Histological Subtypes of Lung Adenocarcinoma Have Differential ^{18}F-Fluorodeoxyglucose Uptakes on the Positron Emission Tomography/Computed Tomography Scan

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Introduction: Previous studies have shown that lung squamous cell carcinoma has higher ^{18}F-fluorodeoxyglucose (FDG) uptake on positron emission tomography (PET) than adenocarcinoma. We hypothesized that histological subtypes of lung adenocarcinoma were also different in ^{18}F-FDG uptake.

Methods: Patients who had preoperative PET/computed tomography (CT) scan and had undergone complete resection for lung adenocarcinoma between April 2007 and December 2009 were enrolled in this study. Because of the limitation of spatial resolution on PET/CT, tumors less than 1 cm were excluded for analysis. Two independent classification systems were used to categorize histological subtypes of adenocarcinoma; one was modified from the current World Health Organization classification and the other used the morphological features of the terminal respiratory unit (TRU). The maximal standardized uptake value (SUVmax) on PET/CT and the glucose transporter type 1 (GLUT-1) expression of the tumors were measured and correlated to the histology of lung adenocarcinoma.

Results: One hundred fifty-two patients with 153 primary lung adenocarcinomas were included. There was a significant difference in SUVmax among different histological subtypes. Namely, solid predominant adenocarcinomas had significantly higher SUVmax than those with other predominant histology ($p < 0.001$), and TRU-type adenocarcinomas had significantly lower SUVmax than non-TRU-type adenocarcinomas ($p < 0.001$). Consistently, GLUT-1 expression was higher in tumors with a solid growth pattern than those without ($p < 0.001$) and in tumors with non-TRU type than TRU type ($p < 0.001$).

Conclusions: The histological subtypes of lung adenocarcinomas differ in GLUT-1 expression and ^{18}F-FDG uptake on the PET/CT scan, suggesting that histological subtyping not only has morphological but also biological implications.

Key Words: Lung adenocarcinoma, Histological subtyping, ^{18}F-fluorodeoxyglucose, Positron emission tomography, Glucose transporter type 1.

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Altered metabolism is one of the hallmarks of cancer,[1,2] and increased utilization of glucose is the first to be discovered.[3] It is the basic principle for the development of ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) in oncology.[4] ^{18}F-FDG-PET is now widely used in the clinical diagnosis and staging of variable types of cancers, including non-small cell lung cancer.

Previous studies have consistently shown that pulmonary squamous cell carcinoma displays higher glucose transporter type 1 (GLUT-1) expression and ^{18}F-FDG uptake than adenocarcinoma.[5–7] However, whether histological subtypes of adenocarcinoma also differ in ^{18}F-FDG uptake is still not clear. In the current World Health Organization (WHO) classification of lung cancer, adenocarcinomas are mainly categorized as acinar, papillary, bronchioloalveolar, solid with mucin production, and mixed type.[8] This classification is not clinically useful because pure subtype adenocarcinoma is rare. In the new International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society (IASLC/ATS/ERS) international multidisciplinary classification, the category of mixed type is no longer used, and adenocarcinoma is classified according to its predominant histology.[9] Previous studies have already used this approach and found significant prognostic implication of this classification.[10–12]

In addition to the WHO classification, there are other classification systems. For example, Japanese researchers used the morphological features of the terminal respiratory unit (TRU) to classify lung adenocarcinomas as TRU type or non-TRU type.[13] Besides morphological differences, TRU-type adenocarcinoma is more likely to contain thyroid transcription factor-1 (TTF-1) expression and epidermal growth factor receptor (EGFR) mutations,[13,14] implying that the mo-

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lecular mechanism of carcinogenesis varies between TRU-type and non-TRU-type adenocarcinomas.[14,15] A possible difference in ^{18}F-FDG uptake between these two types of adenocarcinoma has not been elucidated.

In this study, we hypothesized that histological subtypes of lung adenocarcinoma were different in ^{18}F-FDG uptake. Using two independent classification systems, we evaluated the ^{18}F-FDG uptake on PET/computed tomography (CT) in various histological subtypes of lung adenocarcinoma. We showed a significant difference in standardized uptake value (SUV), a semiquantitative parameter to evaluate ^{18}F-FDG uptake, among various histological subtypes of lung adenocarcinoma and a correlation with GLUT-1 expression. Our study results support that lung adenocarcinoma comprises a heterogeneous group of diseases, and histological subtyping possesses both morphological and biological implications.

PATIENTS AND METHODS

Patients

We identified a cohort of patients who underwent complete surgical resection for lung adenocarcinoma at a tertiary medical center during the period of April 2007 through December 2009. Patients were included if they had undergone a preoperative PET/CT scan. Tumors less than 1 cm in diameter were excluded because of the consideration that the limited spatial resolution of PET/CT might interfere with the interpretation. The pathological staging was based on the 7th edition of the tumor, node, metastasis classification for lung cancer.[16] This study was first approved by the Committee of Pathology Specimen and then was approved by the Institution Review Board of Taipei Veterans General Hospital. All patients had provided written informed consent to the Residual Sample Bank before operation.

Histological Classification

Two classifications of lung adenocarcinoma were used. The first was modified from the current WHO classification[8] with the approach proposed by the new IASLC/ATS/ERS international multidisciplinary classification.[9] Tumors were recorded for the percentage of each morphological growth pattern, namely, solid, papillary, acinar, and lepidic growth, in a 5% increment and classified according to the most predominant growth pattern. The second classification system was modified from the studies of Dr. Yatabe.[13,14] Tumors were classified as TRU type if the cancer cells were characterized morphologically by a cuboidal or dome-shaped free cell contour. Non-TRU-type cancer cells were characterized by their smoothly contoured luminal border. In both classification systems, a population of less than 10% was considered insignificant.

^{18}F-FDG PET/CT

All patients fasted for at least 6 hours, and their blood glucose levels were required to be less than 180 mg/dl before examination. Fifty minutes after intravenous injection of 370 MBq of ^{18}F-FDG, the PET/CT imaging was obtained from the head to the upper portion of the thigh on an integrated PET/CT scanner (Discovery VCT, GE Healthcare, Waukesha, WI). A low-dose CT scan for attenuation correction and localization was performed with a 64-slice multidetector CT of the hybrid scanner, followed by an emission scan with 3D-mode acquisition. The raw data of PET imaging were reconstructed into a 128 × 128 matrix using an iterative reconstruction algorithm (iteration 2 and subset 28). For semiquantitative analysis of ^{18}F-FDG uptake, SUV was assessed on the Xeleris Workstation (GE Healthcare). The maximal SUV (SUVmax) of the lung tumor was measured by drawing a 1.0-cm diameter region of interest within the lesion on the slice with the highest uptake.

Immunohistochemical Staining of GLUT-1

Tumor specimens from patients who underwent surgery between March 2008 and December 2009 were available and approved for further testing. Immunohistochemical staining was performed as described previously.[17] Briefly, representative sections (3 μm in thickness) were cut from the formalin-fixed paraffin-embedded block. Tissue slides were heated at 56°C overnight, deparaffinized with xylene, and rehydrated with ethanol. Slides were then placed evenly in a prewarmed 0.1 M citrate buffer (pH = 6.4) and heated in a microwave for antigen retrieval. Hydrogen peroxide (3%) was used to block endogenous peroxidase. A rabbit antihuman GLUT-1 polyclonal antibody (1:800 dilution; Millipore, Billerica, MA) was then used to incubate the tissue slides at room temperature for 1 hour. Antigen-antibody reactions were visualized after slides were reacted with a secondary antibody (Dako REAL EnVision Detection System, Dako Denmark A/S, Denmark) at room temperature for 1 hour. All slides were counterstained with hematoxylin. The intensity of GLUT-1 staining was categorized using a 4-point scale: 0, same as negative control; 1+, weak staining; 2+, moderate staining; and 3+, strong staining. Each slide was read independently by two authors (C.-H.C. and Y.-C.Y.).

Statistical Analysis

Because the measurement of SUVmax is semiquantitative and the distribution was not normal, nonparametric tests were used to analyze the significance of difference between groups. Spearman rank correlation was performed to analyze the correlation between the percentage of specific growth pattern and SUVmax and between GLUT-1 expression and SUVmax. A p value less than 0.05 was considered statistically significant. When multiple comparisons were performed, the cutoff level of α error was reduced to 0.05/(number of tests) (Bonferroni correction). SPSS Statistics 17.0 (SPSS Inc., Chicago, IL) was used to carry out the analysis and construct the figures.

RESULTS

Patient and Tumor Characteristics

This study included 152 patients with 153 primary lung adenocarcinomas. Table 1 summarizes the demographic data and tumor characteristics of patients. Most tumors (79%) were stage I or II, and the median size was 2.5 cm (range =

TABLE 1. Patient Demographics and Tumor Characteristics

	n (%)
Gender	
Male	69 (45.4)
Female	83 (54.6)
Age (yr)	
Median (range)	64 (35–87)
Tumor size (cm)	
Median (range)	2.5 (1.0–7.5)
Predominant subtypes	
Solid	26 (17.0)
Papillary	74 (48.4)
Acinar	44 (28.8)
Lepidic	8 (5.2)
Others	1 (0.7)
TRU/non-TRU	
TRU	52 (34.0)
Non-TRU	83 (54.2)
Mixed	18 (11.8)
Type of operation	
Pneumonectomy	1 (0.7)
Lobectomy	138 (90.2)
Segmentectomy	2 (1.3)
Wedge resection	12 (7.8)
Staging	
IA	34 (22.2)
IB	69 (45.1)
IIA	16 (10.5)
IIB	7 (4.6)
IIIA	20 (13.1)
IIIB	1 (0.7)
IV	6 (3.9)
SUVmax	
Median (range)	4.5 (0.6–19.6)

TRU, terminal respiratory unit; SUVmax, maximal standardized uptake value.

1.0–7.5 cm). ^{18}F-FDG PET/CT was performed before the operation by a median of 6 days (range = 0–83 days), and the median SUVmax was 4.5 (range = 0.6–19.6).

According to the current WHO classification, only 12 tumors can be categorized into one of the four major subtypes of adenocarcinoma (7 solid, 3 papillary, 1 acinar, and 1 bronchioloalveolar carcinoma), and the others (92%) were all mixed-type adenocarcinoma. Using the modified WHO classification described above, the most common subtype was papillary predominant adenocarcinoma, followed by acinar, solid, and lepidic predominant adenocarcinoma. Tumors were also classified as TRU-type or non-TRU-type adenocarcinoma as described previously. However, we encountered a practical problem: we found 18 tumors (11.8%) having both TRU- and non-TRU-type morphology. We then created a mixed-type category in this study. TRU-type morphology was the predominant histology in 13 of the 18 cases.

Association Between Modified WHO Histological Classification and SUVmax

Using modified WHO histological classification, a significant difference in SUVmax was found among the four major subtypes ($p < 0.001$), and solid predominant adenocarcinoma had significantly higher SUVmax than the other subtypes (all p values <0.001; Figure 1*A*). We also found that tumors with a solid growth pattern had higher SUVmax than those without ($p < 0.001$). A positive correlation exhibited between the percentage of solid growth pattern in a tumor and its SUVmax (Spearman $\rho = 0.545$, $p < 0.001$; Figure 1*B*). Because tumor size has major influence on SUVmax, we conducted further analysis to determine a possible association between tumor size and histological subtypes. We found that tumor size did not differ significantly among the four histological subtypes ($p = 0.323$).

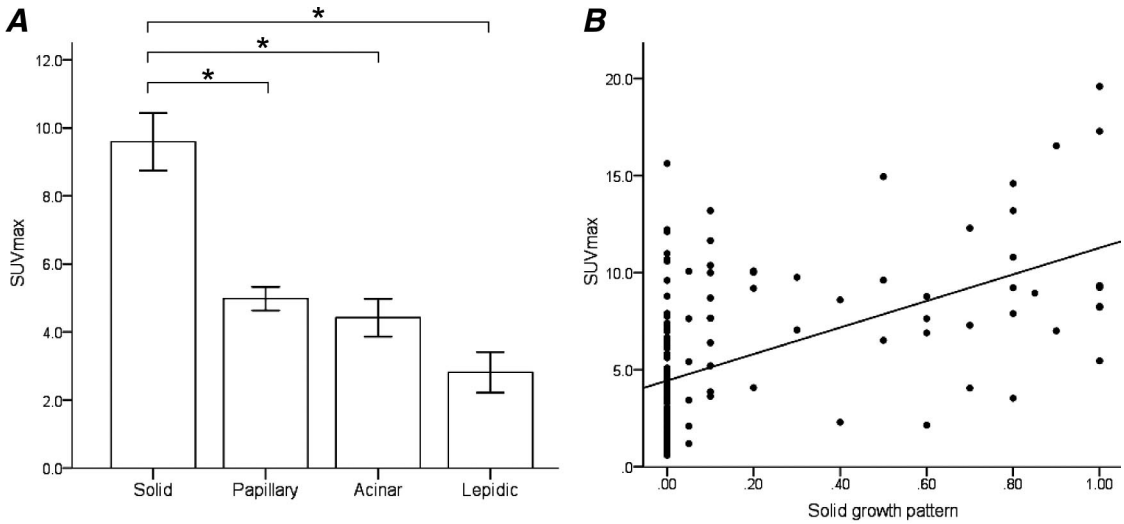

FIGURE 1. SUVmax in different subtypes of lung adenocarcinomas categorized according to the predominant histological growth pattern. Solid predominant adenocarcinoma has higher SUVmax than other subtypes (*A*), and there is a correlation between the percentage of solid growth pattern and SUVmax (*B*). *p less than 0.001. SUVmax, maximal standardized uptake value.

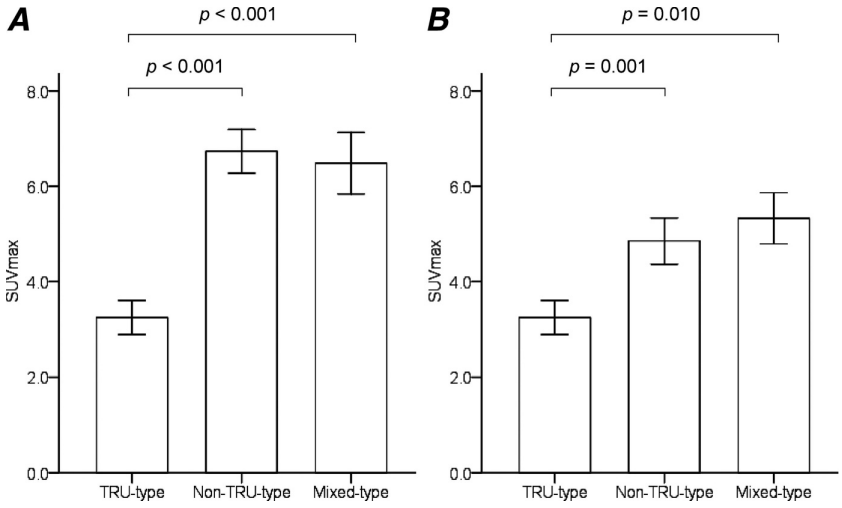

FIGURE 2. SUVmax in TRU-type and non-TRU-type lung adenocarcinomas. TRU-type adenocarcinoma has significantly lower SUVmax than the non-TRU type in all patients (*A*) and also in the subgroup, excluding those with a solid growth pattern (*B*). SUVmax, maximal standardized uptake value; TRU, terminal respiratory unit.

Association Between TRU Histological Classification and SUVmax

To confirm the importance of histology on ^{18}F-FDG-PET, we next evaluated whether ^{18}F-FDG uptake differed between TRU-type and non-TRU-type adenocarcinomas. Indeed, TRU-type adenocarcinoma demonstrated significantly lower SUVmax than the non-TRU type ($p < 0.001$; Figure 2*A*). Because we had shown that solid growth pattern had significant influence on SUVmax and had evaluated tumors with a solid growth pattern as the non-TRU type, we performed a subgroup analysis ($n = 108$) excluding tumors with a solid growth pattern. Again, TRU-type adenocarcinomas exhibited lower SUVmax than nonsolid non-TRU-type adenocarcinomas ($p = 0.001$; Figure 2*B*).

GLUT-1 Expression in Different Subtypes of Adenocarcinomas

To explore the mechanism for differential ^{18}F-FDG uptake in tumors, we evaluated the GLUT-1 expression in 64 patients whose tumor specimens were available. No significant difference was evidenced in both patient demographics and tumor characteristics between those who had and had not been examined for GLUT-1 expression (Supplementary Table 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A100). In this cohort, 40 tumors (62.5%) had positive staining for GLUT-1 (weak in 19, moderate in 14, and strong in 7), and a close correlation between SUVmax and GLUT-1 expression was found (Spearman $\rho = 0.536$, $p < 0.001$; Figure 3). Consistent with the observation above, we noted higher GLUT-1 expression in tumors with a solid growth pattern than those without ($p = 0.002$) and also in tumors with non-TRU type than TRU type ($p = 0.001$) (Table 2). In addition, tumors with an acinar growth pattern had lower GLUT-1 expression than those without ($p = 0.008$). Interestingly, for those with mixed TRU and non-TRU-type adenocarcinoma, GLUT-1 expression was typically higher in non-TRU than TRU histology in the same tumor (Figure 4). Together, these data suggested that subtypes of lung adenocarcinomas differed in ^{18}F-FDG uptake, which may exert through the differential expression of GLUT-1 protein.

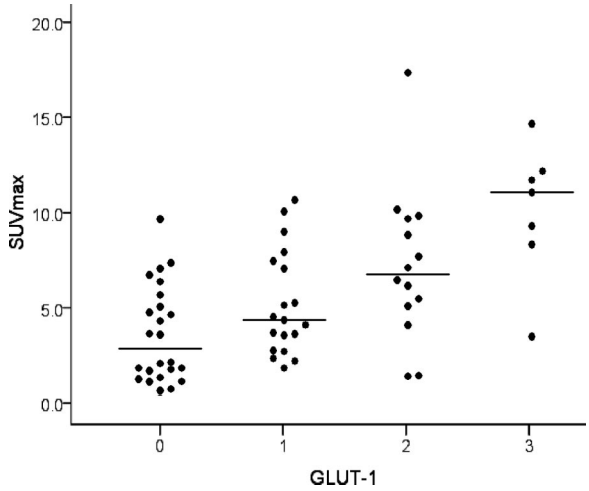

FIGURE 3. SUVmax in lung adenocarcinomas categorized according to the GLUT-1 immunohistochemical staining intensity ($p < 0.001$). SUVmax, maximal standardized uptake value; GLUT, glucose transporter type 1.

DISCUSSION

Adenocarcinoma and squamous cell carcinoma are the two major types of non-small cell lung cancer, and further subclassification is not commonly used clinically. However, increasing evidence indicates that lung adenocarcinoma comprises a heterogeneous group of diseases with various prognosis.[10–12] Our data supported this hypothesis. We showed that in two independent classification systems, histological subtypes of lung adenocarcinoma differed in ^{18}F-FDG uptake. These results suggest that the dysregulated glucose metabolism one of the hallmarks of cancer, is dissimilar in these tumors. Therefore, histological subtyping of lung adenocarcinoma is relevant not only for its morphological significance but also for its biological and clinical implications.

In the current WHO classification, lung adenocarcinoma can be further categorized according to its histology; however, it is not widely used. The clinical application is limited because less than 20% of lung adenocarcinomas

TABLE 2. Correlations Between GLUT-1 Expression and Clinicopathological Variables

	GLUT-1 Staining Intensity				
	0	1+	2+	3+	*p*
Gender (%)					0.136[a]
Male	25.9	25.9	29.6	18.5	
Female	45.9	32.4	16.2	5.4	
Age (%)					0.199[a]
<70 yr	31.0	38.1	21.4	9.5	
≥70 yr	50.0	13.6	22.7	13.6	
WHO histological pattern					
Solid (%)					
Absent	50.0	28.3	15.2	6.5	0.002[a]
Present	5.6	33.3	38.9	22.2	
Papillary (%)					
Absent	35.7	28.6	7.1	28.6	0.094[a]
Present	38.0	30.0	26.0	6.0	
Acinar (%)					
Absent	0	0	50.0	50.0	0.008[a]
Present	40.0	31.7	20.0	8.3	
Lepidic (%)					
Absent	30.4	34.8	23.9	10.9	0.294[a]
Present	55.6	16.7	16.7	11.1	
TRU/non-TRU type (%)					0.001[a]
TRU	69.6	17.4	13.0	0	
Non-TRU	21.2	36.4	21.2	21.2	
Tumor size (cm) (median)	2.9	2.0	2.5	4.0	0.196[b]
SUVmax (median)	2.8	4.3	6.7	11.0	<0.001[b]

[a] Fisher's exact test.
[b] Spearman rank correlation test.
WHO, World Health Organization; TRU, terminal respiratory unit; SUVmax, maximal standardized uptake value.

contain pure histology and most tumors are in the same category, mixed-type adenocarcinoma.[18] Our study concurred with this finding and showed that 92% of the tumors were mixed type. However, the histological growth patterns, namely, acinar, papillary, lepidic, and solid, do have prognostic implications. For example, a solid growth pattern is associated with poor prognosis[19] and bronchioloalveolar carcinoma, which is defined by pure lepidic growth pattern without invasion, demonstrates an excellent outcome.[20] Several studies have therefore modified the WHO classification by classifying lung adenocarcinoma according to its predominant histology and have shown the usefulness of this strategy.[10–12] In fact, it has been adapted for the new IASLC/ATS/ERS classification. In this study, we used the same approach and showed that solid predominant adenocarcinomas exhibited higher ^{18}F-FDG uptake than the others and there was a correlation between the percentage of solid growth pattern and SUVmax. Because tumors with high SUV demonstrate aggressive behavior,[21,22] our finding provides further evidence to support that a solid growth pattern in lung adenocarcinoma associates with poor prognosis.

With regard to the association between lepidic growth pattern and ^{18}F-FDG uptake, we found a lower SUV in lepidic predominant adenocarcinoma; however, the difference did not reach statistical significance (versus papillary predominant, $p = 0.049$; versus acinar predominant, $p = 0.335$; Figure 1*A*). Previous investigators noted a lower SUV in bronchioloalveolar carcinoma[5,23–25]; however, contradictory results were also reported.[7] Of all patients in this study, there was only one bronchioloalveolar carcinoma, and less than 6% ($n = 8$) of tumors were classified as lepidic predominant adenocarcinoma. The SUVmax of these tumors ranged from 0.8 to 5.0 and half of them were above 2.5 (a common cutoff value used to differentiate malignant from benign disease). Because of the limited case number, this study cannot conclude the role of lepidic growth pattern in ^{18}F-FDG uptake. A larger cohort of patients is needed to address this issue.

Recently, Japanese researchers have proposed another histological classification of lung adenocarcinoma. TRU-type adenocarcinoma is characterized by a cuboidal or dome-shaped free cell contour, which is morphologically similar to type II pneumocytes, Clara cells, or nonciliated bronchiolar epithelium. Non-TRU-type adenocarcinoma is characterized by cancer cells with a smoothly contoured luminal border and basally oriented nuclei. Genetically, TRU-type and non-

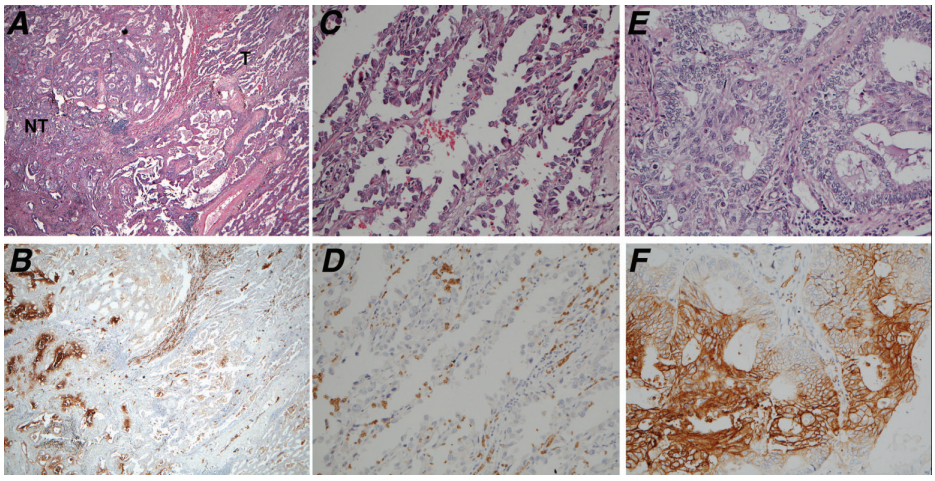

FIGURE 4. A representative case of lung adenocarcinoma with mixed TRU (T) and non-TRU (NT) morphology (*A*; HE stain, 20×), which is apparently highlighted by the immunohistochemical staining of GLUT-1 (*B*). The magnified view of the right field in panel A shows cancer cells with characteristic TRU morphology (*C*; HE stain, 200×) and the GLUT-1 staining is negative (*D*). The magnified view of the left field in panel A shows cancer cells with characteristic non-TRU morphology (*E*; HE stain, 200×), and the GLUT-1 staining is strongly positive (*F*). TRU, terminal respiratory unit; HE, hematoxylin and eosin; GLUT, glucose transporter type 1.

TRU-type adenocarcinomas are distinct, at least, in the frequencies of TTF-1 expression and EGFR mutations. In this study, we showed that these two subtypes of lung adenocarcinoma also differed in glucose metabolism. TRU-type adenocarcinomas had lower GLUT-1 expression and lower ^{18}F-FDG uptake than non-TRU-type tumors. Interestingly, in this series, we identified cases with mixed TRU and non-TRU histology, and GLUT-1 seemed to be preferentially overexpressed in the non-TRU component in the same tumor. This observation further supports that cancer cells with TRU and non-TRU morphology are biologically different.

In this study, applying the strategy proposed by previous researchers,[10–12] we modified the current WHO pathological classification by using the predominant histology in a tumor. This strategy is also used in the new IASLC/ATS/ERS classification. However, this new system has other modifications. For example, formerly bronchioloalveolar carcinomas without invasion are now considered adenocarcinoma in situ and those with minimal invasion ($\leq$5 mm) are called minimally invasive adenocarcinomas. In our series, only one case fulfills the criteria of adenocarcinoma in situ and, therefore, it will hardly have influence on our study results. The new classification system separates micropapillary from papillary growth pattern. In our study, we did not find any association between papillary growth pattern and SUVmax or GLUT-1 expression. However, because tumors with micropapillary pattern are considered to have more aggressive biological behavior, it is possible that micropapillary pattern may associate with high ^{18}F-FDG uptake. Further studies are needed to address this issue.

EGFR mutations at the tyrosine kinase domain are frequently found in lung adenocarcinomas.[9] Several researchers have attempted to find the association between EGFR mutation status and ^{18}F-FDG uptake; however, the results are inconsistent. Some suggested that tumors with EGFR mutations had lower ^{18}F-FDG uptake,[26,27] while others found EGFR mutant tumors had higher ^{18}F-FDG uptake.[28] In addition, the association between the histological subtypes of adenocarcinoma and EGFR mutations is also controversial. A number of clinical studies suggested that bronchioloalveolar carcinomas or tumors with bronchioloalveolar features were more likely to have EGFR mutations.[29–31] Recent genetic correlation studies; however, found a close correlation between papillary and micropapillary growth pattern and EGFR mutations.[10]

This study has several limitations. First, we only enrolled tumors $\geq$1 cm in size; therefore, the results may not apply to tumors less than 1 cm (many bronchioloalveolar carcinomas are in this category). We excluded these small tumors because we assessed that the spatial resolution of PET imaging may underestimate their SUV, resulting in inappropriate evaluation of the relationship between the ^{18}F-FDG uptake and histological growth pattern of tumors. Survival analysis was not performed due to the limited case number and follow-up time. Previous studies have shown that a solid growth pattern and high SUV are both poor prognostic factors. This study provided a direct link between them, and the results of survival analysis seem unlikely to influence it. In addition, we showed a link between TRU-type histology and low SUV, suggesting that TRU-type lung adenocarcinoma has better prognosis than the non-TRU type, which needs to be analyzed in a larger database. Third, we were not able to map the distribution of SUV and histological growth pattern in the same tumor. We did observe a correlated distribution of GLUT-1 expression and a specific histological growth pattern. A prospectively designed study using the next generation high-resolution PET machine may help to elucidate it.

In conclusion, lung adenocarcinoma comprises a heterogeneous group of diseases, and the histological subclassification possesses both morphological and biological implications. In this study, we demonstrated that histological subtypes of lung adenocarcinomas exhibited differential ^{18}F-FDG uptake on the PET/CT scan. Our results support the classification strategy used in the new IASLC/ATS/ERS classification system, which provides more prognostic information than the current WHO classification. This study also suggests that TRU morphology may also have prognostic implication, which deserves further confirmation.

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