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ORIGINAL ARTICLE

Accuracy of ^{18}F-FDG in Detecting Stage I Lung Adenocarcinomas According to IASLC/ATS/ERS Classification

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Background Only a small number of studies have explored the clinicopathological features of pulmonary adenocarcinoma (PA) associated with ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) false-negative (FN) results. Herein, we investigated the FDG-PET diagnostic performance by stratifying PAs according to International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) classification.

Methods From January 2002 to December 2016, all consecutive patients who underwent pulmonary resection for stage I PA at six thoracic surgery institutions were retrospectively reviewed. The diagnostic performance of FDG-PET was analysed according to IASLC/ATS/ERS classification and two validated subclassifications. Univariable and multivariable logistic analysis were used to identify predictors of FDG-PET FN results.

Results Five hundred and fifty (550) patients with stage I PA were included in the analyses. Most of the patients were male (n=354 [64.4%]) and smokers (n=369 [67.1%]). Ninety-seven (n=97 [17.6%]) FN cases were observed at FDG-PET imaging. On multivariable analysis, a lepidic pattern was found to be independently associated with FDG-PET FN results (odds ratio [OR], 3.20; p<0.001), while a solid pattern more commonly presented with a positive finding (OR, 0.40; p=0.066). According to Nakamura's classification, we observed an independent association between lepidic pattern and FDG-PET FN results (OR, 3.17; p<0.001), while solid/micropapillary patterns were independently related with increased FDG uptake (OR, 0.35; p=0.021). According to Yoshizawa's classification, Intermediate-grade tumours were independently correlated with FN FDG-PET results (OR, 2.78; p=0.005).

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Conclusions In our cohort, histopathological features were significantly associated with FDG uptake. In particular, some adenocarcinoma subtypes (mostly Lepidic pattern) have a tendency towards FN FDG-PET findings. The correlation between computed tomography findings, clinical characteristics, and FDG uptake is mandatory, in order to tailor the precise diagnostic and therapeutic pathway for each patient.

Keywords Pulmonary adenocarcinoma • PET • False negative • IASLC/ATS/ERS classification

Introduction

Currently, ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) represents a pivotal tool in the diagnostic work-up of solitary pulmonary nodules and in the staging pathway of non-small cell lung cancer (NSCLC) [1,2]. Nevertheless, FDG-PET has a low sensitivity with respect to ground glass opacity and, consequently, is not clearly indicated as a diagnostic tool in this radiological scenario [3,4]. However, the overall rate of false-negative (FN) findings is not negligible, which is also true in solid-type nodules, particularly pulmonary adenocarcinoma [5–8]. Consequently, the proper interpretation of a nodule negative at FDG-PET imaging is crucial for a timely, correct diagnosis and therapeutic treatments. A small number of studies have tried to identify the clinical characteristics and radiological features associated with FN FDG-PET findings.

In recent years, there has been a growing awareness of the clinical implications of the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) histopathological classification of lung adenocarcinomas [9]. Several studies have evaluated the association between IASLC/ATS/ERS patterns and clinical characteristics, tumour features, cells of origin, mutational profile, and prognosis [10–14]. Nevertheless, only a few studies have tried to find a correlation between IASLC/ATS/ERS histopathological pattern and FDG-PET findings [15].

The aim of our study was to explore the diagnostic performance of FDG-PET in stage I pulmonary adenocarcinoma (PA). Moreover, we explored the association between FN PET results and IASLC/ATS/ERS histological pattern, individually and clustered according to two validated subclassifications [16,17].

Materials and Methods

From January 2002 to December 2016 all consecutive patients who underwent lung surgical resection with curative intent for stage I PA at six thoracic surgery institutions were retrospectively reviewed. All patients were preoperatively evaluated as previously described [18]. Briefly, the preoperative patient assessment encompassed chest radiographs; thoracic and upper-abdominal computed tomography (CT) scans, and whole-body FDG-PET; fibreoptic bronchoscopy; and electrocardiograms and lung function tests.

The FDG-PET scans were reviewed by two nuclear medicine physicians with expertise in thoracic neoplasms. Surgical procedures were performed either via thoracotomy (muscle-sparing axillary or posterolateral) or video-assisted thoracic surgery. Exclusion criteria included any preoperative treatment regimen (e.g., chemotherapy and radiotherapy).

Data concerning age, sex, smoking habit, side of intervention, tumour size and location, type of surgical resection, pathological "tumour, node, metastasis" (pTNM) stage (according to the seventh edition), predominant histological pattern, and histological grade were included in the final dataset.

Histological grading was categorised into well- (G1), moderately (G2), and poorly differentiated (G3) carcinoma according to degree of architecture and cytological atypia.

The predominant adenocarcinoma patterns were determined according to the IASLC/ATS/ERS criteria [9]. Specimens from all cases prior to 2014, or not initially classified according to IASLC/ATS/ERS, were further reviewed by local pathologists. The predominant patterns were clustered according to the subclassifications proposed by Nakamura et al. (lepidic vs acinar/papillary vs solid/micropapillary vs not otherwise specified [NOS] – other) [16] and Yoshizawa et al. (lepidic/acinar/papillary vs solid/micropapillary/mucinous/colloid vs NOS – other) [17].

The standardised uptake value (SUV) was normalised by body weight, and the SUV_{max} was calculated as the highest tumour voxel value for the primary lung tumour in each patient. As widely accepted [2], we adopted a SUV_{max} cutoff value of 2.5 when discriminating a positive from a negative result on FDG-PET/CT imaging. Figure 1 demonstrates a patient with a lung adenocarcinoma (lepidic pattern) with a FN PET result before surgery. The study was approved by the institutional review board of each participating centre.

Statistical Analysis

Categorical data are presented as n (%), and continuous data as median with interquartile range (IQR). Factors associated with an augmented concordance between preoperative FDG-PET findings and histological results were assessed with linear and logistic regression models. Univariate and multivariate analysis were performed. Tumour size was tested during univariate analysis as a predictor of SUV_{max}, but as this parameter is strictly linked with "T" stage (especially in stage I tumours), it was not included in the multivariate model. All statistical analyses were performed using STATA (version 13; StataCorp, College Station, TX, USA).

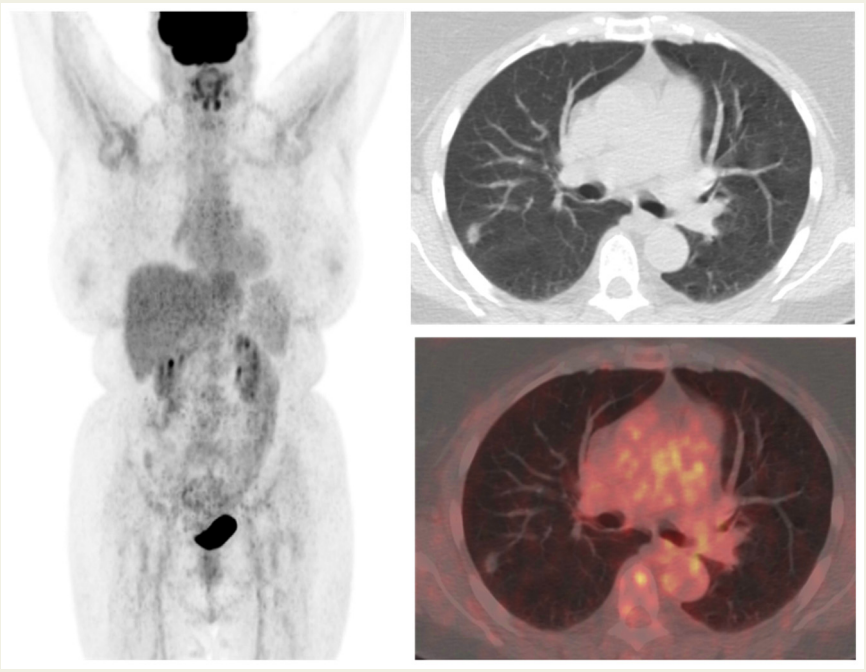

Figure 1 A representative case of a pulmonary adenocarcinoma with almost absent uptake at preoperative ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scan.

Results

According to the inclusion criteria, 550 patients with stage I PA were included in the analyses. Population demographics and clinical, radiological, surgical, and pathological characteristics are reported in Table 1.

Most of the patients were male (n=354 [64.4%]) and smokers (n=369 [67.1%]); median age at the time of surgery was 69 years (IQR, 63–74 years). Pathological stage Ia was more commonly observed (n=383 [69.6%]), and mean± standard deviation tumour size was 2.35±1.05 cm. On univariate analysis, tumour size was associated with higher SUV_{max} (coefficient, 0.08; 95% confidence interval [CI], 0.05–0.11; p<0.001).

Concordance Between IASLC/ATS/ERS Histological Pattern and FDG-PET Imaging

At the final pathological analysis, the most frequently observed predominant pattern was acinar (n=240 [43.6%]), followed by papillary (n=89 [16.2%]), solid (n=83 [15.1%]), lepidic (n=79 [14.4%]), and micropapillary (n=23 [4.2%]). The median SUV_{max} was 4.6 (IQR, 3–8.4). According to the IASLC/ATS/ERS classification, the median SUV_{max} was 4.6 (IQR, 3–8.6) for predominantly acinar adenocarcinomas, 4.5 (IQR, 3.3–7.6) for papillary, 5.7 (IQR, 3.4–11.3) for solid, 3.2 (IQR, 1.8–6.2) for lepidic, 4.1 (IQR, 3.1–7.3) for mucinous, and 5 (IQR, 3.3–8.2) for micropapillary adenocarcinomas (Figure 2).

The FDG-PET results correctly identified 453 stage I PA (82.4%). According to the IASLC/ATS/ERS classification, we observed 39 (16.3%) FN cases in the predominantly acinar group, 14 (15.7%) in the papillary, five (6.0%) in the solid, 33 (41.7%) in the lepidic, four (14.8%) in the mucinous, and one (4.3%) in the micropapillary groups.

At univariate analysis, a predominantly lepidic pattern were found to be associated to a FN finding at FDG-PET imaging (odds ratio [OR], 3.70; 95% confidence interval [CI], 2.10–6.50; p<0.001), while solid histology more commonly presented a SUV_{max}>2.5 (OR, 0.33; 95% CI 0.13–0.87; p=0.025). Pathological TNM stage Ib (OR, 0.30; 95% CI 0.16–0.56; p<0.001), a history of smoking (OR, 0.51; 95% CI 0.29–0.89; p<0.001), and a higher tumour grade (OR 0.34, 95% CI 0.24 to, 0.50, p=0.017) were more likely to be related to a positive FDG-PET finding. When we clustered the cohort according to the subclassification of Nakamura et al. [16], we observed a correlation between lepidic histology and a SUV_{max}<2.5 (OR, 3.76; 95% CI 2.22–6.39,), while solid/micropapillary histology was associated with higher radiotracer uptake (OR, 0.31; 95% CI 0.13–0.75; p=0.009). According to the subclassification of Yoshizawa et al. [17], an intermediate-grade adenocarcinoma pattern was more commonly associated with FN FDG-PET findings (OR, 3.39; 95% CI 1.71–6.74; p<0.001) (Table 2).

At multivariate analysis, a predominantly lepidic pattern was found to be independently associated with a FN finding at FDG-PET imaging (OR, 3.20; 95% CI 1.77–5.80; p<0.001), while solid histology more commonly presented with a SUV_{max}>2.5 (OR, 0.40; 95% CI 0.15–1.06; p=0.066).

Table 1 Patient characteristics.

	N=550
Median (IQR) age (yr)	69 (63–74)
Sex	
Female	196 (35.6)
Male	354 (64.4)
Smoking History	
Never	84 (15.3)
Not known	97 (17.6)
Yes	369 (67.1)
Side	
Left	225 (40.9)
Right	325 (59.1)
Location	
Lower zone	167 (30.4)
Upper zone	383 (69.6)
Median (IQR) FDG-PET SUV_{max}	4.6 (3–8.4)
FDG-PET - SUVmax	
<2.5	97 (17.6)
>2.5	453 (82.4)
Surgical resection	
Major	483 (87.8)
Sub-Lobar	67 (12.2)
pTNM	
IA	383 (69.6)
IB	167 (30.4)
Tumour Grade (n=508)	
G1	96 (18.9)
G2	262 (51.6)
G3	150 (29.5)
IASLC/ATS/ERS	
Acinar	240 (43.6)
Colloid	4 (0.7)
Lepidic	79 (14.4)
Micropapillary	23 (4.2)
Mucinous	27 (4.9)
NOS	5 (0.9)
Papillary	89 (16.2)
Solid	83 (15.1)
Nakamura	
Acinar – papillary – mucinous	356 (64.7)
Lepidic	79 (14.4)
NOS – colloid	9 (1.6)
Solid – micropapillary	106 (19.3)
Yoshizawa[a]	
High grade	137 (24.9)
Intermediate grade	408 (74.2)
NOS – other	5 (0.9)

Data are n (%) unless otherwise stated.

Abbreviations: IQR, interquartile range; FDG-PET, 18F-fluorodeoxyglucose positron emission tomography; SUV_{max}, standard uptake value (maximum); pTNM, pathological TNM; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; NOS, not otherwise specified.

[a]Intermediate grade: lepidic/acinar/papillary; high grade: solid/micropapillary/mucinous/colloid.

According to the subclassification of Nakamura et al. [16], we observed an independent association between lepidic histology and a SUV_{max}<2.5 (OR, 3.17; 95% CI 1.81–5.55; p<0.001), while solid/micropapillary histology was independently related to a positive uptake value (OR, 0.35; 95% CI 0.14–0.85; p=0.021). Finally, when we clustered the cohort according to the subclassification of Yoshizawa et al. [17], intermediate-grade adenocarcinoma pattern was independently correlated with FN FDG-PET findings (OR, 2.78; 95% CI 1.37–5.63; p=0.005) (Table 3).

Discussion

Although FDG-PET represents a cornerstone in the diagnostic pathway of NSCLC [1,2], FN cases are not uncommon. Negative radiometabolic findings should be correlated with the clinical features and with CT imaging, so that a malignant lung nodule is not misdiagnosed. Indeed, the histological features of pulmonary adenocarcinomas are predictive of FDG-PET results, as reported in the present study.

In this context, the results of our study, conducted on a surgical cohort of 550 patients with stage I PA, suggest that (1) the histopathological findings were associated with FDG-PET uptake; (2) some histological patterns have a higher tendency for FN FDG-PET findings; (3) the FN rate is especially high in lepidic and not negligible in acinar, papillary, and mucinous subtypes.

In the last year, several studies have demonstrated that FDG-PET sensitivity and specificity can be influenced by several factors that affect the homogeneity of SUV_{max} values: patient age; blood glucose concentration; weight; tumour size; anatomical location; percentage of solid component at CT; tumour invasiveness; and tumour grade have been reported [5,8,19,20]. Moreover, the sensitivity of FDG-PET in routine clinical practice has been shown to be lower than in the academic setting [21]. Congruently, our study on a large population of patients with histologically proven PA revealed a not inconsiderable number of FN findings (n=97 [17.6%]). Therefore, clinicians should be cautious in evaluating negative FDG-PET findings in solitary pulmonary nodules, especially if one or more risk factors are present.

The low sensitivity of FDG-PET findings in histological subtypes characterised by less aggressive biological behaviour is well documented (e.g., bronchopulmonary carcinoid, bronchioloalveolar carcinoma, and minimally invasive carcinoma) [22–24]. Nevertheless, some studies have reported a

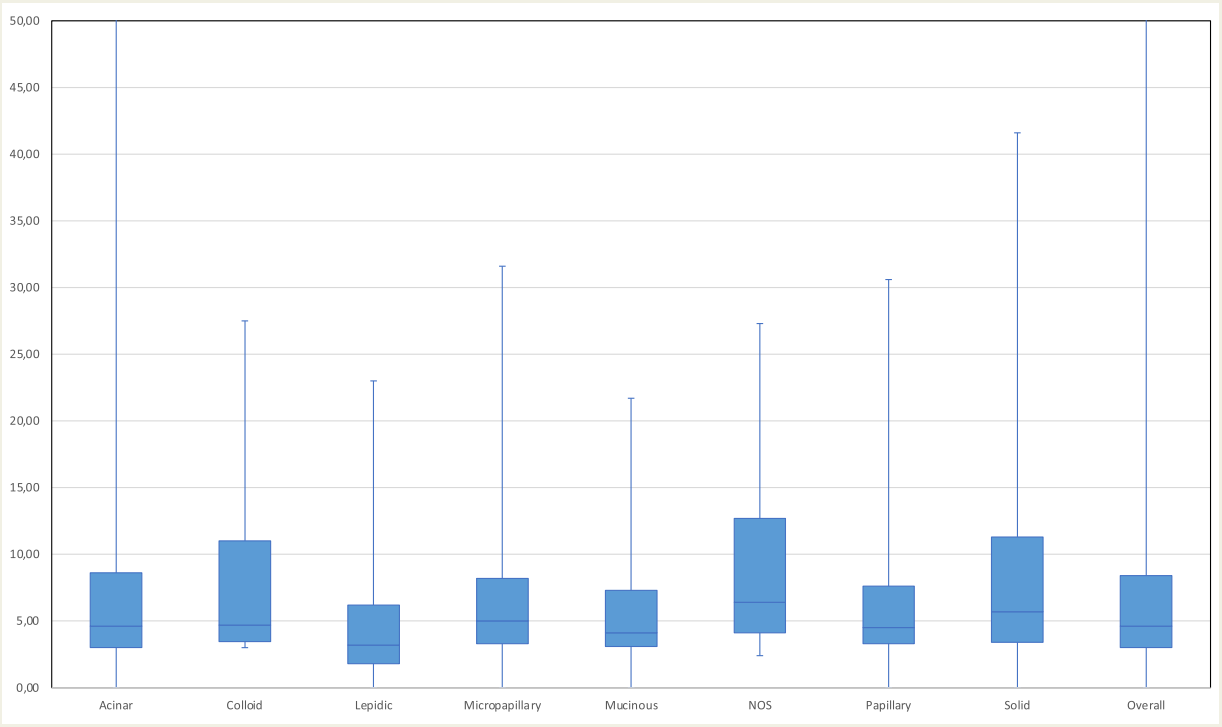

Figure 2 Box-and-whisker plots illustrate the distribution of maximum standardised uptake values according to International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society-predominant patterns.

Table 2 Univariable logistic regression analysis for false-negative 18F-fluorodeoxyglucose positron emission tomography findings.

	OR	95% CI	P-value
IASLC/ATS/ERS			
Acinar	(Ref.)		
Lepidic	3.70	2.10–6.50	<0.001
Micropapillary	0.23	0.031–1.79	0.16
Mucinous	0.90	0.29–2.74	0.85
NOS	1.29	0.14–11.8	0.82
Papillary	0.96	0.49–1.87	0.91
Solid	0.33	0.13–0.87	0.025
Nakamura et al. [16]			
Acinar – papillary	(Ref.)		
Lepidic	3.76	2.22–6.39	<0.001
NOS – colloid	0.66	0.080–5.34	0.69
Solid – micropapillary	0.31	0.13–0.75	0.0093
Yoshizawa et al. [17] [a]			
High grade	(Ref.)		
Intermediate	3.39	1.71–6.74	<0.001
NOS – other	3.17	0.32–31.2	0.32

Abbreviations: OR, odds ratio; CI, confidence interval; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; NOS, not otherwise specified.
[a]Intermediate grade: lepidic/acinar/papillary; high grade: solid/micropapillary/mucinous/colloid.

remarkable FN rate in invasive lung adenocarcinoma, compared to other histological types such as squamous cell carcinoma, adenosquamous carcinoma, and large-cell carcinoma [8]. For this reason, we focussed on invasive lung adenocarcinoma only, and our results indicate a not inconsiderable risk of FN findings in this context [12,25].

Recently, there has been increasing interest in the clinical implications of IASLC/ATS/ERS histopathological patterns of lung adenocarcinomas [10–16]. Different studies have reported the effect of adenocarcinoma subtype on SUV_{max} [17,21,26]. In particular, Nakamura et al. [16] analysed 255 surgically treated lung adenocarcinomas, and included minimally invasive, stage I–III disease. The authors grouped the different patterns into three different clusters of similar biological behaviours that correlated with 18F-FDG avidity. In our cohort of invasive stage I adenocarcinoma, the clusters of Nakamura et al. [16] showed a similar correlation with SUV_{max} findings. Moreover, Kadota et al. [26] analysed a cohort of 222 patients with stage I adenocarcinoma of the lung demonstrating a higher SUV_{max} in predominantly micropapillary and solid subtypes. Similarly, some have documented a comparable association between IASLC/ATS/ERS histopathological subtypes and FDG PET findings [17]. Nevertheless, these studies were monocentric and conducted on a relatively small cohort of patients, substantially limiting the power of the statistical analysis. Our multicentre study, which was conducted in a cohort of 550 patients with stage I lung adenocarcinoma, confirmed that the FDG-PET

Table 3 Multivariable-adjusted logistic regression analysis for false-negative 18F-fluorodeoxyglucose positron emission tomography findings.

Multivariable Analysis[a]	OR	95% CI	P-value
IASLC/ATS/ERS			
Acinar	(Ref.)		
Lepidic	3.20	1.77–5.80	<0.001
Micropapillary	0.23	0.029–1.75	0.15
Mucinous	1.05	0.34–3.30	0.93
NOS	0.97	0.10–9.22	0.98
Papillary	1.02	0.51–2.01	0.96
Solid	0.40	0.15–1.06	0.066
Nakamura et al. [16]			
Acinar – papillary	(Ref.)		
Lepidic	3.17	1.81–5.55	<0.001
NOS – colloid	0.52	0.063–4.28	0.54
Solid – micropapillary	0.35	0.14–0.85	0.021
Yoshizawa et al. [17] [b]			
High grade	(Ref.)		
Intermediate	2.78	1.37–5.63	0.005
NOS – other	1.86	0.18–19.1	0.60

Abbreviations: OR, odds ratio; CI, confidence interval; IASLC, International Association for the Study of Lung Cancer; ATS, American Thoracic Society; ERS, European Respiratory Society; NOS: not otherwise specified.
[a]Account for smoking history, pathological TNM stage, and tumour grade.
[b]Intermediate grade: lepidic/acinar/papillary; high grade: solid/micropapillary/mucinous/colloid.

FN rate correlates with IASLC/ATS/ERS classification, and is particularly high in adenocarcinomas with a lepidic pattern and relatively low in those with a solid pattern. Moreover, the FN findings were not inconsiderable in the acinar, papillary, and mucinous subtypes, which are characterised by a more aggressive behaviour than lepidic adenocarcinomas.

Our study had some limitations, which are principally related to the retrospective nature of the analysis. Moreover, differences in FDG-PET technologies and equipment between different centres may have affected the data collected. Nevertheless, we think that the multicentre design of the study enhances the realism of the findings and consequently supports our conclusions.

Conclusion

Histopathological findings in PAs were significantly associated with FDG uptake. In particular, some adenocarcinoma subtypes (mostly those with a lepidic pattern and, to a lesser extent, acinar, papillary, and mucinous patterns) have a tendency towards FN FDG-PET findings. Thus, the incorporation of radiometabolic findings with the clinical characteristics of patients and the lesion's radiological features is mandatory in order to tailor the precise diagnostic and therapeutic pathway for each patient.

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Conflict of Interest

There are no conflicts of interest to disclose.

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