans were performed during one breath hold and covered the area from the apex of the lung to the bottom of the lung. Iodine contrast material was administered intravenously when necessary if there were no contraindications. The tube voltage was 120 kVp, and the tube current was automatically modulated according to body size. Since the scans were not for screening purposes, a conventional radiation dose protocol, rather than a low-dose protocol, was used. Reconstruction was performed in 1.0-nm and 5.0-mm axial slices. A high-frequency algorithm was used for the lung field, and a low-frequency algorithm was used for the mediastinum as a reconstruction kernel.

### 18F-FDG PET data acquisition

Patients were asked to fast for at least 4 h before measuring blood glucose levels. If glucose levels were <200 mg/dL, 4 MBq/kg of radiotracer was intravenously injected. After 50-70 min, 18F-FDG images were obtained from the head to the upper thighs. A combined PET/CT system (DISCOVERY 600; GE Medical Systems, Milwaukee, USA) or a combined 3T PET/magnetic resonance system (SIGNA, GE Medical systems) was used.

Board-certified radiologists specializing in nuclear medicine interpreted the 18F-FDG PET/CT or PET/MR images. Regions of interest (ROIs) were drawn to encompass the tumours, and the SUVmax in the ROIs were recorded in the diagnostic reports. If the SUVmax values were not included in the diagnostic report, a physician with board certification in diagnostic radiology and nuclear medicine (ANONYMIZED, 17 years of experience) measured and recorded SUVmax in the same fashion.

### Image evaluation

Based on previous literature, we hypothesized that the following four factors may be associated with 18F-FDG accumulation: air bronchogram, concave shape, pleural attachment, and emphysema.[14-17] These four characteristics are illustrated in Figure 2. An air bronchogram was defined

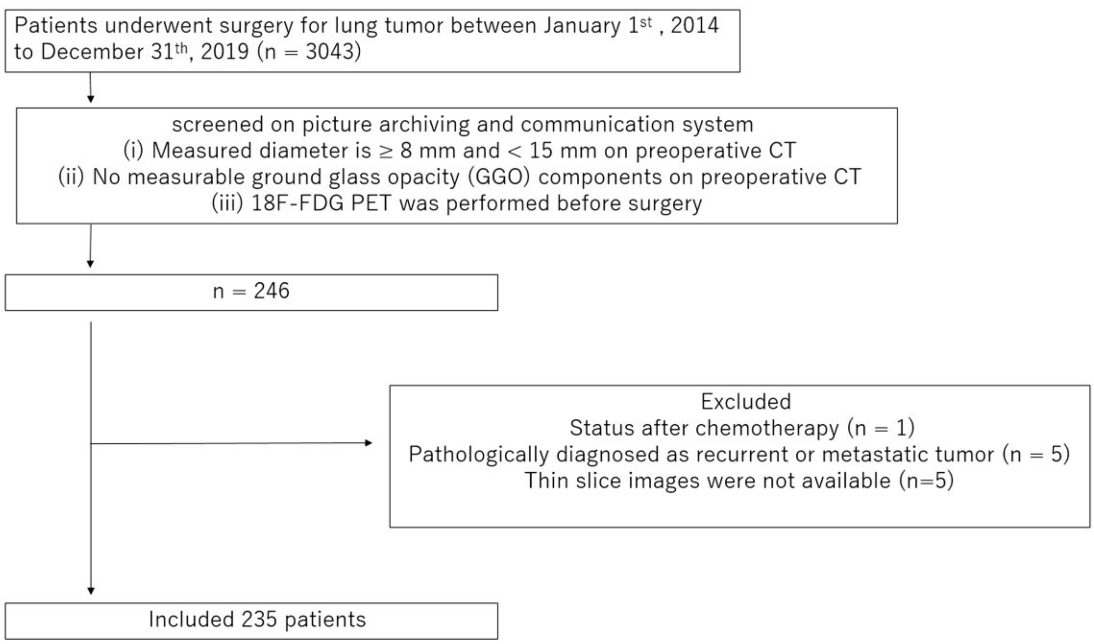


**Figure 1.** Flow chart showing the detailed inclusion and exclusion criteria.

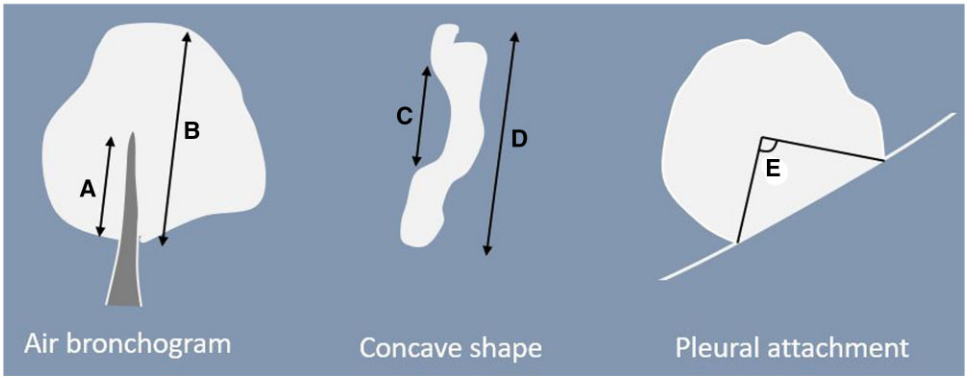


**Figure 2.** Schema of the definitions of air bronchogram, concave shape, and pleural attachment. An air bronchogram was defined as a continuous bronchus identifiable from the outside of the tumour to the inside of the tumour, and the length of bronchus in the tumour (A) was at least one-third of the maximum diameter of the tumour (B). Concave shape was considered positive when the tumour had an indentation and the length of the indentation (C) was greater than half the largest diameter of the tumour (D). Pleural attachment was considered positive when the degree to which the tumour was in contact with the pleura (E) was more than 90 degrees.

as a continuous bronchus identifiable from the outside of the tumour to the inside of the tumour, in which the length of the bronchus in the tumour was at least one-third of the maximum diameter of the tumour. Concave shape was defined as tumours with an indentation, in which the length of the indentation was greater than half of the largest diameter of the tumour. Pleural attachment was defined as contact with the pleura of more than 90 degrees. These features were evaluated with multiplanar reconstructions if necessary. The presence of emphysema was evaluated based on the Fleischner Society classification system.[18] This category was considered positive when any subtype of emphysema was detected on the background lung.

Two board-certified radiologists (HS, 8 years of experience and NK, 12 years of experience), who were blinded to the 18F-FDG PET images and other related clinical information, evaluated the preoperative images. If a discrepancy occurred, a senior thoracic radiologist (ANONYMIZED, 35 years of experience), who was blinded to the 18F-FDG PET images and other related clinical information, evaluated the image and decided the category.

## Statistical analysis

Since normality could not be confirmed with the Shapiro-Wilk test in all groups or subgroups, SUVmax values were compared with Mann-Whitney U tests between groups with or without each image characteristic. The concordance of image characteristics between two radiologists was evaluated with kappa coefficients.[19] R statistical software version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) was used to conduct all statistical analyses, and *P*-values $\leq .05$ were considered statistically significant.

# Results

## SUVmax values according to CT image characteristics

The study included 235 patients (median age, 69 [IQR: 62-75]; 151 men and 84 women). Table 1 shows the age, sex, smoking history, diameter on preoperative CT, and pathological diagnosis of the study patients.

**Table 1.** Patient characteristics.

| | Values |
|---|---|
| Age (years) | 69 [62–75] |
| **Sex** | |
| Male | 151 (64.3%) |
| Female | 84 (35.7%) |
| **Smoking status** | |
| Ever-smoker | 178 (75.7%) |
| Never-smoker | 57 (24.3%) |
| Pack-years of ever-smokers* | 42.5 [30–64.5] |
| Measured size on preoperative CT (cm) | 1.2 [1.05–1.35] |
| **Histological subtype** | |
| Adenocarcinoma | 174 (74.0%) |
| Squamous cell carcinoma | 43 (18.3%) |
| Small cell carcinoma | 5 (2.1%) |
| Carcinoid | 5 (2.1%) |
| Large cell carcinoma | 3 (1.3%) |
| Pleomorphic carcinoma | 2 (0.9%) |
| Adenosquamous carcinoma | 1 (0.4%) |
| Others (unclassifiable) | 2 (0.9%) |

Data are shown as a value (percentage) or a median [interquartile range].
*Two patients were excluded from the calculation since they had a history of smoking, but the exact number of cigarettes was unknown.

SUVmax values of lesions with each image characteristic are summarized in Table 2. The SUVmax values of lesions with air bronchograms were significantly lower than the SUVmax values of lesions without air bronchograms (median [IQR]; 1.55 [0.99-2.37] vs 2.56 [1.61-3.98], $P < .001$). Similarly, lesions with a concave shape had significantly lower SUVmax values compared with SUVmax values in lesions without a concave shape (1.66 [0.98-2.56] vs 2.45 [1.56-3.77], $P < .001$). Conversely, lesions arising from emphysematous lungs had significantly higher SUVmax values than lesions arising from non-emphysematous lungs (2.90 [1.96-4.91] vs. 1.69 [1.10-2.63], $P < 0.001$). No significant difference in SUVmax values between lesions attaching to pleura and lesions not attaching to pleura was detected. Examples of these findings are shown in Figures 3-5.

Kappa coefficients for the two readers are shown in Table 3. The agreement was almost perfect for air bronchograms, pleural attachment, and background emphysema ($\kappa = 0.882$-$0.937$), and substantial for concave shape ($\kappa = 0.779$).

## Subanalyses based on air bronchogram and background emphysema

Significant differences in SUVmax values and almost perfect interobserver agreement were detected for air bronchogram and background emphysema image features. Thus, we subanalysed SUVmax values of lesions categorized using these two image characteristics. The results of the subanalyses are shown in Table 4. In both emphysema positive and emphysema negative groups, SUVmax values were significantly lower in lesions with air bronchograms compared with SUVmax values in lesions with no air bronchograms ($P = .004$ and $P < .001$). Lesions with air bronchograms arising from non-emphysematous lungs had a median SUVmax of 1.41 [IQR: 0.93-1.82], and SUVmax values were below 2.5 in 52 out of 58 (89.7%) lesions, whereas lesions without air bronchograms arising from emphysematous lungs had a median SUVmax of 3.50 [IQR: 2.18-5.59] and only 32.7% (18 out of 55) of the lesions had SUVmax values below 2.5. The subanalyses are shown in Figure 6.

**Table 2.** SUVmax values according to image characteristics.

| Image characteristics | | $SUV_{max}$ | *P*-value |
|---|---|---|---|
| Air bronchogram | Positive ($n = 86$) | 1.55 (0.99, 2.37) | <.001* |
| | Negative ($n = 149$) | 2.56 (1.61, 3.98) | |
| Concave shape | Positive ($n = 81$) | 1.66 (0.98, 2.56) | <.001* |
| | Negative ($n = 154$) | 2.45 (1.56, 3.77) | |
| Pleural attachment | Positive ($n = 87$) | 2.33 (1.44, 3.48) | .444 |
| | Negative ($n = 148$) | 2.01 (1.30, 3.32) | |
| Emphysema | Positive ($n = 83$) | 2.90 (1.96, 4.91) | <.001* |
| | Negative ($n = 152$) | 1.69 (1.10, 2.63) | |

Data are shown as medians. Data in parenthesis are interquartile ranges. Asterisk indicates significant differences.

## Discussion

18F-FDG PET is recommended the differential diagnosis of 8-15 mm lung nodules, and therefore elucidating the imaging features of 8-15 mm lung cancers showing low 18F-FDG accumulation (false negatives) with 18F-FDG PET is desirable. Our results demonstrate that the presence of air bronchograms or concave shape is associated with significantly lower SUVmax values on 18F-FDG PET, whereas background emphysema is associated with significantly higher SUVmax values among small solid lung cancers ≥8 and <15 mm.

Currently, Lung-Rads® 2022 recommends a 3-month follow-up LDCT or 18F-FDG PET for nodules ≥8 and <15 mm detected on LDCT.[4] However, this study shows that small lung cancers with certain image characteristics tend to accumulate very low levels of 18F-FDG. Thus, pulmonary nodules with these characteristics should not be evaluated for benignancy or malignancy using 18F-FDG accumulation due to the risk of false-negative results. Evaluation using 18F-FDG PET is expensive and not as widely available as CT. Therefore, avoiding 18F-FDG PET for small nodules with image characteristics associated with low 18F-FDG accumulation may reduce unnecessary examinations and prevent delays in proper diagnosis.

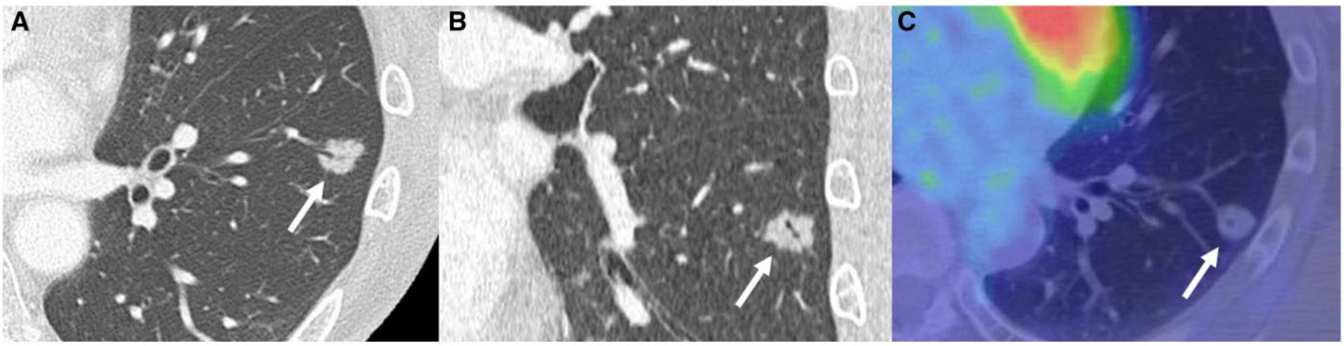


**Figure 3.** (A) Axial image and (B) reconstructed coronal image of a 1.35-cm adenocarcinoma in a 60-year-old male patient arising from non-emphysematous lung. The tumour shows an internal air bronchogram. (C) No 18F-FDG avidity was detected in the tumour, and the SUVmax was 0.93.

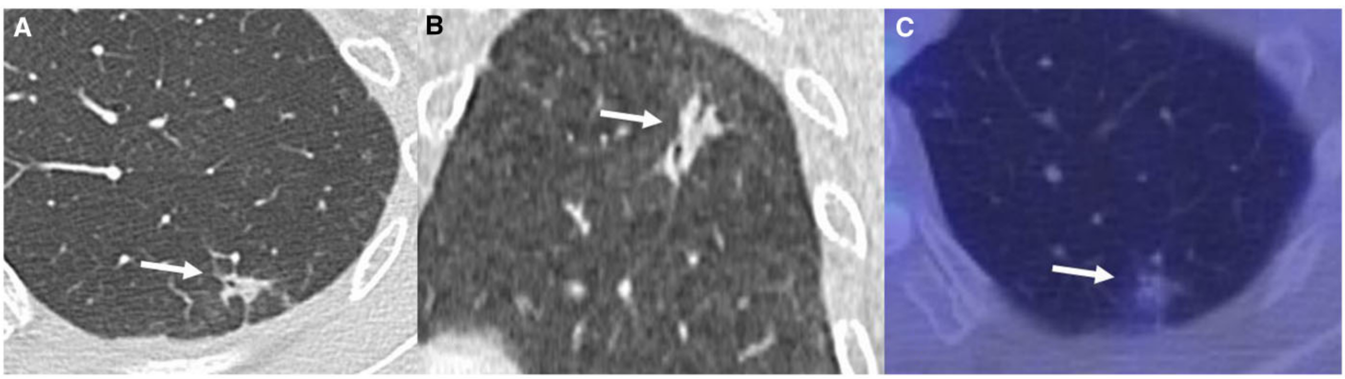


**Figure 4.** (A) Axial image and (B) reconstructed coronal image of a 1.25-cm adenocarcinoma in a 75-year-old female patient arising from non-emphysematous lung. The tumour shows an internal air bronchogram and concave shape. (C) No 18F-FDG avidity was detected in the tumour and the SUVmax was 0.98.

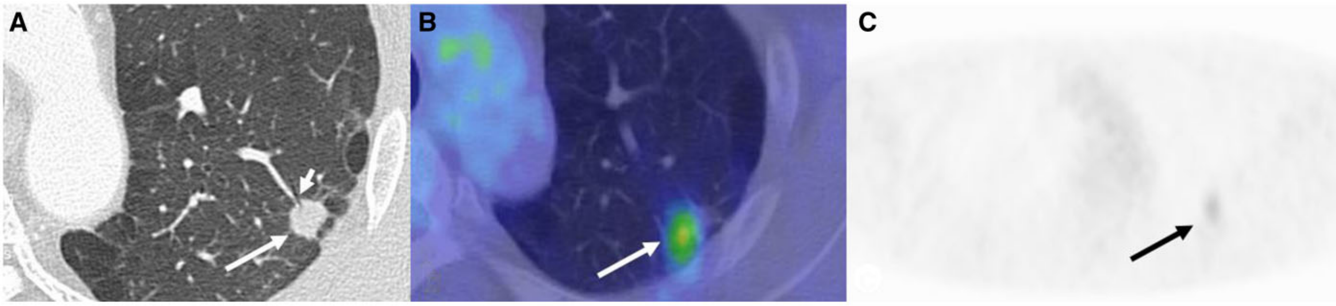


**Figure 5.** (A) A 1.3-cm adenocarcinoma in a 54-year-old male patient arising from emphysematous lung. The tumour did not show an internal air bronchogram. Instead, the bronchus was suddenly disrupted at the border of the tumour (short arrow). (B, C) Accumulation of 18F-FDG was detected in the tumour, and the SUVmax was 3.56.

**Table 3.** Interobserver agreement (kappa coefficients) for each image characteristic.

| Image characteristics | Kappa coefficient |
|---|---|
| Air bronchogram | 0.882 |
| Concave shape | 0.779 |
| Pleural attachment | 0.937 |
| background emphysema | 0.927 |

In the present study, air bronchograms were associated with lower 18F-FDG accumulation in small lung cancers. Interreader agreement was particularly high for air bronchograms, indicating that this characteristic may be useful for the qualitative assessment of pulmonary nodules. A previous study indicated that certain patterns of air bronchograms are associated with the invasiveness of lung adenocarcinoma.[14,20] In particular, disruption or obstruction of air bronchograms is more common in invasive adenocarcinoma than in precancerous lesions. Therefore, air bronchogram would be observed in the early stages of lung cancer growth and disappear as the tumour develops and the inside of the bronchus becomes occluded.

Concave shape also correlated with low accumulation of 18F-FDG in this study. In adenocarcinomas presenting as pure ground glass nodules (GGN), the more concave the shape, the greater the likelihood of having an invasive component.[21] Therefore, adenocarcinomas with pure GGN may become more concave in shape as the invasive component grows and becomes a solid nodule. Lung adenocarcinomas that progress from pure GGN to subsolid nodules and eventually to solid nodules tend to grow slowly and have a favourable prognosis.[22,23] This may explain why a concave shape is associated with lower 18F-FDG accumulation. However, in the current study, the interreader agreement for concave shape was lower than that for air bronchogram or emphysema. In addition, since the combination of air bronchogram and emphysema could predict low 18F-FDG accumulation, the combination of these two findings may be useful enough in clinical practice.

Lung cancer presenting as a subsolid nodule is associated with a better prognosis and low 18F-FDG avidity.[22-25] Internal air bronchograms and concave shape are both commonly observed among adenocarcinomas presenting as subsolid nodules.[14,21,26,27] In addition, both of these CT image characteristics are associated with the growth of invasive components of adenocarcinoma presenting as a subsolid nodule.[14,21] We included lung cancers without measurable GGO components based on preoperative diagnostic reports. Hence, lesions with air bronchograms and concave shapes in the present study may include a large number of lung adenocarcinomas that were originally subsolid nodules but developed into nodules with very little GGO portions, which is radiologically immeasurable, in the process of tumour growth.

The presence of emphysema was associated with high 18F-FDG avidity. Although emphysema is a risk factor for lung cancer, distinguishing lung cancer from benign lung nodules is more challenging in emphysematous lungs than in non-emphysematous lungs.[28] Our results suggest that 18F-FDG PET is particularly useful for stratifying malignancy risk in nodules arising from emphysematous lungs. However, we included only patients with lung cancer in this study, and a validation study to compare 18F-FDG accumulation in malignant and benign lung nodules in emphysematous lungs is needed.

Lung cancers arising from non-emphysematous lungs with air bronchograms exhibited particularly low 18F-FDG avidity. Almost 90% of lesions arising from non-emphysematous lungs with air bronchograms exhibited SUVmax values below 2.5, which is commonly used as the threshold between malignancy and benignancy. Visual assessment is also frequently used for lung nodule assessment, but it has been reported to have comparable diagnostic performance with SUVmax.[29] This result implies that using 18F-FDG PET to evaluate 8-15 mm lung nodules with these imaging features would result in a large number of false negatives. Thus, diagnostic 18F-FDG PET examinations for lesions arising from non-emphysematous lungs with air bronchograms are not recommended. On the other hand, two-thirds of lung cancers without air bronchogram arising from emphysematous lungs exhibited SUVmax values above 2.5. Considering the high risk of lung cancer in emphysema and the difficulty in differentiating between benign and malignant nodules,[28] $\geq$8 and $<$15 mm lung nodules with these imaging features (no air bronchogram and the presence of background emphysema) are good candidates for diagnostic 18F-FDG PET examination.

There are several limitations to this study. First, we only investigated pathologically confirmed lung cancer. Further studies, including both benign and malignant nodules, should be conducted to create detailed criteria for using 18F-FDG PET to evaluate lung nodules $\geq$8 and $<$15 mm based on CT image features. Secondly, we evaluated preoperative CT images, and therefore, patients were scanned using standard dose CT protocols, which are different from lung cancer

**Table 4.** SUVmax values according to air bronchogram and background emphysema.

| Image characteristics | | $SUV_{max}$ | *P*-value |
|---|---|---|---|
| Emphysema (+) | Air bronchogram positive ($n = 28$) | 2.39 (1.38, 3.10) | .004* |
| | Air bronchogram negative ($n = 55$) | 3.50 (2.18, 5.59) | |
| Emphysema (−) | Air bronchogram positive ($n = 58$) | 1.41 (0.93, 1.82) | <.001* |
| | Air bronchogram negative ($n = 94$) | 2.16 (1.41, 3.28) | |

Data are shown as medians. Data in parenthesis are interquartile ranges.
Asterisk indicates significant differences.



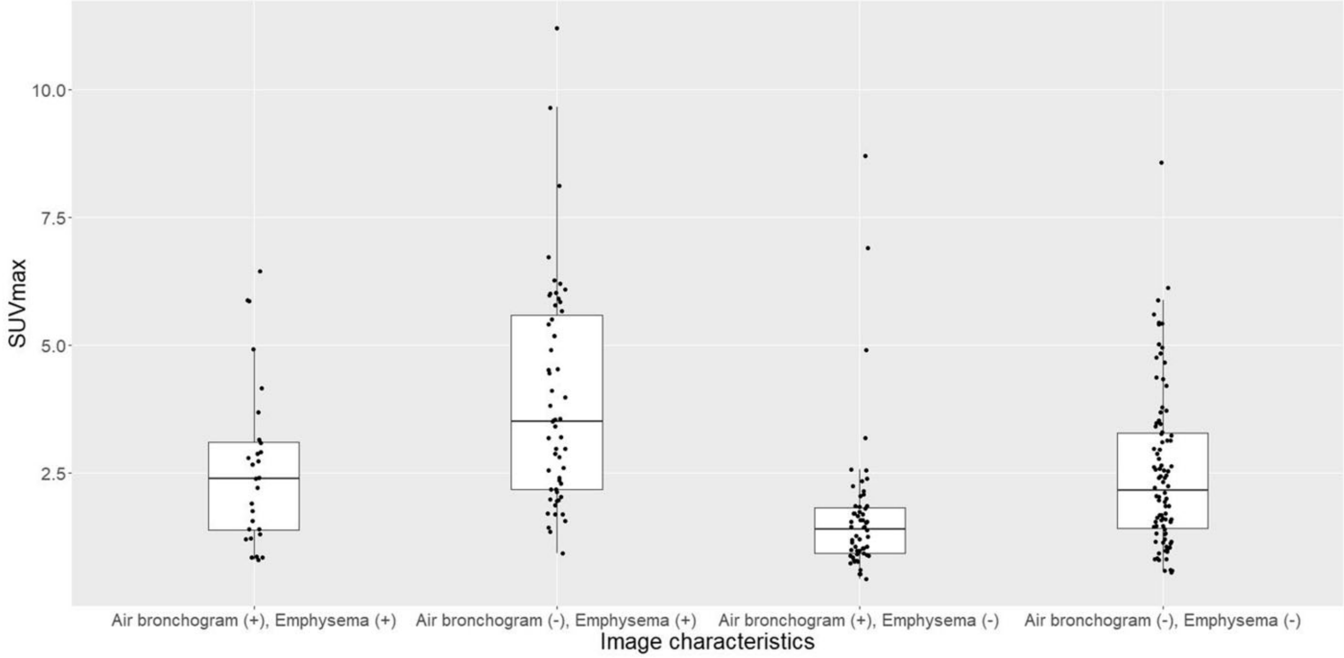


**Figure 6.** Box plots and scatter plots showing SUVmax values according to air bronchogram and background emphysema. The medians and interquartile ranges are shown in the box plots. Tumours arising from emphysematous lungs without air bronchograms tended to have high SUVmax values. On the other hand, tumours arising from non-emphysematous lungs with air bronchograms tended to have low SUVmax values, and most tumours had SUVmax values below 2.5.

screening CT protocols. Although visualization of small nodules is affected by radiation doses to some extent, the effects of radiation dose on image evaluation would be minimal because the image characteristics investigated in this study are relatively straightforward. Thirdly, we did not subcategorize the study population based on histological subtypes. This was because we aimed to generalize the study population to apply our results for the management of undiagnosed and intermediate-sized nodules found on screening CT. Further studies to correlate CT imaging features or FDG avidity with pathological subtypes are desirable.

## Conclusion

In conclusion, the presence of air bronchograms and the absence of background emphysema are associated with significantly low 18F-FDG accumulation in solid lung cancers between 8 and 15 mm. 18F-FDG PET is not recommended for lung nodules arising from non-emphysematous lungs with air bronchograms, as approximately 90% of lung cancers with these image features showed SUVmax values below the 2.5 threshold.

## Funding

None declared.

## Conflicts of interest

None declared.

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