Original Article

Value of combining serum carcinoembryonic antigen and PET/CT in predicting *EGFR* mutation in non-small cell lung cancer

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Background: We sought to investigate the associations between pretreatment serum Carcinoembryonic antigen (CEA) level, ^{18}F-Fluoro-2-deoxyglucose (^{18}F-FDG) uptake value of primary tumor and epidermal growth factor receptor (EGFR) mutation status in non-small cell lung cancer (NSCLC).

Methods: We retrospectively reviewed medical records of 210 NSCLC patients who underwent EGFR mutation test and ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) scan before anti-tumor therapy. The associations between *EGFR* mutations and patients' characteristics, serum CEA, PET/CT imaging characteristics maximal standard uptake value (SUVmax) of the primary tumor were analyzed. Receiver-operating characteristic (ROC) curve was used to assess the predictive value of these factors.

Results: *EGFR* mutations were found in 70 patients (33.3%). *EGFR* mutations were more common in high CEA group (CEA ≥7.0 ng/mL) than in low CEA group (CEA <7.0 ng/mL) (40.4% *vs.* 27.6%; P=0.05). Females (P<0.001), non-smokers (P<0.001), patients with adenocarcinoma (P<0.001) and SUVmax <9.0 (P=0.001) were more likely to be EGFR mutation-positive. Multivariate analysis revealed that gender, tumor histology, pretreatment serum CEA level, and SUVmax were the most significant predictors for *EGFR* mutations. The ROC curve revealed that combining these four factors yielded a higher calculated AUC (0.80).

Conclusions: Gender, histology, pretreatment serum CEA level and SUVmax are significant predictors for *EGFR* mutations in NSCLC. Combining these factors in predicting *EGFR* mutations has a moderate diagnostic accuracy, and is helpful in guiding anti-tumor treatment.

Keywords: Non-small cell lung cancer (NSCLC); epidermal growth factor receptor (EGFR); carcinoembryonic antigen; maximal standard uptake value; positron emission tomography/computed tomography (PET/CT)

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Introduction

Lung cancer is the leading cause of cancer-related death in the world. About 85% of lung cancers are non-small cell lung cancers (NSCLC). The epidermal growth factor receptor (*EGFR*) is a transmembrane glycoprotein, which contributes to tumor cell proliferation, differentiation, angiogenesis and anti-apoptosis. Some studies had shown that *EGFR* mutations are more common in females, non-smokers, East Asians, and patients with adenocarcinoma (1,2). *EGFR* Tyrosine kinase inhibitors (*EGFR*-TKIs) had been proved to be more efficient than conventional chemotherapy in *EGFR* mutation-positive NSCLC patients (3,4). Meanwhile, *EGFR*-TKIs have little effect in patients with wild-type *EGFR* (5). Thus, clarifying patients' *EGFR* mutation status is very important before anti-tumor therapy. However, sometimes it is hard to get enough tumor tissues for *EGFR* mutation testing, especially in advanced stage

patients. Therefore, developing other noninvasive methods to predict *EGFR* mutation status is necessary. ^{18}F-Fluoro-2-deoxyglucose (^{18}F-FDG) positron emission tomography/computed tomography (PET/CT) has been widely used in staging and evaluating the treatment effect of NSCLC. FDG uptake, usually using SUVmax of the primary tumor, can reflect tumor cell proliferation and glucose metabolism (6). Some studies have reported that SUVmax can be used to predict *EGFR* mutation status in NSCLC (7-11). However, there is no consensus conclusion. Thus more studies are needed to investigate the association between SUVmax and *EGFR* mutation status in NSCLC. Tumor markers are widely used to diagnose, monitor therapy response and recurrence in NSCLC (12,13). Carcinoembryonic antigen (CEA) is one of the most commonly used tumor markers in NSCLC. Some studies had shown that CEA is a significant prognostic predictor in patients treated with *EGFR*-TKIs (14-16). Some researchers also proposed that CEA level have some relation with *EGFR* mutation status (17). However, no consensus conclusions were reached.

Few studies had investigated the value of combining clinical features, pretreatment serum CEA level and SUVmax of the primary tumor in predicting *EGFR* mutation status in NSCLC. Thus, the purpose of this study is to analyze these clinical parameters in NSCLC and evaluate whether they can help predicting the *EGFR* mutation status in NSCLC.

Methods

Patients and inclusion criteria

This study was approved by our institutional review board (approval 2013-07 revision one). We retrospectively reviewed the medical records of all patients who were diagnosed NSCLC, underwent *EGFR* mutation test and ^{18}F-FDG PET/CT scan less than one month before receiving any therapy between March 2011 and December 2014 at our hospital (the First Affiliated Hospital of Sun Yat-sen University). Patients' characteristics were gathered by a chart, including age, gender, smoking status and pretreatment serum CEA level. Smoking status was defined as follows: never-smokers had smoked less than 100 cigarettes during their lifetime; current smokers were those who were still smoking or had quit smoking less than 1 year at the time of diagnosis; the remaining patients were categorized as former smokers. Pathological characteristics including tumor histology, grade and stage were collected. Patients were staged according to the 7th edition of the *American Joint Committee on Cancer (AJCC) Staging Manual* (18). We excluded five patients who had immeasurable lesions.

PET/CT scanning

PET/CT scans were performed with a Gemini GXL 16 scanner (Philips, Netherlands) in three-dimensional acquisition mode. All patients were required to fast for at least 6 h to make sure the blood glucose level was no more than 140 mg/dL before ^{18}F-FDG injection. After i.v. injection of 5.18 MBq/kg ^{18}F-FDG one hour later, imaging was obtained using a low-dose (120 kVp, 140 mA, 0.5 s per CT rotation, 5 mm collimation, 7.5 mm slice thickness, 1.25 mm pitch) two-slice CT scan from the head to the proximal thighs. Subsequently, PET images were acquired with a time of 3 min per bed position in 3-dimensional mode. After that, PET images were fused with the attenuation correction CT images to reconstruct PET/CT image using ordered-subset expectation maximization (OSEM) (4 iterations and 8 subsets). The final images were displayed by Xeleris Software (Philips, Netherlands).

PET data analysis

The FDG-PET data were analyzed by two experienced nuclear medicine physicians who were blind to the *EGFR* mutation status. Regions of interest (ROI) were placed on the primary tumors and mediastinal lymph nodes with abnormal FDG uptake on reconstructed PET/CT images. To minimize variation according to the size of ROIs, the maximum pixel activity within the ROI was recorded to calculate the SUVmax [SUVmax = maximum pixel activity/(injected dose/body weight)].

EGFR mutational analysis

Genomic DNA was extracted from tumor tissue using QIAamp DNA Formalin-fixed paraffin-embedded Tissue Kit (Qiagen. Hilden, Germany) following the manufacturer's protocols. The DNA was diluted to 2–3 ng/μL in *EGFR* mutation test. The *EGFR* mutation detection kit (Amoy Diagnostics, Xiamen, China), which is based on the Amplified Refractory Mutation System (ARMS) technology, was used to identify the 29 most common types of *EGFR* mutations from exon 18 to 21. All experiments were performed following the manufacturer's protocols. Briefly, ten nanograms genomic DNA was

added to 45 μL PCR master mix containing PCR primers, fluorescent probes, Taq DNA polymerase and PCR buffer for each assay. The PCR cycling concluded 3 steps: firstly, 1 cycle of 95 ℃ for 5 min; secondly, 15 cycles of 95 ℃ for 25 s, 64 ℃ for 20 s, 72 ℃ for 20 s; thirdly, 31 cycles of 93 ℃ for 25 s, 60 ℃ for 35 s, 72 ℃ for 20 s. After 47 cycles of amplification, the fluorescent signal was collected from FAM and HEX channels. The results were analyzed following the manufacturer's protocols.

Statistical analysis

Student's *t*-test was used to analyze continuous variables. The results were expressed as the mean ± standard deviation (SD). Fisher's exact test or Pearson's chi-square test was used to analyzing categorical variables. A receiver operating characteristic (ROC) curve was generated to obtain the SUVmax and CEA cut-off values. The predictive value of the established criteria was assessed by calculating the area under the ROC curve (AUC). Multivariate logistic regression analysis was performed to test the associations between clinical factors and *EGFR* mutations. The multivariate logistic regression equation was used to predict a certain patient's *EGFR* mutation status. A two-sided P value of less than 0.05 was considered to be statistically significant. All statistical analyses were performed using SPSS software (version 20.0; SPSS, Chicago, IL).

Results

Patient characteristics and their associations with EGFR mutations

The baseline characteristics of patients are summarized in *Table 1*. In total, 210 patients (132 males and 78 females) were included in this study. Male (n=132; 62.9%), non-smoker (n=120; 57.1%) and advanced stage (III-IV) (n=152; 72.4%) accounted for the majority of the population. The median SUVmax of primary tumors was 8.5 (4.8–12.9). Among them, 70 patients (33.3%) were found to be *EGFR* mutation-positive, the rest were wild-type *EGFR*. The predominant mutation subtypes were the L858R point mutation in exon 21 (n=35; 16.7%) and the exon 19 deletion (n=31; 14.8%). The rest included L861Q point mutation in exon 21 (n=2; 1.0%), S768I missense mutation in exon 20 (n=1; 0.5%) and G719X point mutation in exon 18 (n=1; 0.5%). Univariate analysis was used to evaluate the association between clinical factors and *EGFR* mutation status. Results were summarized in *Table 2*. *EGFR* mutations were more frequent in females than males (57.7% *vs.* 18.9%; P<0.001), in never-smokers than smokers (47.5% *vs.* 14.4%; P<0.001), in patients with adenocarcinomas than non-adenocarcinomas (41.0% *vs.* 8.2%; P<0.001). Neither tumor grade (P=0.081) nor tumor size (P=0.316) showed relevance with *EGFR* mutation status.

Association between SUVmax and EGFR mutations

The ROC curve revealed that the SUVmax cutoff point was 9.0, and the calculated AUC was 0.62 (95% CI, 0.54–0.70). According to the selected SUVmax cutoff point 9.0, which the sensitivity, specificity, positive and negative predictive values for predicting *EGFR* mutation were 70.0%, 54.3%, 43.3% and 78.4%, patients were divided into two groups: low SUVmax group (<9.0) and high SUVmax group (≥9.0). *EGFR* mutations were found more frequently in the low SUVmax group than in the high SUVmax group (43.6% *vs.* 22.0%; P=0.001).

Association between CEA and EGFR mutations

The ROC curve revealed that the CEA cutoff point was 7.0 ng/mL, and the calculated AUC was 0.56 (95% CI, 0.47–0.64). According to the selected CEA cutoff point 7.0 ng/mL, which the sensitivity, specificity, positive and negative predictive values for predicting *EGFR* mutation were 54.3%, 60.0%, 40.4% and 72.5%, patients were divided into two groups: low CEA group (<7.0 ng/mL) and high CEA group (≥7.0 ng/mL). *EGFR* mutations were found more frequently in high CEA group than in the low CEA group (40.4% *vs.* 27.6%; P=0.05).

Multivariate analysis

We included all variables with P<0.2 in univariate analysis, including SUVmax, gender, tumor histology, CEA, smoking status, age and tumor grade in the multivariate logistic regression analysis, despite smoking status (P=0.121), age (P=0.864) and tumor grade (P=0.364), the rest were statistically significant predictors for *EGFR* mutation (*Table 3*).

ROC curve analysis revealed that the combination of these four factors had a relatively high predictive value as the calculated AUC was 0.80 (95% CI, 0.74–0.86) (*Figure 1*). Using the cutoff point 0.3432, which was selected by maximum Youden's index, the sensitivity and specificity for predicting *EGFR* mutations were 81.4% and 72.1%,

Table 1 Characteristics of 210 patients

Characteristics	Value
Age (years)	59 [53–67]
Gender	
Male	132 (62.9)
Female	78 (37.1)
Smoking status	
Never	120 (57.1)
Current or former	90 (42.9)
American Joint Committee on Cancer (AJCC) stage	
I	46 (21.9)
II	12 (5.7)
III	35 (16.7)
IV	117 (55.7)
Sampling procedures	
Surgery	82 (39.0)
Bronchoscopic biopsy	70 (33.3)
Ultrasound/CT-guided biopsy	26 (12.4)
Medical thoracoscopy	15 (7.1)
Lymph node biopsy	7 (3.3)
Pleural effusion cell blocks	1 (0.5)
Other procedures	9 (4.3)
Tumor histology	
Adenocarcinoma	161 (76.7)
Squamous cell carcinoma	34 (16.2)
Adenosquamous cell carcinoma	5 (2.4)
Large cell carcinoma	3 (1.4)
Sarcomatoid carcinoma	2 (0.9)
Other NSCLC	5 (2.4)
Tumor grade	
Poor	45 (21.4)
Moderate	53 (25.2)
Well	6 (2.9)
Undefined	106 (50.5)
EGFR mutational status	
Wild-type	140 (66.7)
Deletion in exon 19	31 (14.8)
L858R in exon 21	35 (16.7)
L861Q in exon 21	2 (1.0)
S768I in exon 20	1 (0.5)
G719X in exon 18	1 (0.5)
CEA (ng/mL)	
<7	116 (55.2)
≥7	94 (44.8)
Tumor size (cm)	3.2 [2.1–4.7]
SUVmax	8.5 [4.8–12.9]

Data are shown as median [range] or number (percentage).

respectively.

Multivariate logistic regression formulation was performed as follows: $Y = e^x/(1+ e^x)$, $X = -8.273+1.713 \times$ gender $+1.402 \times$ histology $+0.735 \times$ CEA $+0.921 \times$ SUVmax. Compare patients' calculated values with cutoff point 0.3432 (*Table 4*). If the value was higher than 0.3432 we concluded patient is *EGFR* mutation-positive, otherwise *EGFR* wild-type.

Discussion

Determination of the molecular profile has become standard practice in the management of patients with NSCLC. However, this assessment is frequently impaired by insufficient tumor tissue or technically deficiency (19). Therefore, alternative noninvasive strategies, such as ^{18}F-FDG PET/CT, serum CEA, for predicting the mutation profile could help overcome these limitations and could be of value.

Our results show that ^{18}F-FDG uptake is significantly increased in NSCLC tumors harboring *EGFR* mutations. We found that SUVmax lower than 9.0 was a significant predictor for *EGFR* mutations. Previous studies have shown

Table 2 Association between clinical features and *EGFR*

Characteristics	Wild-type EGFR (N=140)	Mutation EGFR (N=70)	*EGFR* mutation rate (%)	P value
Age (years)	62 [54–69]	58 [52–63]		0.064
Gender				<0.001
Male	107	25	18.9	
Female	33	45	57.7	
Smoking status				<0.001
Never	63	57	47.5	
Current or former	77	13	14.4	
AJCC stage				0.482
I	31	15	32.6	
II	7	5	41.7	
III	27	8	22.9	
IV	75	42	35.9	
Tumor histology				<0.001
Adenocarcinoma	95	66	41.0	
Other NSCLC	45	4	8.2	
Tumor grade				0.081
Poor	37	8	17.8	
Moderate	34	19	35.8	
Well	3	3	50.0	
Undefined	66	40	37.7	
CEA (ng/mL)				0.050
<7	84	32	27.6	
≥7	56	38	40.4	
Tumor size (cm)	3.3 (2.1–5.0)	3.0 (2.1–4.1)		0.316
SUVmax				0.001
<9	62	48	43.6	
≥9	78	22	22.0	

Table 3 Multivariate analysis for various predictive factors of *EGFR* mutation

Parameters	Regression coefficients	P value	OR	95% CI
Female	1.713	<0.001*	5.545	2.816–10.920
CEA ≥7 ng/mL	0.735	0.038*	2.086	1.040–4.181
SUVmax <9	0.921	0.011*	2.511	1.236–5.102
Adenocarcinoma	1.402	0.017*	4.063	1.286–12.839
Age		0.864		
Smoking status		0.121		
Tumor grade		0.364		

*, significance at P<0.05. OR, odds ratio; CI, confidence interval.

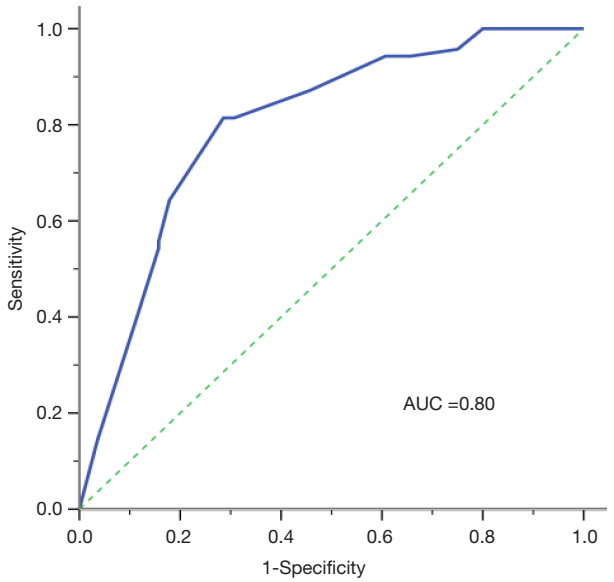

Figure 1 ROC curve of combining four factors (SUVmax, gender, histology, CEA) for predicting *EGFR* mutation. For predicting *EGFR* mutation, the AUC was 0.80 (95% CI, 0.74–0.86).

Table 4 Scores for predicting *EGFR* mutation

Characteristics	Score
Gender	
Male	1
Female	2
Histology	
Non-adenocarcinoma	1
Adenocarcinoma	2
CEA	
<7.0 ng/mL	1
≥7.0 ng/mL	2
SUVmax	
≥9.0	1
<9.0	2

contradictory results. Huang *et al.* indicated that patients with SUVmax higher than 9.5 were more likely to be *EGFR* mutation-positive (11). Study of Ko *et al.* was in accordance with Huang *et al.*, they concluded that SUVmax higher than 6.0 was a significant predictor for *EGFR* mutations (9). The possible reason for the different results observed is that for acquiring further information in NSCLC patients, the histological type of our study cases was not only adenocarcinoma but also included non-adenocarcinoma (23.3%), which has been shown to have a different FDG uptake and distinct tumor biology. Conversely, Mak *et al.* reported that high FDG uptake value (normalized SUVmax >5) correlated with *EGFR* wild-type genotype in Western NSCLC patients (10). As their study included mostly white people 88% (88/100), their result may only represent Western people. Na *et al.* investigated 100 South Korean NSCLC patients, concluded that patients with low SUVmax (<9.2) was more likely to be *EGFR* mutation-positive (7). However, their study has a relatively small sample size (n=100), and *EGFR* mutation rate was only 21%, lower than common Asian populations. Our study included 210 NSCLC patients with stage I to IV and tumor histology which contains adenocarcinoma, squamous cell carcinoma, adenosquamous cell carcinoma and other subtypes of NSCLC, both smokers and nonsmokers, thus could be the better representative of NSCLC patients of the Asian population.

Our study found that patients with lower SUVmax were more likely to be *EGFR* mutation-positive, the reasons as follows: (I) In NSCLC, SUVmax differs in histology types: Squamous cell carcinoma always had a higher SUVmax than adenocarcinoma (20-23). A series of studies had confirmed that FDG uptake value had much to do with glucose transports (GLUTs). In NSCLC, GLUT1 is dominant in deciding FDG uptake value. Expression of GLUT1 in squamous cell carcinoma is much higher than adenocarcinoma (20,21), which would lead to an increase in FDG uptake. As *EGFR* mutations more frequently happen in adenocarcinoma than squamous cell carcinoma, the underlying reason that patients with lower SUVmax are more likely to be *EGFR* mutation-positive may be caused by histology difference. (II) This result maybe relates with hypoxia-inducible factor (HIF-1) protein. HIF-1 was shown to be related to regulating the genes responsible for increased utilization of glucose and energy metabolism (24). And cell lines with *EGFR* mutations expressed high basal levels of HIF-1α (25). ^{18}F-FDG uptake is also shown to be associated with the presence of HIF-1 in other malignancies including cervix, cancer of the brain, the oral cavity and breast (24,26,27). However, some studies reported that there was no correlation or negative correlation between SUVmax and HIF-1 (24,28). (III) SUVmax also differs in subtypes of lung adenocarcinoma: Chiu *et al.* reported that

GLUT1 expression and FDG uptake values were lower in terminal-respiratory-unit (TRU) type adenocarcinoma than non-TRU type (29). TRU-type adenocarcinoma is more likely to be *EGFR* mutation-positive (30). Besides, SUVmax of lepidic carcinomas, which is more common to be *EGFR* mutation-positive, is usually lower than other types of adenocarcinoma (31,32).

Currently, serum CEA is widely used in diagnosing and evaluating treatment in NSCLC, especially in adenocarcinoma. Some studies had reported that pretreatment serum CEA level could predict therapy effect of *EGFR*-TKIs in NSCLC. High level of pretreatment CEA indicates a good response to *EGFR*-TKIs and a better prognosis than normal CEA level (14-16). Shoji *et al.* first reported the relationship between serum CEA level and *EGFR* mutation in NSCLC (17). Their study pointed out that patients with higher serum CEA level at the time of recurrence were more likely to be *EGFR* mutation-positive than those with lower serum CEA level.

The mechanism of CEA predicting *EGFR* mutation status is not clear. Li *et al.* found that in NSCLC *EGFR* mutation had a positive correlation with CEA level in tumor tissue (r=0.237, P=0.003) (33). As both CEA and activation of *EGFR* signal pathway inhibits apoptosis, one possible hypothesis may be that elevated CEA level is caused by activation of anti-apoptosis signal pathway conducted by *EGFR* mutation (34,35). Our study is in accordance with Shoji *et al.*, pointing out that *EGFR* mutation is more likely to happen in NSCLC patients with pretreatment serum CEA level higher than 7.0 ng/mL, predicting value of sensitivity and specificity were 54.3% and 60.0%, respectively.

Although previous studies have reported that variable FDG uptake, serum CEA levels are correlated with mutation status, respectively, one parameter alone is not sufficiently powerful and confident for predicting mutation status. The major strength of our study was that we established reliable clinical and imaging criteria for the prediction of *EGFR* mutation: high SUVmax and serum CEA levels. Our study combined pretreatment CEA level, SUVmax, gender and tumor histology in predicting *EGFR* mutation status, which is more efficient than a single factor like CEA level or SUVmax. The combining calculated AUC was 0.80, sensitivity and specificity for predicting *EGFR* mutation was 81.4% and 72.1%, while the calculated AUC of SUVmax and serum CEA were 0.62 and 0.56 respectively.

There are some limitations in our study: firstly, although the sample size of our study is larger than the other similar reported studies, it is still relatively small. Secondly, it is a retrospective study and needs prospective study to confirm our conclusion. Moreover, the mechanism in detail between SUVmax and *EGFR* mutation is still not clear. More basic experimental research is needed.

Conclusions

In conclusion, combining the use of pretreatment serum CEA level, SUVmax, gender and tumor histology is practical in predicting *EGFR* mutation status in NSCLC patients, especially when there isn't enough tumor tissue or are unable to do *EGFR* mutation test. However, large multi-center prospective clinical trials are needed to confirm the current conclusion.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This study was approved by our institutional review board (approval 2013-07 revision one, The First Affiliated Hospital of Sun Yat-sen University).

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