Original Article

Association between cigarette smoking history, metabolic phenotypes, and *EGFR* mutation status in patients with non-small cell lung cancer

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Background: Cigarette smoking exerts a significant impact on metabolic phenotypes and epidermal growth factor receptor (*EGFR*) mutation status; however, their correlation remains insufficiently established. Therefore, the aim of this study was to investigate the association between cigarette smoking history, metabolic phenotypes, and *EGFR* mutation status in patients with non-small cell lung cancer (NSCLC).

Methods: We retrospectively analyzed 198 consecutive patients with NSCLC who underwent ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) before treatment and were tested for *EGFR* mutation status between September 2019 and March 2022. Metabolic phenotypes, including the maximum standardized uptake value (SUVmax) of the primary tumors (pSUVmax), metastatic lymph nodes (nSUVmax), and distant metastases (mSUVmax) were assessed. Patients were classified into never-smokers and smokers based on detailed smoking history. The correlations between smoking status, metabolic parameters, and *EGFR* mutation status were evaluated in patients with NSCLC.

Results: We observed *EGFR* mutations in 73 (60.3%) of 121 never-smokers and 18 (23.4%) of 77 smokers (P<0.001). *EGFR*-mutant NSCLC had a lower pSUVmax than that of *EGFR* wild-type (WT; 8.9±4.5 *vs.* 12.7±6.9, P<0.001). Smokers had a higher pSUVmax than never-smokers (12.5±6.4 *vs.* 9.9±5.9, P=0.004). With the increase of cumulative smoking dose, the pSUVmax increased significantly (r=0.198, P=0.005). There was no significant difference between nSUVmax and mSUVmax in patients with or without *EGFR* mutation and smoking history. Cumulative smoking dose, pSUVmax, and their combination predicted *EGFR* mutation status with areas under the receiver operating characteristic (ROC) curves (AUCs) 0.688, 0.673, and 0.753, respectively.

Conclusions: Our findings indicate that cigarette smoking may be one of the triggers for increased pSUVmax and decreased *EGFR* mutations, further suggesting that *EGFR* mutations are associated with low pSUVmax, which may guide clinicians in risk stratification and treatment strategy selection for patients with NSCLC.

Keywords: Smoking status; ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG); epidermal growth factor receptor (*EGFR*); non-small cell lung cancer (NSCLC)

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Introduction

Despite significant improvements in diagnosis and treatment, lung cancer remains one of the most common malignancies and the leading cause of cancer-related mortality worldwide (1,2). A large amount of evidence has demonstrated that cigarette smoking is a risk factor for lung cancer (3,4). Epidemiological and molecular genetic differences have been found between patients with non-smoking-associated lung cancer and tobacco-associated lung cancer (4-7). Never-smokers with non-small cell lung cancer (NSCLC) frequently have the following characteristics female gender, young age and a histological diagnosis of epidermal growth factor receptor (*EGFR*) mutated adenocarcinoma (ADC) (8,9). Moreover, this subgroup demonstrates a more favorable prognostic outlook when juxtaposed with their smoking counterparts. This clinical advantage is mainly determined by their elevated responsiveness to *EGFR* tyrosine kinase inhibitors (TKIs), such as osimertinib, afatinib, gefitinib, erlotinib and by the absence of smoking-related comorbidities (10,11). Lung ADC patients who had smoked more than 15 pack-years or quit less than 25 years ago have been shown to be less likely to have detectable *EGFR* mutations (12). In clinical practice, molecular detection of *EGFR* can be limited by invasive procedures, sampling errors, and long processing time (13). Liquid biopsy represents a non-invasive useful tool to identify *EGFR* alterations; nevertheless, it is worth noting that the sensitivity of this technique is around 65% (14). These data may help clinicians to assess the likelihood of *EGFR* mutations in patients with lung ADC when the results of *EGFR* mutation status are not available.

Positron emission tomography/computed tomography (PET/CT) with ^{18}F-fluoro-2-deoxy-D-glucose (^{18}F-FDG), a molecular imaging modality, has been widely used in clinical diagnosis, staging, response evaluation, and prognosis of lung cancer (15-17). Several metabolic parameters, including maximum standard uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), could reflect the metabolic activity of ^{18}F-FDG (18,19). In patients with advanced or metastatic NSCLC, high MTV and TLG usually represent a lower progression-free survival (PFS) and overall survival (OS) (20). In addition, we previously reviewed the correlation between *EGFR* mutation status and metabolic activity of ^{18}F-FDG in NSCLC (21). It has been reported that primary lung cancers with lower SUVmax may represent a higher incidence of *EGFR* mutations (22,23), but opposite results have also been observed (24,25). Accordingly, further studies are needed to verify these findings, so that clinicians can accurately predict *EGFR* mutations and evaluate the prognosis.

The effect of cigarette smoking on ^{18}F-FDG metabolic activity of primary lung cancer was investigated in our previous study. Our results suggested that the metabolic activity of ^{18}F-FDG in early primary lung cancer may be influenced by cigarette smoking (26). Accordingly, we speculate that there may be a significant causal relationship between them, which may guide clinicians in risk stratification and treatment strategy selection for patients with NSCLC. Thus, we performed a retrospective analysis to investigate the association and potential causation between cigarette smoking, metabolic phenotypes, and *EGFR* mutation status in patients with NSCLC. We present this article in accordance with the STARD reporting

Highlight box

Key findings

- The metabolic activity of ^{18}F-fluoro-2-deoxy-D-glucose was found to be higher in smokers with primary non-small cell lung cancer (NSCLC) compared to never-smokers, while the incidence of epidermal growth factor receptor (*EGFR*) mutation exhibited a decrease.

What is known and what is new?

- Never-smokers diagnosed with NSCLC demonstrate a more favorable prognosis and exhibit a superior response to *EGFR* tyrosine kinase inhibitors compared to their smoking counterparts.
- In patients diagnosed with NSCLC, smokers exhibited a higher maximum standardized uptake value of primary tumors (pSUVmax) and a lower incidence rate of *EGFR* mutations in comparison to never-smokers.

What is the implication, and what should change now?

- Our findings provide insights into the potential impact of cigarette smoking and pSUVmax on the development and progression of NSCLC, which may have implications for personalized targeted *EGFR* therapies.

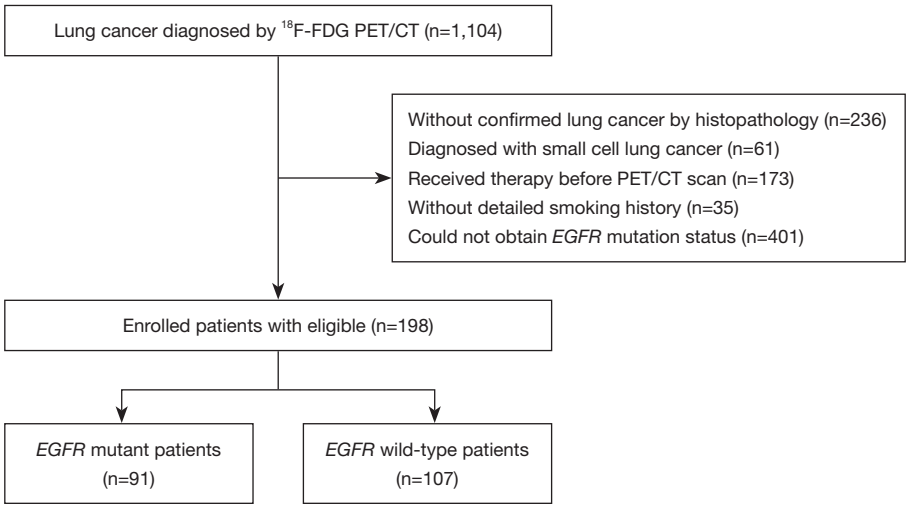

Figure 1 Flowchart of patient selection. ^{18}F-FDG, ^{18}F-2-fluoro-2-deoxyglucose; PET/CT, positron emission tomography/computed tomography; *EGFR*, epidermal growth factor receptor.

checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1371/rc).

Methods

Patient selection

From September 2019 to March 2022, we performed a retrospective analysis of 1,104 consecutive patients with lung cancer who were initially diagnosed by ^{18}F-FDG PET/CT imaging at Ningbo No.2 Hospital (Ningbo, China). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board (IRB) of Ningbo No.2 Hospital (No. YJ-NBEY-KY202108401). The requirement for written informed consent was waived due to the anonymous nature of the retrospective data.

Patients who met the following criteria were further analyzed in our study: (I) confirmation of NSCLC, and classification into ADC, squamous cell carcinoma (SCC), and NSCLC-others, by histopathology; (II) ^{18}F-FDG PET/CT scanning had been performed before any treatment; (III) the status of *EGFR* mutations was determined by tissue-based analysis (27); (IV) a detailed cigarette smoking history was obtained. Finally, a total of 198 patients met our criteria and were analyzed in our study (*Figure 1*). The clinical characteristics [including age at diagnosis, sex, smoking status, tumor-node-metastasis (TNM) stage, and histopathological type] and metabolic features of ^{18}F-FDG [including SUVmax of the primary tumors (pSUVmax), metastatic lymph nodes (nSUVmax), and distant metastases (mSUVmax)] based on *EGFR* mutation status are summarized in *Table 1*.

Technique of PET/CT scan

All patients underwent PET/CT using a GE Discovery 710 PET scanner (GE Healthcare, Milwaukee, WI, USA). They were required to fast for more than 6 hours before PET/CT examination. The concentration of blood glucose was required to be less than 7.0 mmol/L before intravenous injection of ^{18}F-FDG with 5.2–7.4 MBq/kg. We performed PET/CT scan 45–60 minutes after administration of ^{18}F-FDG. Low-dose CT scan with 140 kV, 10 mA, 0.5 second rotation time, and 40 mm collimation was performed to evaluate the features of anatomy. In addition, CT scan data of an iterative algorithm was used for reconstruction. Subsequently, PET scanning in 3-dimensional (3D) mode was performed from the skull base to upper thigh at 2.5 minutes per bed position. Finally, the transverse, sagittal, and coronal PET, CT, and fused PET/CT images were obtained on a Xeleris workstation (GE Healthcare) for evaluation.

Analysis of PET/CT imaging

All PET and CT images were consistently evaluated by two senior nuclear physicians based on clinical data. The level of

Table 1 Association between clinical characteristics and the status of *EGFR* mutation in patients with NSCLC

Characteristics	Total	*EGFR*-mutant	*EGFR* wild-type	P value
Age at diagnosis				0.763
No. of patients [%]	198 [100]	91 [46]	107 [54]	
Mean ± SD, years	66.3±8.9	66.5±9.0	66.1±9.0	
Range, years	34–86	36–85	34–86	
Sex, n [%]				<0.001
Male	121 [61]	39 [43]	82 [77]	
Female	77 [39]	52 [57]	25 [23]	
Smoking status, n [%]				<0.001
Never smokers	121 [61]	73 [80]	48 [45]	
Smokers	77 [39]	18 [20]	59 [55]	
Clinical TNM stage, n [%]				0.140
I	64 [32]	35 [38]	29 [27]	
II	30 [15]	15 [16]	15 [14]	
III	36 [18]	11 [12]	25 [23]	
IV	68 [34]	30 [33]	38 [36]	
Histological types, n [%]				<0.001
ADC	152 [77]	85 [93]	67 [63]	
SCC	34 [17]	5 [5]	29 [27]	
NSCLC-others	12 [6]	1 [1]	11 [10]	
pSUVmax				<0.001
No. of patients [%]	198 [100]	91 [46]	107 [54]	
Mean ± SD	10.9±6.2	8.9±4.5	12.7±6.9	
Range	0.5–37.7	0.6–20.7	0.5–37.7	
nSUVmax				0.934
No. of patients [%]	102 [52]	42 [21]	60 [30]	
Mean ± SD	10.0±5.3	10.1±5.2	10.0±5.3	
Range	3.1–31.0	3.4–27.0	3.1–31.0	
mSUVmax				0.274
No. of patients [%]	69 [35]	29 [15]	40 [20]	
Mean ± SD	9.7±5.7	8.8±5.9	10.3±5.5	
Range	0.5–29.8	0.5–29.8	2.6–27.4	

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; SD, standard deviation; TNM, tumor-node-metastasis; ADC, adenocarcinoma; SCC, squamous cell carcinoma; pSUVmax, maximum standardized uptake value of primary tumor; nSUVmax, maximum standardized uptake value of metastatic lymph nodes; mSUVmax, maximum standardized uptake value of distant metastases.

^{18}F-FDG uptake within the lesion was defined as abnormal when it was higher than the surrounding background. The SUVmax was used to quantify the uptake intensity of ^{18}F-FDG. A 2-dimensional (2D) region of interest (ROI) was manually drawn at the edge of the tumor focus and placed in the tumor area with the highest ^{18}F-FDG uptake. The peak SUV on the pixel with the highest count in the ROI was defined as SUVmax. The calculation formula was as follows: SUV = [radioactive concentration in the ROI (MBq/g)]/[injected dose (MBq)/patient's total body weight (g)]. Based on visual qualitative analysis, metastatic lymph nodes were considered when the uptake of ^{18}F-FDG was greater than the background mediastinal blood pool (28).

Assessment of cigarette smoking status

All patients underwent a face-to-face interview prior to the PET/CT scan, during which detailed information regarding their smoking history was obtained. The patients were classified into two groups based on cigarette smoking status: smokers and never-smokers. Patients were strictly defined as smokers if they had smoked ≥100 cigarettes in their lifetime, regardless of whether they had quit or not, and the remaining others were defined as never-smokers (8,12). The pack-year index is a parameter reflecting the cumulative smoking dose, which is calculated by multiplying the smoking period (year) by the number of cigarettes smoked every day (29). The number of pack-years is the number of packs smoked per day multiplied by the number of years smoked, with 1 pack-year being 1 day and 1 pack of accumulated smoking for 1 year, and so on.

Statistical analysis

We used descriptive statistics to express the demographic data of our included patients. The quantitative data were analyzed as mean ± standard deviation (SD). The clinical characteristics such as age, gender (male *vs.* female), histopathological subtypes (ADC, SCC, and NSCLC-others), clinical stage (I, II, III, and IV), and smoking status (never-smokers *vs.* smokers), were compared between patients with and without *EGFR* mutations by Fisher's exact test analysis or chi-squared test. PET/CT parameters, including pSUVmax, nSUVmax, and mSUVmax, were compared between patients with or without *EGFR* mutations by Mann-Whitney test. Receiver operating characteristic (ROC) curves were constructed using factors that differed significantly between patients with and without *EGFR* mutations. The area under the ROC curve (AUC) was calculated to evaluate the predictive value. A two-sided P value <0.05 was considered statistically significant. All statistical analyses and graphic designs were performed using GraphPad Prism 9.0 software (GraphPad Software, San Diego, CA, USA).

Results

Patient characteristics

Patient characteristics stratified according to the status of *EGFR* mutations are summarized in *Table 1*. *EGFR* mutation was observed in 73 (60.3%) of 121 never-smokers and 18 (23.4%) of 77 smokers (P<0.001). Of the 198 patients, significant differences of sex (male *vs.* female), smoking status (smokers *vs.* never-smokers), and histopathological subtypes (ADC, SCC, and NSCLC-others) were observed between patients with and without *EGFR* mutations, but the age and clinical TNM stage showed no significant difference.

Association between EGFR mutation status and cigarette smoking history

In terms of cigarette smoking history, never-smokers had a higher rate of *EGFR* mutations than smokers [60.3% (73/121) *vs.* 23.4% (18/77), P<0.001]. With the increase of cigarette smoking dose, the incidence of *EGFR* mutations decreased significantly. *EGFR* mutation rates were 20% in patients who smoked >20 pack-years, 35% in patients who smoked 1–20 pack-years, and 60% in patients who never smoked (*Table 2*).

Association between metabolic parameters and cigarette smoking status

The correlations between metabolic parameters (pSUVmax, nSUVmax, and mSUVmax) and the status of cigarette smoking (smokers and never-smokers) are presented in *Table 3*. We found that smokers had a higher pSUVmax than never-smokers (12.5±6.4 *vs.* 9.9±5.9, P=0.004), but no significant differences were observed between them for nSUVmax (10.8±4.9 *vs.* 9.5±5.5, P=0.229) and mSUVmax (10.1±5.6 *vs.* 9.5±5.8, P=0.651). In addition, with the increase of cigarette smoking dose, the pSUVmax increased significantly (r=0.198, P=0.005, *Figure 2*).

Table 2 Incidence of *EGFR* mutations by pack-years

No. of pack-years	Patients			P value
	Total No.	No. with mutations	% with mutations	
0 (never smokers)	121	73	60	NA
1–20	17	6	35	0.067
21–30	15	3	20	0.005
31–40	20	4	20	0.001
>40	25	5	20	<0.001

P values compare pack-year categories with mutation rates in never smokers. *EGFR*, epidermal growth factor receptor; NA, not applicable.

Table 3 Comparation of metabolic phenotypes between smokers and never-smokers

Metabolic parameters	Patients			P value
	Total No.	Smokers	Never-smokers	
pSUVmax				0.004
No. of patients [%]	198 [100]	77 [39]	121 [61]	
Mean ± SD		12.5±6.4	9.9±5.9	
Range		0.5–35.2	0.6–37.7	
nSUVmax				0.229
No. of patients [%]	102 [52]	43 [22]	59 [30]	
Mean ± SD		10.8±4.9	9.5±5.5	
Range		3.2–24.5	3.1–31.0	
mSUVmax				0.651
No. of patients [%]	69 [35]	25 [13]	44 [22]	
Mean ± SD		10.1±5.6	9.5±5.8	
Range		2.6–27.4	0.5–29.8	

pSUVmax, maximum standardized uptake value of primary tumor; SD, standard deviation; nSUVmax, maximum standardized uptake value of metastatic lymph nodes; mSUVmax, maximum standardized uptake value of distant metastases.

Association between metabolic phenotype, cigarette smoking, and EGFR mutation status

A significantly lower pSUVmax was observed in patients with *EGFR* mutant NSCLC than those with *EGFR* wild-type (8.9±4.5 *vs.* 12.7±6.9, P<0.001). There was no significant difference between nSUVmax and mSUVmax in patients with or without *EGFR* mutations (*Table 1*). In addition, we provided representative PET/CT images of two patients with *EGFR* mutations and *EGFR* wild-type NSCLC (*Figure 3*).

Based on these results, we performed ROC curve analysis to assess the value of predicting *EGFR* mutations in patients with NSCLC. The AUC was 0.688 [95% confidence interval (CI): 0.614–0.762] for cumulative smoking dose with sensitivity of 60.7% and specificity of 77.6% (*Figure 4A*), and 0.673 (95% CI: 0.599–0.747) for pSUVmax with sensitivity of 59.1% and specificity of 64.6% (*Figure 4B*). A multivariate logistic regression analysis was performed which showed that the AUC was 0.753 (95% CI: 0.685–0.821) when we combined cumulative smoking dose and pSUVmax with sensitivity of 66.3% and specificity of 74.0% (*Figure 4C*).

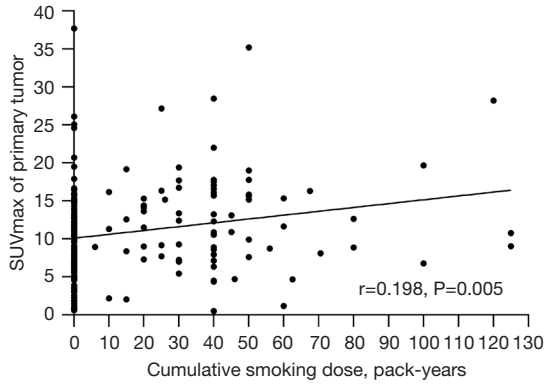

Figure 2 Association between cumulative smoking dose and pSUVmax in patients with NSCLC. A significant correlation was observed between cumulative smoking dose (pack-years) and pSUVmax in patients with NSCLC (r=0.198, P=0.005). SUVmax, maximum standardized uptake value; pSUVmax, SUVmax of primary tumor; NSCLC, non-small cell lung cancer.

Discussion

In the present study, we observed a potential association between cigarette smoking and increased pSUVmax as well as decreased *EGFR* mutations in patients with NSCLC, thereby suggesting a plausible link between low pSUVmax and *EGFR* mutations. Based on cumulative smoking dose and pSUVmax, we obtained a moderate predictive value of *EGFR* mutations in patients with NSCLC.

The molecular genetic features of NSCLC have been evaluated by many studies, and patients with *EGFR* mutations usually benefit from targeted therapy with TKIs (30-32). However, almost all patients with NSCLC treated with *EGFR*-TKIs will inevitably develop drug resistance (33). Unfortunately, it is difficult to predict when resistance will occur during treatment. Thus, it is of great significance to evaluate *EGFR* mutations and prognosis in

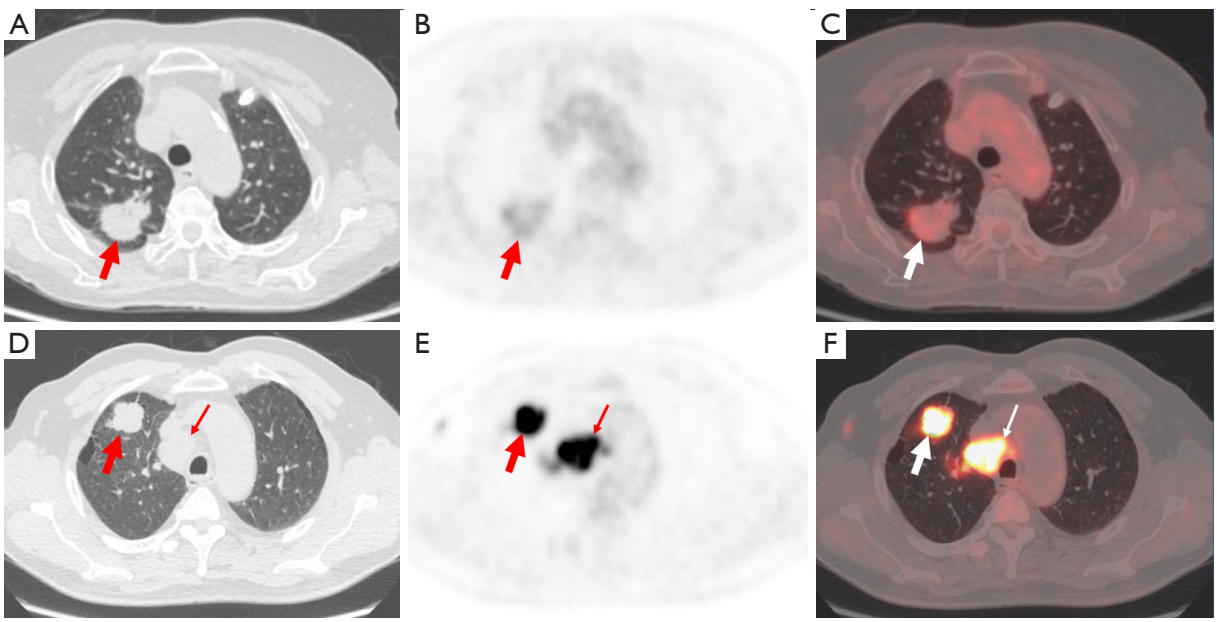

Figure 3 Representative ^{18}F-FDG PET/CT images in patients with or without *EGFR* mutations. A 75-year-old woman with lung adenocarcinoma had never smoked. Axial chest CT (A), PET (B), and fusion PET/CT (C) images showed a nodule in the posterior upper lobe of right lung with a mild uptake of ^{18}F-FDG (pSUVmax 3.61, thick arrows). A 69-year-old man with lung adenocarcinoma had a cumulative smoking dose of 100 pack-years. Axial chest CT (D), PET (E) and fusion PET/CT (F) images showed a nodule in the anterior upper lobe of right lung with markedly uptake of ^{18}F-FDG [pSUVmax 19.69 (thick arrows) and nSUVmax 17.39 (thin arrows)]. ^{18}F-FDG, ^{18}F-fluoro-2-deoxy-D-glucose; PET/CT, positron emission tomography/computed tomography; pSUVmax, maximum standardized uptake value of primary tumor; nSUVmax, maximum standardized uptake value of metastatic lymph nodes.

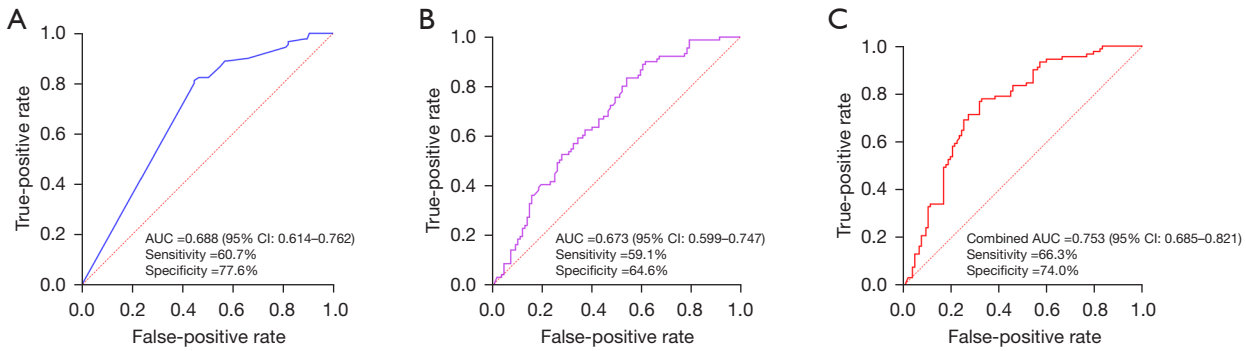

Figure 4 The AUCs of cumulative smoking dose (A), metabolic phenotype (pSUVmax, B), and combined these 2 factors (C) to predict *EGFR* mutation status in patients with NSCLC. AUC, area under the curve; CI, confidence interval; pSUVmax, maximum standardized uptake value of primary tumor; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

patients with lung cancer. Shigematsu *et al.* reported that *EGFR* mutations were found in 45% of never-smokers and only 7% of smokers (32); the frequency of *EGFR* mutations was negatively correlated with cigarette smoking exposure. Pham *et al.* (12) reported that among tobacco-related lung cancer patients with *EGFR* mutations, 39% were exposed for ≤15 pack-years and 7.48% were exposed for >15 pack-years. In our findings, *EGFR* mutations occurred in 60% of never smokers, compared with 35% of those who smoked 1–20 pack-years and 20% of those who smoked >20 pack-years. When we predicted *EGFR* mutations based on cumulative smoking dose, the AUC was 0.688 with a sensitivity of 60.7% and a specificity of 77.6%. These data may help clinicians to assess the likelihood of *EGFR* mutations in patients with NSCLC, but their predictive value is relatively low and further studies are needed.

Metabolic phenotypes, namely, pSUVmax, nSUVmax, and mSUVmax, have been used to predict *EGFR* mutation status in patients with NSCLC (34-36). Ko *et al.* retrospectively analyzed the predictive value of ^{18}F-FDG PET/CT for *EGFR* mutation status, and the results showed that patients with SUVmax ≥6 were more likely to have *EGFR* mutations (35). However, Lee *et al.* found that ^{18}F-FDG uptake in NSCLC had no significant clinical value in predicting *EGFR* mutation status (36). Conversely, Lv *et al.* demonstrated that low pSUVmax <7.0 was associated with mutant *EGFR* status in patients with NSCLC (34). In addition, the association between SUVmax and *EGFR* mutation status in lung ADC may be influenced by smoking status, particularly among individuals with a positive smoking history (37). These conflicting findings prompted us to further evaluate the association between metabolic activity and *EGFR* mutation status. In our results, we found that patients with *EGFR* mutations had a lower pSUVmax than those without *EGFR* mutation. In addition, there were no significant differences of nSUVmax and mSUVmax between patients with *EGFR* mutant NSCLC and *EGFR* wild-type. The AUC was 0.673 when we used pSUVmax to predict *EGFR* mutation status with sensitivity of 59.1% and specificity of 64.6%.

It has been shown that patients with lung cancer who have smoked and have high pSUVmax generally have lower survival rates than those who have never smoked and have low pSUVmax (16,20,38). *EGFR* mutations in lung cancer patients are commonly found in never-smokers (35). To our knowledge, a paradoxical association between *EGFR* mutation status and metabolic phenotype has been observed in NSCLC patients (22,24,25), but this situation still needs further research and verification. Moreover, the direct relationship between cigarette smoking, metabolic phenotypes, and *EGFR* mutation status has not been reported in NSCLC patients. In this study, we found that smoking patients had a higher pSUVmax and a lower rate of *EGFR* mutations than never-smokers, and patients with *EGFR* mutations had a lower pSUVmax than those with *EGFR* wild-type. Thus, we performed a multivariate logistic regression analysis using cumulative smoking dose and pSUVmax to predict *EGFR* mutation status. Our results showed a moderate predictive value, and the AUC was 0.753 with a sensitivity of 66.3% and a specificity of 74.0%. Based on these results, we suggest that cigarette smoking may be one of the inducements for the increase of pSUVmax and the decrease of *EGFR* mutation, and further confirm that *EGFR* mutation is related to the low pSUVmax, which may provide additional information to guide clinicians in risk stratification and treatment strategy selection for patients

with NSCLC.

Although we elucidated the association between cigarette smoking, metabolic phenotypes, and *EGFR* mutation status in patients with NSCLC, our study had some limitations. First, the number of patients we retrospectively analyzed was relatively small, and the results need to be confirmed by extensive prospective analysis. Second, not all patients were tested for *EGFR* mutations, and there may have been bias in the selection of patients. Third, it would be of great significance if we could monitor the therapeutic response of patients with NSCLC and assess their prognosis based on the results of cigarette smoking and metabolic phenotypes. Overall, further studies are needed to verify these findings.

Conclusions

Our study comprehensively analyzed the association between cigarette smoking, metabolic phenotype, and the status of *EGFR* mutations in patients with NSCLC. Compared to never-smokers and with the increase of cumulative smoking dose, the metabolic activity of ^{18}F-FDG in primary tumors increased significantly and the incidence of *EGFR* mutations decreased notably. We also observed that the status of *EGFR* mutations correlates with low pSUVmax. A moderate predictive value of *EGFR* mutations was found based on cumulative smoking dose and pSUVmax. These observations may guide clinicians to stratify the risk of NSCLC patients and select treatment strategies. Further prospective and retrospective studies are needed to confirm our findings and extend our study.

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Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1371/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1371/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1371/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-1371/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Institutional Review Board of Ningbo No.2 Hospital (No. YJ-NBEY-KY202108401). Due to the retrospective nature of this study, the need for written informed consent was waived.

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