

Biological Significance of ^{18}F -FDG PET/CT Maximum Standard Uptake Value for Predicting *EGFR* Mutation Status in Non-Small Cell Lung Cancer Patients

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Purpose: To investigate the potential of maximum standardized uptake value (SUVmax) in predicting epidermal growth factor receptor (*EGFR*) mutation status in non-small cell lung cancer (NSCLC) patients.

Methods: Clinical data of 311 NSCLC patients who had undergone both *EGFR* mutation test and ^{18}F -FDG PET/CT scans between January 2013 and December 2017 at our hospital were retrospectively analyzed. Patients were sub-grouped by their origin of SUVmax. Univariate and multivariate analyses were performed to investigate the association between clinical factors and *EGFR* mutations. Receiver operating characteristic curve (ROC) analysis was performed to confirm the predictive value of clinical factors. In vitro experiments were performed to confirm the correlation between *EGFR* mutations and glycolysis.

Results: *EGFR*-mutant patients had higher SUVmax than the wild-type patients in both primary tumors and metastases. In the multivariate analysis, SUVmax, gender and histopathologic type were determined as independent predictors of *EGFR* mutation status for patients whose SUVmax were obtained from the primary tumors; while for patients whose SUVmax were obtained from the metastases, SUVmax, smoking status and histopathologic type were regarded as independent predictors. ROC analysis showed that SUVmax of the primary tumors (cut off >10.92), not of the metastases, has better predictive value than other clinical factors in predicting *EGFR* mutation status. The predict performance was improved after combined SUVmax with other independent predictors. In addition, our in vitro experiments demonstrated that lung cancer cells with *EGFR* mutations have higher aerobic glycolysis level than wild-type cells.

Conclusion: SUVmax of the primary tumors has the potential to serve as a biomarker to predict *EGFR* mutation status in NSCLC patients.

Keywords: non-small cell lung cancer, epidermal growth factor receptor, SUVmax, receiver operating characteristic curve

Introduction

Lung cancer is the leading cause of cancer-related death in the world.¹ Non-small cell lung cancer (NSCLC), accounts for 80–85% of lung cancer cases, is the most common type of lung cancer. In recent years, epidermal growth factor receptor (*EGFR*) tyrosine kinase inhibitors (TKIs), represented by gefitinib, erlotinib and osimertinib, have revolutionized the treatment of NSCLC by prolonging the

survival time and improving the quality of life of patients.^{2,3} Therefore, assessment of *EGFR* mutation status before treatment is vital for NSCLC patients. Although demographic characteristics such as gender, smoking status and histopathologic type are reported to correlate with the presence of *EGFR* mutation, they are insufficient to predict it. Current routine gene mutation test often involves invasive procedures such as tissue biopsy; however, it is not always feasible to obtain adequate amount of tissues to perform *EGFR* mutation test when the primary tumor is not resectable, particularly for advanced-stage NSCLC patients.

In recent years, many studies had focused on the relationship between CT imaging characteristics and *EGFR* mutation.^{4–7} Fluorine-18 fluorodeoxyglucose (¹⁸F-FDG) positron emission tomography/computed tomography (PET/CT) is an imaging technology widely used in staging or restaging tumors and evaluating the therapeutic response of NSCLC patients.⁸ The maximum standardized uptake value (SUVmax), an important metabolic parameter used in ¹⁸F-FDG PET/CT, can reflect the metabolic activity of tumors.⁹ Given that the *EGFR* signaling pathway plays important roles in cell survival and proliferation and the glucose metabolism has close relationship with disease aggressiveness and cell proliferation, researchers assumed that SUVmax may be used to predict the *EGFR* mutation status.¹⁰ In the past few years, several studies have investigated the correlation between SUVmax and *EGFR* mutation status; however, the value of SUVmax in predicting *EGFR* mutation status remains controversial. Some reports showed that there was no difference between *EGFR*-mutants and wild-type lung cancers regarding SUVmax.^{11,12} In contrast, other evidences indicated that patients with lower^{13–19} or higher^{20–22} SUVmax were more likely to have *EGFR* mutations.

In this retrospective study, we try to explore the potential of SUVmax in predicting *EGFR* mutation status in NSCLC patients. In addition to the analysis of clinical data, in vitro experiments were also performed to confirm the correlation between *EGFR* mutations and glycolysis.

Patients and Methods

Patient Selection

Medical records from 311 patients with histopathologically confirmed NSCLC who had undergone *EGFR* mutation test and ¹⁸F-FDG PET/CT scanning prior to receiving treatment between January 2013 and December 2017 at

our institute were retrospectively analyzed. Clinical characteristics, including age, gender, smoking history, histopathologic type, clinical stage, *EGFR* mutation status and SUVmax of the biopsy site, either from the primary tumors or from the metastases, were obtained from each patient. Clinical staging was based on the American Joint Committee on Cancer 7th edition TNM staging system of NSCLC.

EGFR Mutation Test

EGFR mutation test was performed on tissue biopsies of all patients using an amplification refractory mutation system (ARMS) with the ADx-ARMS *EGFR* Mutation Test Kit (Amoy Diagnostics Co., Ltd., Xiamen, China) as previously described.²³

¹⁸F-FDG PET/CT Scanning

¹⁸F-FDG PET/CT scanning was performed in all patients using the Biograph TruePoint 16 PET/CT (Siemens Medical Systems/CTI, Knoxville, TN, USA). All patients were required to fast for 6 h before examination. Serum glucose levels were measured and confirmed to be less than 6.6 mmol/L prior to ¹⁸F-FDG injection. One hour before image acquisition, approximately 5.5 MBq/kg of ¹⁸F-FDG, provided by the PET Center of the Daping Hospital, was intravenously administered to each patient. After an initial low-dose non-contrast CT scan, standard PET imaging was performed with an acquisition time of 2.5 min/bed at three-dimensional mode. Images were then reconstructed using an iterative reconstruction algorithm. All PET/CT images were reviewed by an experienced nuclear physician on a GE AW 4.0 workstation (GE Healthcare, Milwaukee, WI, USA). Volume of interest (VOI) was drawn on the biopsies to derive SUVmax as previously described.²⁴ ¹⁸F-FDG PET/CT scanning was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. Data collection was retrospectively performed and approved by the Ethical Committee of the Army Medical University (ethics approval number: 2,020,101).

Cell Culture

Human NSCLC cell lines PC-9 (del19), H1299 (wild-type) and H460 (wild-type) were cultured in RPMI-1640 (Hyclone) with Earle's salts at 37°C, with 5% CO₂ and 90% humidity. RPMI-1640 medium was supplemented with 10% FBS (Gibco), 2 mmol/L L-glutamine (Gibco), 100U/mL penicillin (HyClone) and 100μg/mL

streptomycin (Hyclone). All cell lines were obtained from ATCC (Manassas, VA, USA) except for PC-9 which was generously provided by Prof. J. Xu and Dr. M. Liu (Guangzhou Medical University, Guangzhou, China). PC-9 cell line authentication was performed by Shanghai OrigiMed Clinical Laboratory Co., Ltd (Shanghai, China). The use of PC-9 cell line was recorded (not approved due to lack of authority) by the Ethical Committee of the Army Medical University.

Lactate Production and Glucose Consumption

After 48h culture, lactate and glucose levels of H460 and PC-9 cells were quantified using the K627-100 Lactate Assay kit (BioVision, Mountain View, CA, USA) and K686-100 Glucose Assay kit (BioVision, Mountain View, CA, USA) according to the manufacturer's instructions. All experiments were performed in triplicate.

FLAG-Tagged EGFR Expression

EGFR wild-type H460 and H1299 cells were transiently transfected with empty vector or FLAG-tagged plasmids containing either wild-type EGFR or mutant EGFR (del19 or L858R) using Lipofectamine 2000 (Life Technologies, CA, USA) according to the manufacturer's instructions. Western blot was performed to detect the exogenous expression of EGFR. Glucose consumption and lactate production experiments were performed 48h after transfection. All experiments were performed in triplicate.

Statistical Analysis

Continuous variables and categorical variables were analyzed using Student's *t*-test and Pearson's chi-square test, respectively. Significant parameters were selected for further multivariate logistic regression analysis to investigate the association between clinical features and EGFR mutation status. Receiver operating characteristic (ROC) curve analysis was performed using the MedCalc version 12.3 Software (Mariakerke, Belgium). All analyses except for ROC curve analysis were performed using SPSS 19.0 (SPSS Incorporated, Chicago, IL, USA). A *p* value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Of the 311 patients, 60.8% (189/311) were males and 39.2% (122/311) were females. The majority of patients

were diagnosed with adenocarcinoma (74.9%, 233/311) and squamous carcinoma (14.1%, 44/311). There were 12.9% (40/311) with stage I–IIIa, 15.8% (49/311) with stage IIIb and 71.4% (222/311) with stage IV. 41.2% (128/311) of patients were EGFR-mutant and 58.8% (183/311) were EGFR wild-type. Among the 128 EGFR-mutant patients, majority had mutation either on exon 19 (49.2%, 63/128) or exon 21 (43.0%, 55/128). In addition, 1 patient (0.78%) had mutation on exon 18, 1 patient (0.78%) had mutation on exon 20 and 8 patients (6.25%) had multiple EGFR mutations. The clinical features of participants are listed in Table 1.

Correlation Between SUVmax and EGFR Mutation Status

Interestingly, our results showed that the mean SUVmax of the primary tumors was significantly higher than that

Table 1 Baseline Clinical Features of the Included Patients

Characteristics	Values
No. of patients	311
Age, years	60.21±11.09
Smoking status	
Nonsmoker	167 (53.7%)
Smoker/ex-smoker	144 (46.3%)
Gender	
Female	122 (39.2%)
Male	189 (60.8%)
Histopathologic type	
Adenocarcinoma	233 (74.9%)
Squamous carcinoma	44 (14.2%)
Others	34 (10.9%)
Clinical stage	
I ~ IIIa	40 (12.9%)
IIIb	49 (15.8%)
IV	222 (71.3%)
Biopsy sites	
Primary tumors	200 (64.3%)
Metastases	111 (35.7%)
SUVmax of the primary tumors	12.31±6.52
SUVmax of the metastases	10.76±5.90
Mutation location	
Exon 19	63 (49.2%)
Exon 21	55 (43.0%)
Others ^a	10 (7.8%)

Note: ^aMutation location on exons except for exon19 or 21.

Abbreviation: SUVmax, maximum standard uptake value.

of the metastases (12.31 ± 6.52 vs 10.76 ± 5.90 , $P=0.038$). To explore the correlation between SUVmax and *EGFR* mutation status in NSCLC patients, we divided patients into two groups according to origin of SUVmax. Our results showed that *EGFR*-mutant patients had higher SUVmax than the wild-type patients in both primary tumors (Figure 1A) and metastases (Figure 1C). Similar results also observed in the analyses based on *EGFR* mutation spectra, in which patients with exon 19 or exon 21 mutation or other mutations had higher SUVmax than the wild-type patients in both primary tumors (Figure 1B) and metastases (Figure 1D).

Univariate and Multivariate Analyses of Clinical Features

Considering the primary tumors had significant higher SUVmax than the metastases, to avoid the influence of heterogeneity, following univariate and multivariate analyses were performed on different patients stratified by the origin of SUVmax. As shown in Tables 2 and 3, in the univariate analyses, SUVmax, gender, smoking status and histopathologic type were significantly associated with *EGFR* mutation status; while, in the multivariate analyses, SUVmax, gender and histopathologic type were determined as independent predictors of

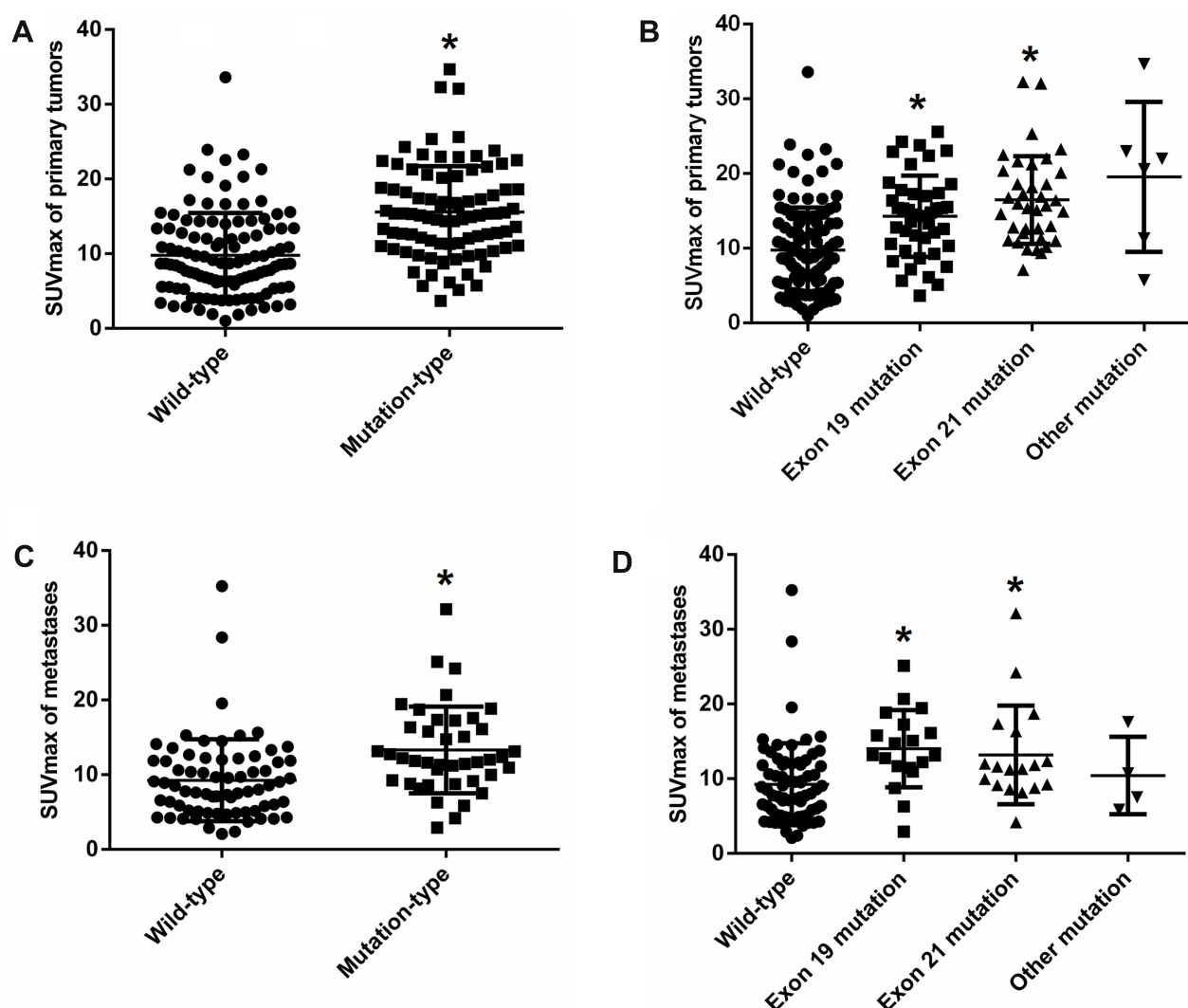


Figure 1 Association between SUVmax and *EGFR* mutation. (A) Comparison of the SUVmax of the primary tumors between *EGFR* wild-type ($n=113$) and *EGFR*-mutant ($n=87$) NSCLC patients; (B) Comparison of the SUVmax of the primary tumors according to *EGFR* mutation locations; other mutation did not take part in comparison because of little number of cases; (C) Comparison of the SUVmax of the metastases between *EGFR* wild-type ($n=70$) and *EGFR*-mutant ($n=41$) NSCLC patients. (D) Comparison of the SUVmax of the metastases according to *EGFR* mutation locations; other mutation did not take part in comparison because of little number of cases. * $P < 0.05$, vs wild-type group.

Abbreviations: SUVmax, maximum standard uptake value; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

Table 2 Univariate and Multivariate Analyses for NSCLC Patients with SUVmax Obtained from Primary Tumors

Characteristics	Wild-Type (n=113)	EGFR-Mutant (n=87)	Univariate P value OR (95% CI)	Multivariate P value OR (95% CI)
Age, Years	60.1±10.4	59.0±12.3	0.511 0.992 (0.967–1.017)	
SUVmax	9.8±5.7	15.6±6.1	0.000 1.183 (1.116–1.254)	0.000 1.207 (1.133–1.286)
Gender				
Female	32 (28.3)	49 (56.3)	0.000 0.306 (0.170–0.552)	0.009 0.297 (0.120–0.734)
Male	81 (71.7)	38 (43.7)		
Smoking status				
Never smoker	56 (49.6)	58 (66.7)	0.015 0.491 (0.275–0.876)	
Former or current smoker	57 (50.4)	29 (33.3)		
Clinical stage				
I ~ IIIa	20 (17.7)	11 (12.6)	0.327 1.486 (0.670–3.293)	
IIIb or IV	93 (82.3)	76 (87.4)		
Histopathologic type				
Non-Ad	40 (35.4)	13 (14.9)	0.001 3.119 (1.542–6.308)	0.001 4.471 (1.900–10.517)
Ad	73 (64.6)	74 (85.1)		

Abbreviations: NSCLC, non-small cell lung cancer; SUVmax, maximum standard uptake value; EGFR, epidermal growth factor receptor; OR, odds ratio; CI, confidence interval; Ad, adenocarcinoma.

Table 3 Univariate and Multivariate Analyses for NSCLC Patients with SUVmax Obtained from Metastases

Characteristics	Wild-Type (n=70)	EGFR-Mutant (n=41)	Univariate P value OR (95% CI)	Multivariate P value OR (95% CI)
Age, Years	61.4±11.9	60.0±12.6	0.574 0.990 (0.959–1.022)	
SUVmax	9.3±5.5	13.3±5.8	0.002 1.139 (1.051–1.236)	0.000 1.234 (1.111–1.372)
Gender				
Female	19 (27.1)	22 (53.7)	0.005 0.322 (0.143–0.722)	
Male	51 (72.9)	19 (46.3)		
Smoking status				
Never smoker	24 (34.3)	29 (70.7)	0.000 0.216 (0.094–0.497)	0.012 0.149 (0.034–0.655)
Former or current smoker	46 (65.7)	12 (29.3)		
Clinical stage				
I ~ IIIa	8 (11.4)	1 (2.4)	0.189 5.161 (0.622–42.850)	
IIIb or IV	62 (88.6)	40 (97.6)		
Histopathologic type				
Non-Ad	24 (34.3)	1 (2.4)	0.000 20.870 (2.701–161.266)	0.007 50.938 (2.970–873.75)
Ad	46 (65.7)	40 (97.6)		

Abbreviations: NSCLC, non-small cell lung cancer; SUVmax, maximum standard uptake value; EGFR, epidermal growth factor receptor; OR, odd ratio; CI, confidence interval; Ad, adenocarcinoma.

EGFR mutation status in patients whose SUVmax were obtained from the primary tumors, and SUVmax, smoking status and histopathologic type were independent predictors of EGFR mutation status in patients whose SUVmax were obtained from the metastases.

ROC Curve Analysis

Based on the multivariate analyses results, ROC curve analyses were performed to determine the discrimination values of these clinical features to predict EGFR mutation status. Our results showed that, in patients whose

SUVmax was obtained from the primary tumors, SUVmax (cut off >10.92; AUC=0.773; sensitivity=78.2%; specificity=66.4%; 95% CI=0.709 to 0.829) has better *EGFR* mutation predictive value than gender (cut off ≤0; AUC=0.640, sensitivity=56.3%; specificity=71.7% and 95% CI=0.569 to 0.707) and histopathologic type (cut-off of >0; AUC=0.602; sensitivity=85.1%; specificity=35.4%; 95% CI=0.531 to 0.761). A combined variable, derived by including all three factors into a logistic regression analysis, can better predict *EGFR* mutation status (cut off >0.3003, AUC=0.825, sensitivity=87.4%, specificity=63.7% and 95% CI=0.766 to 0.875) (Figure 2A). In patients whose SUVmax were obtained from the metastases, SUVmax (cut off >10.6; AUC=0.728; sensitivity=70.7%; specificity=70.0%; 95% CI=0.636 to 0.808) has comparable *EGFR* mutation predictive value with smoking status (cut off ≤0; AUC=0.682, sensitivity=70.7%; specificity=65.7% and 95% CI=0.587 to 0.767) and histopathologic type (cut-off of >0; AUC=0.659; sensitivity=73.2%; specificity=34.3%; 95% CI=0.563 to 0.747). The predictive value was significantly improved after combined SUVmax with smoking status and histopathologic type (cut off >0.4852, AUC=0.859, sensitivity=73.2%, specificity=85.7% and 95% CI=0.780 to 0.918) (Figure 2B).

In vitro Investigation of Association Between *EGFR* Mutation and Glycolysis

In vitro, we further investigated the association between *EGFR* mutation and glycolysis. Our results revealed that *EGFR*-mutant PC-9 cells had significantly higher glucose consumption and lactate production than *EGFR* wild-type H460 cells ($P<0.05$, Figure 3A). To further elucidate the role of *EGFR* mutation on glycolysis, we transfected *EGFR* wild-type NSCLC cell lines H1299 and H460 with plasmids carrying wild-type *EGFR* or mutant *EGFR* including del19 or L858R. Our results revealed that the exogenous expression of *EGFR* was increased after plasmids transfection (Figure 3B); besides, the levels of glucose consumption and lactate production were significantly higher in both H1299 and H460 cell lines transiently expressing *EGFR* exon 19 deletion or L858R mutation than those transfected with wild-type *EGFR* or vector ($P<0.05$, Figure 3C). These results demonstrated that the NSCLC cells harboring common *EGFR* sensitizing mutations have higher glycolysis phenotype than the wild-type NSCLC cells.

Discussion

In the present study, our results demonstrated that *EGFR*-mutant patients have higher SUVmax than the wild-type patients in both primary tumors and metastases. Interestingly, SUVmax of the primary tumors was

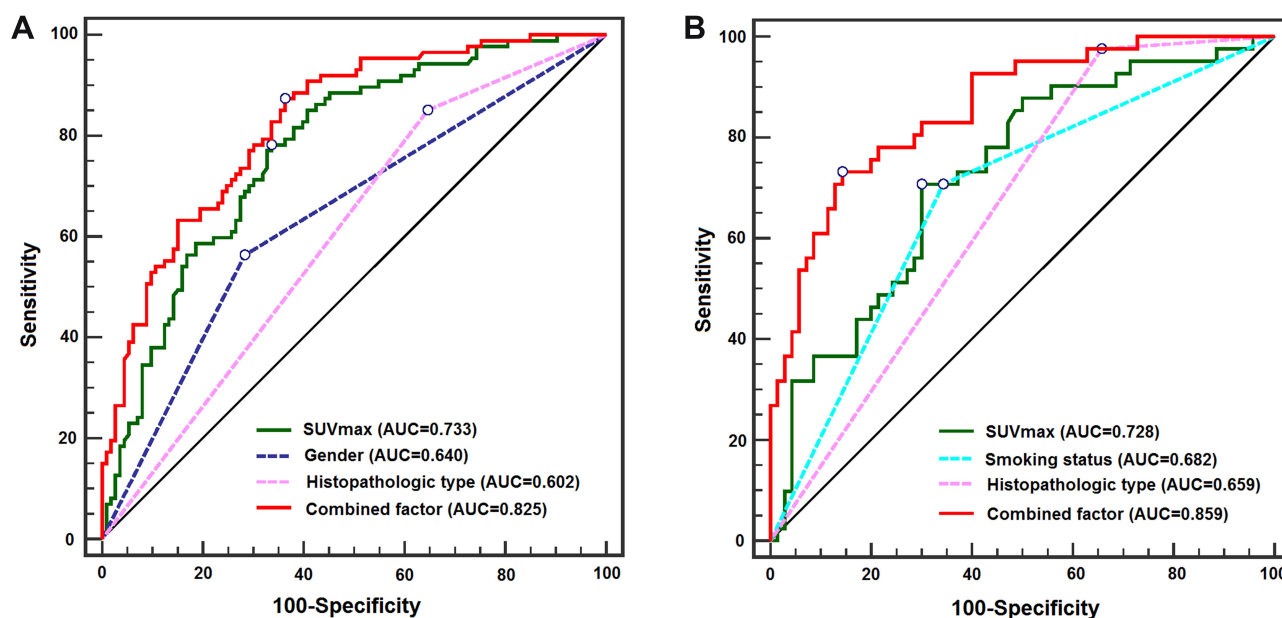


Figure 2 ROC curves of individual predictors and their combination in predicting *EGFR* mutation status. (A) ROC curves of patients with SUVmax obtained from the primary tumors (n=200). SUVmax of the primary tumors has better predictive value than gender and histopathologic type; (B) ROC curves of patients with SUVmax obtained from the metastases (n=111). SUVmax of the metastases has comparable *EGFR* mutation predictive value with smoking status and histopathologic type. Combined SUVmax with other clinical factors improved the predictive performance of individual predictor.

Abbreviations: ROC, receiver operating characteristic curve; *EGFR*, epidermal growth factor receptor; SUVmax, maximum standard uptake value; AUC, area under curve.

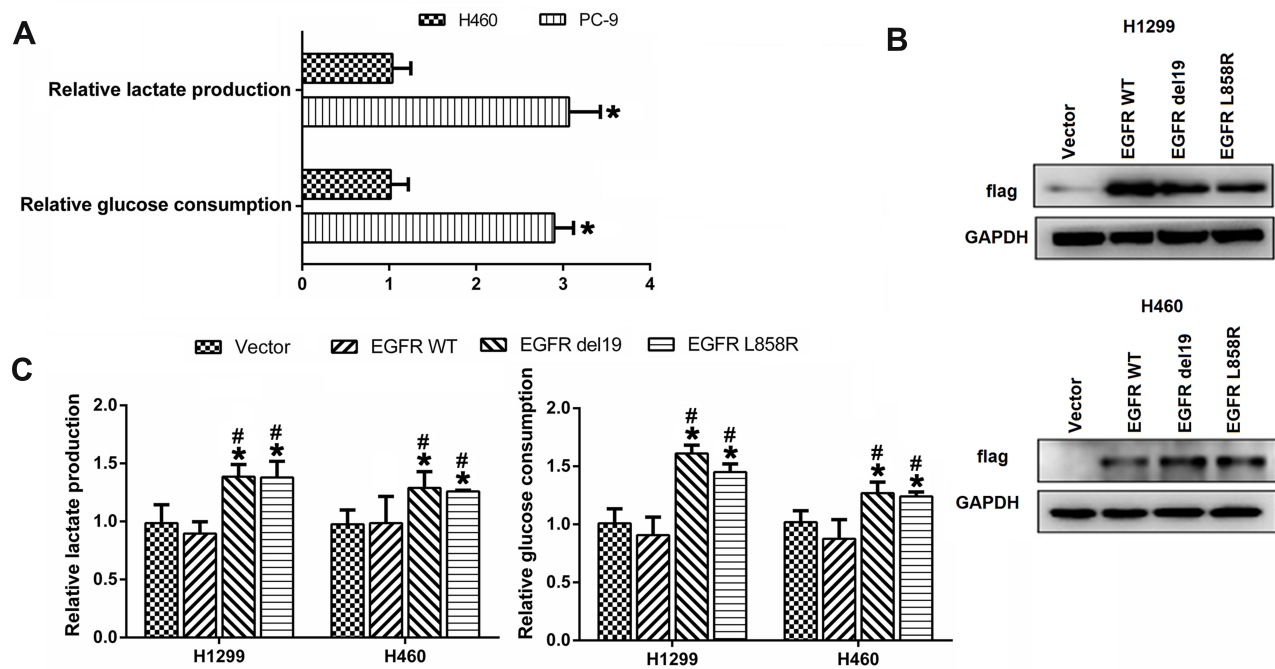


Figure 3 Association between *EGFR* mutation and aerobic glycolysis. (A) Glucose consumption and lactate production in *EGFR* mutant PC-9 cells and *EGFR* wild-type H460 cells. (B) Exogenous expression of *EGFR* determined by Western blot in H1299 cells and H460 cells transiently transfected with vector or FLAG-tagged plasmids containing either wild-type *EGFR* or mutant *EGFR* (del19 or L858R). (C) Glucose consumption and lactate production in H1299 and H460 cells transiently transfected with vector or FLAG-tagged plasmids containing either wild-type *EGFR* or mutant *EGFR* (del19 or L858R). * $P < 0.05$, vs vector group; # $P < 0.05$, vs wild-type group.

Abbreviation: *EGFR*, epidermal growth factor receptor.

significantly higher than that of the metastases. For patients whose SUVmax was obtained from the primary tumors, SUVmax has better *EGFR* mutation predictive value than gender and histopathologic type; while for patients whose SUVmax was obtained from the metastases, the predictive value of SUVmax was comparable with that of the smoking status and histopathologic type. The predict performance was significantly improved after combined SUVmax with other independent predictors. Our in vitro studies also demonstrated that *EGFR*-mutant lung cancer cells have higher aerobic glycolysis level than *EGFR* wild-type cells.

It is well known that *EGFR* mutation status of lung cancer is very important because it indicates induction of *EGFR*-TKIs treatment. Although evidences have suggested that *EGFR* mutation was related with clinical features such as adenocarcinoma, female, never-smoker and Asians,²⁵ more specific and accurate factors are needed to help predict *EGFR* mutation. The potential of SUVmax as a predictor for *EGFR* mutation status has attracted more attention in recent years. Putora et al¹¹ and Lee et al¹² found no statistical difference in the SUVmax between the *EGFR*-mutant and *EGFR* wild-type lung cancers, concluding that SUVmax cannot predict *EGFR* mutation status. In

contrast, more studies had suggested that SUVmax was significantly correlated with *EGFR* mutation status but with opposite findings. Several studies have reported that patients with low SUVmax, with cut-off values from ≤ 2.69 to < 11.5 , were more likely to have *EGFR* mutations than those with high SUVmax.^{13–19} In contrary, some studies have reported that patients with higher SUVmax, with cut-offs from ≥ 6 to > 13.65 , were more likely to have *EGFR* mutations.^{20–22} Our results are in favor that patients with higher SUVmax were more likely to have *EGFR* mutations. The discrepancy of these clinical studies maybe related to many factors such as different evaluation protocol and ethnicity/histopathologic type of included patients. Detailed information about the above-mentioned studies is summarized in Table 4.

One of the highlights of the present study is that we divided patients into two groups and separately analyzed the potential of SUVmax in predicting *EGFR* mutation status because the metabolic phenotype of the primary tumors differs from that of metastases, which was consistent with the observations of Lee et al;²⁶ however, they drew different conclusion from ours and suggested that SUVmax ≤ 7.2 in metastasis could predict *EGFR* mutations with high specificity in stage IV lung adenocarcinoma

Table 4 Summary of the Clinical Studies Evaluated the Relationship Between SUVmax and *EGFR* Mutation Status

Authors	Ethnicity	No. of Patients	<i>EGFR</i> Mutation	Histology	Stage	SUVmax Cut-Off Value
Putora et al ¹¹	Swiss	28	14 (50)	Ad	Unspecified	NA
Lee et al ¹²	South Korean	206	47 (23)	135 Ad, 71 non-Ad	I–IV	NA
Na et al ¹³	Korean	100	21 (21)	53 Ad, 47 non-Ad	I–IV	<9.2
Guan et al ¹⁴	Chinese	316	126 (39.9)	242 Ad, 74 non-Ad	I–IV	≤ 8.1
Cho et al ¹⁵	Korean	61	30 (49.1)	58 Ad, 3 non-Ad	I–IV	<9.6
Takamochi et al ¹⁶	Japanese	734	334 (46)	Ad	I–IV	≤2.69
Lv et al ¹⁷	Chinese	808	371 (45.9)	731 Ad, 77 non-Ad	I–IV	<7
Gao ¹⁸	Chinese	167	73 (43.7)	162 Ad, 5 non-Ad	I–IV	<11.5
Zhu et al ¹⁹	Chinese	139	74 (53.2)	Ad	I–IV	<11.19
Huang et al ²⁰	Chinese	77	49 (64)	Ad	IIIB–IV	≥9.5
Ko et al ²¹	Chinese	132	69 (52)	Ad	I–IV	≥6
Kanmaz et al ²²	Turk	218	63 (28.9)	Ad	I–IV	>13.65

Abbreviations: SUVmax, maximum standard uptake value; *EGFR*, epidermal growth factor receptor; Ad, adenocarcinoma.

patients. In the present study, we found *EGFR*-mutant patients had higher SUVmax than the wild-type patients in both primary tumors and the metastases. Notably, SUVmax obtained from the primary tumors, not from the metastases, has better predictive value than other clinical features in predicting *EGFR* mutation status. When combined SUVmax with other clinical factors such as gender, smoking status and histopathologic type, the prediction ability was profoundly improved.

SUVmax obtained from PET/CT is a semi-quantitative metabolic parameter that indicates the degree of aerobic glycolysis in tumor.²⁷ Considering the controversial correlation between SUVmax and *EGFR* mutation status reported in previous studies, we further used human lung cancer cell lines that harbored *EGFR* mutation or transiently expressing FLAG-tagged *EGFR* mutations such as del19 and L858R to confirm the relationship between *EGFR* mutation and aerobic glycolysis. Our in vitro experiments showed that *EGFR*-mutant NSCLC cells have higher aerobic glycolysis level as compared with the wild-type cells. This was consistent with our clinical observations that *EGFR*-mutant patients had higher SUVmax value than the wild-type patients. In a study performed by Kim et al, authors found that *EGFR*-mutant NSCLCs had significant higher glucose uptake and lactate production compared with wild-type NSCLCs. They concluded that *EGFR* mutation-regulated glycolysis enhancement was required for fueling the tri-carboxylic acid cycle which was essential for survival of *EGFR* mutant NSCLCs.²⁸ In addition, other studies also demonstrated that *EGFR* mutation can increase glycolysis and promotes glucose consumption via activation of the

Akt pathway.^{29,30} Taken together, these evidences indicated that *EGFR* mutant NSCLCs probably had higher aerobic glycolysis level, in other words, higher SUVmax value, than the wild-type NSCLCs.

Although SUVmax seems as a promising factor for predicting *EGFR* mutation status, our findings must be interpreted in the context of the retrospective nature of the study, which may introduce biases. In the future, large-scale, prospective studies are warranted to further validate the value of SUVmax in predicting *EGFR* mutations.

Conclusions

SUVmax of the primary tumors has the potential to serve as a biomarker to predict *EGFR* mutation status in NSCLC patients.

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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