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ORIGINAL ARTICLE

Correlation between *EGFR* mutation status and F^{18}-fluorodeoxyglucose positron emission tomography-computed tomography image features in lung adenocarcinoma

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Abstract

Background: The purpose of this study was to investigate an association between *EGFR* mutation status and ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET-CT) image features in lung adenocarcinoma.

Methods: Retrospective analysis of the data of 139 patients with lung adenocarcinoma confirmed by surgical pathology who underwent preoperative ^{18}F-FDG PET-CT was conducted. Correlations between *EGFR* mutation status, clinical characteristics, and PET-CT parameters, including the maximum standardized uptake value (SUVmax), the mean of the SUV (SUVmean), the peak of the SUV (SUVpeak) of the primary tumor, and the ratio of SUVmax between the primary tumor and the mediastinal blood pool (SUVratio), were statistically analyzed. Multivariate logistic regression analysis was performed to identify predictors of *EGFR* mutation. Receiver operating characteristic curves of statistical quantitative parameters were compared.

Results: *EGFR* mutations were detected in 74 (53.2%) of the 139 lung adenocarcinomas and were more frequent in non-smoking patients. Univariate analysis showed that the SUVmax, SUVmean, SUVpeak, and SUVratio were lower in *EGFR*-mutated than in wild-type tumors. The receiver operating characteristic curves showed no significant differences between their diagnostic efficiencies. Multivariate logistic regression analysis showed that being a never smoker was an independent predictor of *EGFR* mutation.

Conclusion: Quantitative parameters based on ^{18}F-FDG PET-CT have modest power to predict the presence of *EGFR* mutation in lung adenocarcinoma; however, when compared to smoking history, they are not good or significant predictive factors.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide and its incidence is steadily increasing in industrialized countries.[1] Non-small cell lung cancer (NSCLC) accounts for more than 80% of lung cancers and adenocarcinoma is the main histological subtype. *EGFR* mutation status plays an important role in guiding EGFR-based targeted therapy for NSCLC patients; front-line EGFR-tyrosine kinase inhibitor (TKI) therapy is considered the standard of care for advanced NSCLC patients with sensitizing *EGFR* mutations.[2,3] Thus, determining *EGFR* mutation status is essential to identify the NSCLC patients who may benefit from treatment with EGFR-TKIs and, hence, to improve prognosis and the efficacy of EGFR-TKI therapy.

^{18}F-fluoro-2-deoxy-glucose positron emission tomography (^{18}F-FDG-PET), a functional imaging modality based on glucose metabolism, is widely used for the diagnosis, initial staging, and evaluation of treatment efficacy in lung cancer.[4] A previous study showed that EGFR signaling regulates the global metabolic pathway in *EGFR*-mutated lung adenocarcinoma cells and EGFR-TKIs decrease lactate production, glucose consumption, and the glucose-induced extracellular acidification rate.[5] These findings suggest that ^{18}F-FDG uptake on PET may be a noninvasive biomarker for predicting *EGFR* mutation.

However, previous data concerning the association between ^{18}F-FDG uptake and *EGFR* mutation in lung cancer are conflicting and the correlation has not been satisfactorily evaluated.[6–11] Further studies are needed to validate these results. Therefore, we conducted this retrospective study to investigate whether or not ^{18}F-FDG PET could be a valuable method for predicting *EGFR* mutation in lung adenocarcinomas.

Methods

Patients

This retrospective study was approved by our institutional review board and the informed consent requirement was waived. We retrospectively collected data of 560 patients who underwent preoperative PET-CT and were pathologically diagnosed with lung cancer at our institute between June 2016 and October 2017. The inclusion criteria were as follows: (i) visible lung cancer on preoperative PET-CT images (diameter > 1 cm); (ii) surgical resection with histopathologically verified lung adenocarcinoma; (iii) patients were not admistered treatment before surgery; and (iv) resected specimens were examined for *EGFR* mutation. The exclusion criteria were as follows: (i) patients who underwent a biopsy before PET-CT examination; (ii) patients administered neoadjuvant chemotherapy or radiotherapy before surgery; (iii) lesions displaying as ground-glass nodules or part-solid nodules; (iv) FDG uptake similar to adjacent pulmonary parenchyma, which was difficult to measure; and (v) patients without *EGFR* mutation data. In total, 139 patients met the requirements for the study. Clinical and pathologic information (age, gender, smoking history, tumor location, tumor stage, and *EGFR* mutation status) were collected from the hospital's electronic medical records system.

^{18}F-FDG PET-CT scanning

In this study, PET-CT scans were performed using a GE Discovery Elite PET/CT scanner (GE Medical Systems, Waukesha, WI, USA). After a six-hour fast, patients were injected with 4.2 MBq ^{18}F-FDG/kg body weight. After an hour, a spiral CT scan with ~25 effective mAs, 130 kVp, and a 5 mm slice thickness was taken, followed by a PET emission scan from the distal femur to the top of the skull. The PET scanning time was two minutes per bed position, with increments of 16.2 cm (three-dimensional [3D] mode), and all patients were scanned in eight bed positions. PET images were reconstructed using iterative algorithms (ordered-subset expectation maximization, 6 iterations, 8 subsets) to a final pixel size of $5.3 \times 5.3 \times 2.5$ mm. A 6 mm full-width at half maximum Gaussian filter was applied after the reconstruction.

Image analysis

Two board-certified nuclear medicine physicians with eight and five years experience in PET-CT imaging, respectively, reviewed the PET-CT images side by side and reached a consensus on the findings at the workstation (AW4.6, GE Medical Systems). The tumor was delineated and then three-dimensionally reconstructed at the AW4.6 workstation using the PET volume computerized assisted reporting (PETVCAR) software (GE Medical Systems, Waukesha, WI, USA). To quantify the uptake, a volume of interest using a 3D sphere was placed over the primary tumor. The maximum voxel uptake, which reflected the maximal uptake of ^{18}F-FDG within the tumor, was found and its maximum standardized uptake value (SUVmax) was calculated according to the following formula: SUV = tissue radioactivity concentration (becquerels per millilitre)/(injected dose [becquerels]/patient weight [grams]). The mean of the SUV (SUVmean) was determined with a 3D isocontour at 50% of the maximum voxel value and the peak of the SUV (SUVpeak) using a 12 mm diameter spherical volume of interest automatically centred on the tumor area with the maximum uptake. For the mediastinal blood pool, a circular region-of-interest (ROI) with a 10 mm diameter was placed centrally within the ascending

aorta. SUVratio = SUVmax of the primary tumor/SUVmax of the mediastinal blood pool.

EGFR mutation assessment

Genomic DNA was extracted from frozen lung cancer tissues sampled from surgically resected specimens. *EGFR* mutations were analyzed using the peptide nucleic acid-locked nucleic acid PCR clamp method.[12] *EGFR* exons 18, 19, 20, and 21 were tested. Patients were categorized according to the mutation testing as *EGFR*-mutated (*EGFR* +) and wild-type *EGFR* (*EGFR*−).

Statistical analysis

Statistical analysis was performed using two commercially available statistical software packages (SPSS version 19.0, IBM Corp., Armonk, NY, USA; and MedCalc version 15.2.2, Mariakerke, Belgium). Continuous variables were compared using an independent-sample *t* or Mann–Whitney *U* test, while categorical variables were presented as a frequency and were compared using chi-square or rank sum tests. Receiver operating characteristic (ROC) curves for the significant parameters were constructed and the areas under the curve (AUCs) were calculated with a cutoff value, sensitivity, specificity, and positive and negative likelihood ratios (LR). The differences between the AUCs were then compared. Multivariate logistic regression analysis was performed to identify predictors of *EGFR* mutation. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Association between patient characteristics and *EGFR* mutation status

A total of 139 patients with 139 lung adenocarcinomas were included in this study. The pathological type of all lesions was adenocarcinoma, including 135 invasive non-mucinous adenocarcinomas and 4 mixed invasive mucinous/non-mucinous adenocarcinomas. There were no adenocarcinoma in situ or minimally invasive adenocarcinomas. The patients' clinicopathological characteristics are summarized in Table 1. *EGFR* mutations were identified in 74 patients (74/139, 53.2%). Of 139 patients, 62 (62/139, 44.6%) were male and 77 (77/139, 55.4%) were female. Lung cancer with *EGFR* mutation was more frequently identified in women, but there was no significant difference between women and men (59.5% vs. 50.7%). The median age at the time of surgery was 62.5 years for *EGFR*+ patients and 63 years for *EGFR*− patients. In this study, 46 patients (46/139, 33.1%) were classified as current and former smokers and 93 (93/139, 66.9%) were never smokers. Lung cancer with *EGFR* mutation was more frequently identified in never smokers (77.0%; $P < 0.05$). The majority of patients enrolled in this study were in clinical stage I (97/139, 69.8%). There were no significant differences in age, tumor location, or tumor stage between *EGFR*+ and *EGFR*− patients.

Table 1 Association between clinicopathological characteristics and *EGFR* status

Clinicopathological characteristics	Total	*EGFR* status		*P*
		EGFR+ (*n* = 74)	*EGFR*− (*n* = 65)	
Age, mean (range)	62 (28–81)	61 (33–78)	62 (28–81)	0.921
Gender				
Male	62	30	32	0.304
Female	77	44	33	
Smoking history				
Never smoker	93	57	36	0.007
Smoker	46	17	29	
Tumor location				
Right upper lobe	47	26	21	
Right middle lobe	15	10	5	
Right lower lobe	27	14	13	
Left upper lobe	32	17	15	
Left lower lobe	18	7	11	
Stage				
I or II	111	59	52	0.968
III or IV	28	15	13	

Association between ^{18}F-FDG uptake and *EGFR* mutation status

Table 2 shows that the SUVmax, SUVmean, SUVpeak, and SUV ratio of *EGFR*+ tumors were significantly lower than those of *EGFR*− tumors. There were significant differences between *EGFR*+ and *EGFR*− tumors ($P < 0.05$).

Multivariate logistic regression analysis

In the multivariate logistic regression analysis, SUVmax, SUVmean, SUVpeak, SUVratio, and smoking history were

Table 2 Comparisons of quantitative parameters based on FDG uptake measurements between *EGFR*+ and *EGFR*− groups

Parameters	*EGFR* status		*P*
	EGFR+ (*n*)	EGFR− (*n*)	
SUVmax†	7.70 ± 3.93	10.18 ± 5.67	0.004
SUVmean†	4.76 ± 2.49	6.36 ± 3.59	0.003
SUVpeak‡	5.78 ± 3.17	7.93 ± 4.84	0.013
SUVratio‡	4.83 ± 2.95	6.60 ± 4.18	0.010

†Independent-sample *t* and ‡Mann–Whitney *U* tests used for comparisons. FDG, fluorodeoxyglucose; SUV, standardized uptake value.

Table 3 Multivariate logistic regression analysis of the significant clinicopathological characteristics and quantitative parameters based on FDG uptake measurements to predict *EGFR* mutation

		95% CI for OR		
Parameters	OR	Lower	Upper	*P*
SUVmax	1.457	0.595	3.571	0.410
SUVmean	0.440	0.155	2.247	0.440
SUVpeak	0.434	0.527	1.317	0.434
SUVratio	0.935	0.767	1.277	0.935
Smoking history	2.756	1.281	5.929	0.010

CI, confidence interval; FDG, fluorodeoxyglucose; OR, odds ratio; SUV, standardized uptake value.

analyzed together. Smoking history (never smokers) was the the only independent predictor for the presence of *EGFR* mutation in lung adenocarcinoma ($P = 0.010$) (Table 3).

Receiver operating characteristic curve analysis

The AUCs to identify *EGFR* mutation were 0.629, 0.632, 0.622, and 0.626 for SUVmax, SUVmean, SUVpeak, and SUVratio, respectively (Table 4). The cutoff value, sensitivity, specificity, positive LR (+LR), and negative LR (−LR) of each parameter are shown in Table 4. There were no significant differences in AUCs between SUVmax, SUVmean, SUVpeak, and SUVratio (SUVmax vs. SUVmean: $P = 0.482$; SUVmax vs. SUVpeak: $P = 0.498$; SUVmax vs. SUVratio: $P = 0.883$; SUVmean vs. SUVpeak: $P = 0.352$; SUVmean vs. SUVratio: $P = 0.762$; SUVpeak vs. SUVratio: $P = 0.825$) (Fig 1).

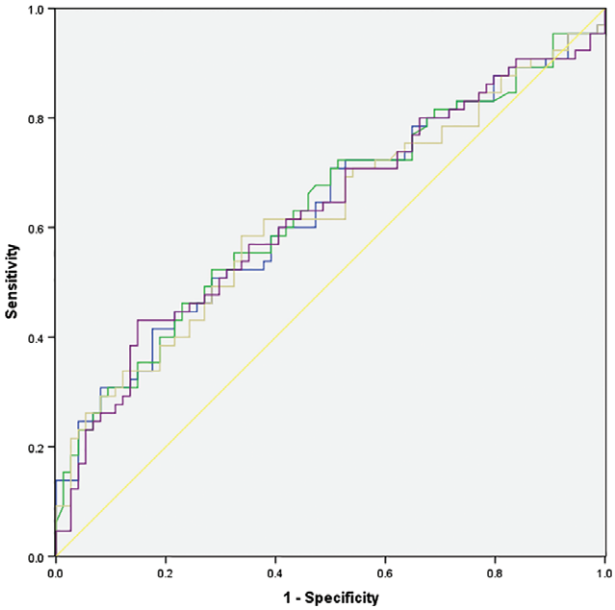

Figure 1 Receiver operating characteristic curve analysis and comparison of the significant quantitative parameters based on fluorodeoxyglucose uptake measurements to predict *EGFR* mutation. (——) SUVmax, (——) SUVmean, (——) SUVpeak, (——) SUVratio, and (——) Reference line. SUV, standardized uptake value.

Discussion

EGFR mutation is one of the most common druggable targets in NSCLC. The availability of effective EGFR-TKIs in first-line therapy requires the timely identification of suitable patients. Therefore, identifying factors to predict a positive *EGFR* mutation are clinically useful. In this study, we found that NSCLC patients with mutated-*EGFR* had lower SUVmax, SUVmean, SUVpeak, and SUVratio measurements based on ^{18}F-FDG PET-CT than NSCLC patients with wild-type *EGFR*. These findings suggest that *EGFR*-mutated lung adenocarcinomas could be biologically indolent with lower levels of glucose metabolism than *EGFR*-wild tumors and these PET-CT parameters could be potentially useful to discriminate the *EGFR* mutation status in NSCLC patients.

As one of the currently available noninvasive imaging methods, PET-CT is widely used for lesion detection, lesion characterization, and clinical staging in patients with lung cancer. PET-CT is based on the fact that the glucose metabolism of a tumor is partly reflected by FDG uptake. Previous studies have shown contradictory results for the correlation between *EGFR* mutation status and FDG uptake. Some data from previous studies revealed that a lower FDG avidity was an independent variate for predicting *EGFR* mutations, while other groups reported that no

Table 4 ROC analysis of the significant quantitative parameters to identify *EGFR* mutation

			95% CI					
Parameters	Cutoff value	AUC	Lower	Upper	Sensitivity (%)	Specificity (%)	+LR	−LR
SUVmax	11.19	0.629	0.535	0.723	41.5	82.4	1.41	0.42
SUVmean	6.06	0.632	0.538	0.726	52.3	71.6	1.50	0.54
SUVpeak	6.92	0.622	0.527	0.717	58.5	66.2	1.59	0.58
SUVratio	6.75	0.626	0.532	0.721	43.1	85.1	1.50	0.35

AUC, area under the curve; CI, confidence interval; LR, likelihood ratio; ROC, receiver operating characteristic; SUV, standardized uptake value.

association existed between FDG uptake and *EGFR* status or that a higher SUVmax predicted *EGFR* mutation.[6–10] In our study, NSCLC patients with *EGFR* mutations had lower FDG uptake measurements including SUVmax, SUVmean, SUVpeak, and SUVratio based on ^{18}F-FDG PET-CT than NSCLC patients with wild-type *EGFR*.

There are several possible reasons for these contradictory results. First, SUVmax, SUVmean, and SUVpeak are semi-quantitative indexes that could vary with different PET scanners, fasting duration, level of plasma glucose, and ROI parameters. Given the limitations of these parameters, we chose another PET-CT parameter, SUVratio, as an alternative variable to explore the relationship between PET-CT and *EGFR* gene mutation status. Our results showed that SUVratio had a statistically significant predictive role for determining *EGFR* mutation status, which indicated that quantitative parameters based on ^{18}F-FDG PET-CT could be regarded as predictors of *EGFR* mutation. Second, the difference between our study and previous reports is the homogeneity of the lesions. Because of the retrospective nature of our study, we selected lesions that were predominately solid and larger than 1 cm in order to minimize partial volume averaging effects in FDG-PET interpretation. The pathological type of the lesions in our study was lung adenocarcinoma, not including squamous cell carcinoma. We suggest that these conditions resulted in a more reliable estimate of FDG uptake in lung cancer. Third, the possible mechanisms of lower FDG uptake and *EGFR* mutation in our study might be related to the following reasons. ^{18}F-FDG PET-CT as a functional imaging modality is based on glucose metabolism. ^{18}F-FDG uptake in NSCLC patients correlates with the expression of GLUT1 in primary tumors and *EGFR* mutation decreases FDG uptake in NSCLC via the NOX4/reactive oxygen species/GLUT1 axis.[13,14] Although our results showed the statistically significant predictive roles of SUVmax, SUVmean, SUVpeak, and SUVratio for determining *EGFR* mutation status, the ROC curves showed no significant differences between their diagnostic efficiencies. Multivariate logistic regression analysis showed that being a never smoker was the only independent predictor of *EGFR* mutation. Moreover, the maximal AUC of these quantitative parameters was only 0.632. These results indicate that these FDG uptake measurements based on ^{18}F-FDG PET-CT have only modest power to predict *EGFR* mutation in lung cancer. Furthermore, when compared with smoking history, they were not good or significant predictive factors.

Our study has some limitations. First, only a relatively small number of patients were evaluated for *EGFR* mutation analysis. Only 74 out of 139 patients had an *EGFR* mutation, which may be a potential selection bias. However, 53.2% of patients had an *EGFR* mutation, which was a relatively high incidence. A recent systematic review showed that *EGFR* mutation frequency in the Asia-Pacific NSCLC/adenocarcinoma subgroup is 47.9%.[15] Second, different driver gene mutations may result in distinct pathway activation and glycolytic features. Previous studies have reported that NSCLC patients with tumors harbouring *K-ras* mutation or *ALK* rearrangement showed significantly higher ^{18}F-FDG uptake than wild-type patients.[9,11] We did not take into consideration the roles of these drivers, which could cause bias in FDG uptake measurements in patients with *EGFR*-wild to some extent.

In conclusion, our results indicate that *EGFR*-mutated lung adenocarcinomas potentially have a lower level of glucose metabolism than wild-type tumors. Quantitative parameters of FDG uptake measurements, such as SUVmax, SUVmean, SUVpeak, and SUVratio have modest power to predict *EGFR* status; however, when compared to smoking history, they are not good or significant predictive factors.

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Disclosure

No authors report any conflict of interest.

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