Original Article

# The predictive value of $^{18}$F-FDG PET/CT in an *EGFR*-mutated lung adenocarcinoma population

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**Background:** A non-invasive, simple, and convenient method to evaluate the presence of epidermal growth factor receptor (*EGFR*) mutations is important for initial treatment decisions in lung adenocarcinoma.

**Methods:** We retrospectively reviewed 297 untreated primary lung adenocarcinoma patients with exact *EGFR* status. Based on their *EGFR* status, the patients were divided into a mutant-type group (138 patients) and wild-type group (159 patients). General patient characteristics and possible factors reflecting the status of *EGFR* were also evaluated.

**Results:** Of the 297 lung adenocarcinoma patients analyzed for *EGFR* status who underwent positron emission tomography (PET)/computed tomography (CT) between January 2013 and December 2017, mutations in the *EGFR* gene were detected in 138 patients (46.5%). *EGFR* mutations were more frequently associated with women, never smokers, and low $^{18}$F-fluoro-2-deoxy-glucose ($^{18}$F-FDG) PET/CT maximal standard uptake value of the primary tumor (pSUVmax). Multivariate analysis indicated that women [odds ratio (OR) =2.853; 95% confidence interval (CI): 1.451–5.611; P=0.002], never smokers (OR =2.414; 95% CI: 1.217–4.789; P=0.012), tumor size <3.5 cm (OR, 2.170; 95% CI: 1.205–3.908; P=0.010), and pSUVmax <8.2 (OR =1.904; 95% CI: 1.098–3.302; P=0.022) were effective predictors of *EGFR* mutation. In addition, the area under the curve (AUC) of pSUVmax and tumor size was 0.623 and 0.600, respectively. Combined with clinical characteristics, including sex and smoking status, the AUC of the 4 predictors was 0.770.

**Conclusions:** These indicators could be helpful for enhancing predictive accuracy of *EGFR* mutations in lung adenocarcinoma patients, especially in those for whom *EGFR* detection is unavailable.

**Keywords:** Epidermal growth factor receptor (EGFR); lung adenocarcinoma; standard uptake value (SUV); mutation

Submitted May 17, 2022. Accepted for publication Jul 12, 2022.
doi: 10.21037/tcr-22-1726
**View this article at:** https://dx.doi.org/10.21037/tcr-22-1726

## Introduction

The introduction of novel therapies, especially the use of tyrosine kinase inhibitors (TKIs), has improved patient outcomes and enabled a significant paradigm shift in the therapeutic agent management of non-small cell lung cancer (NSCLC) (1-5). Numerous randomised clinical trials have shown that mutations in epidermal growth factor receptor (*EGFR*) are frequently present in lung adenocarcinoma. While progression-free survival (PFS) is longer when using TKIs than when using chemotherapy in patients harbouring *EGFR* mutations (6-8), the effectiveness of TKIs is affected by the presence of *EGFR* mutations (9,10). Therefore, molecular profiling of *EGFR* or anaplastic lymphoma kinase (ALK) has been recommended as standard care for patients with advanced-stage adenocarcinoma regardless of race, sex, smoking history, or other clinical factors (1). However, obtaining sufficiently high-quality tumor tissues for *EGFR* testing is challenging in many situations due to a deficiency of biopsy samples and the physical condition of patients. Therefore, a non-invasive, simple, and convenient method to evaluate the presence of *EGFR* mutations is necessary when managing treatment strategies, especially in making initial treatment decisions.

Positron emission tomography (PET) using $^{18}$F-fluoro-2-deoxyglucose ($^{18}$F-FDG) is a widely applied, non-invasive, functional imaging modality based on differential glucose metabolism and is important for diagnosis, staging, assessment of therapeutic efficacy, and radiotherapy planning in lung cancer (11). High rates of $^{18}$F-FDG uptake illustrate both active glucose metabolism and cancer proliferation of malignant cells (12,13). The *EGFR* signalling pathway regulates glucose metabolism and inhibits apoptosis in *EGFR*-mutated lung adenocarcinoma cells, and TKIs act to decrease glucose consumption (14,15). Studies have shown that maximal standard uptake values (SUVmax) are associated with *EGFR* mutational status in both cellular and animal models (16,17). Clinical studies have demonstrated an association between *EGFR* mutations and $^{18}$F-FDG uptake, but the results are conflicting (18-25). We retrospectively analyzed patients with lung adenocarcinoma to investigate whether $^{18}$F-FDG PET could be an accurate indicator for predicting *EGFR* mutations in lung adenocarcinomas. We present the following article in accordance with the STARD reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1726/rc).

## Methods

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by committee of Shanxi Province Cancer Hospital (No. 201835). Individual consent for this retrospective analysis was waived.

### *Study design and inclusion criteria*

We retrospectively examined all untreated primary lung adenocarcinoma patients who had undergone *EGFR* detection and PET/CT simultaneously between January 2013 and December 2017. In total, 432 cases without diseases which influence the standard uptake value (such as diabetes, acute inflammation, and metabolic disease, etc.) were identified, and 297 individuals were ultimately selected. Of these, 135 cases were excluded for one of the following reasons: (I) 73 patients had a history of another malignancy or mixed pathological types; (II) 54 cases had incomplete data; (III) the period between PET/CT and *EGFR* detection exceeded 1 month in 8 individuals.

The parameters of $^{18}$F-FDG PET/CT and clinical information, including age, sex, smoking history, immunohistochemistry (IHC) analysis, *EGFR* status, and tumor/node/metastasis (TNM) stage were obtained from the hospital's medical records. Patients who never smoked or had smoked no more than 100 cigarettes in total were defined as never smokers. The patients were divided into a mutant group (n=138) and a wild-type group (n=159) based on *EGFR* mutational status. TNM staging was based on the International Association for the Study of Lung Cancer (IASLC) 8$^{th}$ TNM Lung Cancer Staging System and clinical testing results. All procedures were performed by at least 2 experienced clinicians according to international guidelines.

### *$^{18}$F-FDG PET/CT scanning and analysis*

A Discovery STE PET/CT system (GE Healthcare, Waukesha, WI, USA) was used to perform PET/CT. The PET/CT center of Shanxi Cancer Hospital provided $^{18}$F-FDG with a radiochemical purity of >95%. Patients fasted for >6 h before examination. The fasting blood glucose concentration was checked and confirmed to be <11 mmol/L before examination. Image scanning was performed 60 min after intravenous injection of $^{18}$F-FDG (0.12–0.15 mCi/kg). PET was performed in

 

the 3-dimensional mode using 3.75 mm per slice. CT was performed using the following parameters: 120 kV, 200 mA, 0.8 s/lap, and 22.5 mm/s bed speed. The images were immediately obtained from the top of the skull to the upper femur (6–8 bed positions and 3 min per bed position). The PET images were reconstructed and attenuation-corrected by CT images. The images were then observed on an Xeleris Workstation (GE Healthcare) for assessment. Two experienced nuclear medicine radiologists reviewed all PET/CT data independently and reached a consensus on the results. The reviewers were blinded to the *EGFR* mutational status.

### *EGFR mutation analysis*

*EGFR* mutations were detected according to the amplification refractory mutation system (ARMS). Four paraffin-embedded wax slices with a continuous 7-μm thickness were taken to extract DNA using the QIAamp DNA FFPE Kit (Qiagen NV, Venlo, The Netherlands) according to the manufacturer's instructions. Polymerase chain reaction was performed to detect *EGFR* mutations using the EGFR 29 Mutation Detection Kit (Amoy Diagnostics, Xiamen, People's Republic of China). All steps were completed according to the ADx-EGFR detection instructions. The results of *EGFR* mutation analyses were interpreted by at least 2 experienced pathologists.

### *IHC analysis*

Tissue samples were acquired through surgical resection or biopsy of the primary tumor, primary or distant lymph node, or local or distant metastases. The samples were fixed in 10% neutral formalin and embedded in paraffin wax. Slices 3-μm thick were taken, one of which was used for hematoxylin and eosin (HE staining), and the rest were used for IHC staining. The process was performed using the fully automated Ventana IHC assay. Positive and negative controls were included in each experiment. The results of pathological diagnoses and IHC tests were interpreted by at least 2 experienced pathologists as being positive for a brown or tan nuclear appearance. Positive results for thyroid transcription factor-1 (TTF-1) were defined as >5% of tumor cells with nuclear staining and positive expression of napsin A. Cytokeratin 7 (CK7) positivity was defined as >50% of tumor cells with nuclear staining. The percentage of nuclei staining positive for Ki67 in tumor cells was denoted with a Ki67 score.

### *Statistical analysis*

All data were analyzed using SPSS for Windows (version 22.0). Clinical characteristics, including age, sex, smoking history, IHC results, and staging, were compared according to the EGFR mutational status using the chi-squared test and the *t*-test. A significant difference was defined as a two-sided P value <0.05. Receiver operating characteristic (ROC) curves were plotted to acquire the cut-off value of maximal standard uptake value of primary tumor (pSUVmax) for predicting *EGFR* mutations. Logistic regression analysis was used to identify independent predictors of *EGFR* mutation.

All variables with P<0.05 in the univariate analysis were further analyzed by multivariate regression analysis. Indicators with P<0.05 in the multivariate analysis were considered to be independent predictors, and the odds ratios (OR) and 95% confidence intervals (CI) of the independent predictors were obtained. In addition, ROC curves and area under the curves (AUCs) were plotted for the combined predictors of *EGFR* mutational status.

## Results

### *Patients and tumor characteristics*

Of the 297 lung adenocarcinoma patients analyzed for EGFR status who underwent PET/CT between January 2013 and December 2017, 138 (46.5%) were identified as having mutant *EGFR*, and 159 participants were wild type. The basic characteristics of the 2 groups are summarized in *Table 1*. The median age of the 297 patients was 59.27 years (range, 30–88 years), and there were 131 women (44.1%) and 166 men (55.9%). In total, 168 (76.1%) were never smokers. In addition, 66 (22.2%), 31 (10.4%), 59 (19.9), and 141 (47.5%) patients had stage I, II, III, and IV disease, respectively. The mutant group contained 69 cases (50.0%) with an exon 19 mutation, 62 patients (44.9%) with an exon 21 mutation, and 7 cases (5.1%) with rare mutations (*Table 1*). The median pSUVmax was 9.52 (range, 0.67–39.20).

### *Association between EGFR mutations and clinical characteristics*

To analyze the association between *EGFR* mutations and clinical information, the characteristics of the 2 groups were compared. *EGFR* mutations were detected more frequently in women (65.2% *vs.* 34.8%, P>0.001), never smokers (76.1% *vs.* 23.9%, P<0.001), and those with positive expression of TTF-1 (96.0% *vs.* 4.0%, P=0.001) and napsin

 

**Table 1** Associations between the 2 groups

| Variables | *EGFR* | | Total (N=297) | P value |
|---|---|---|---|---|
| | Mutant (N=138) | Wild-type (N=159) | | |
| Age (years), mean ± SD [range] | 58.95±9.87 [31–83] | 59.54±10.52 [30–88] | 59.27±10.21 [30–88] | 0.619[a] |
| Gender, n (%) | | | | <0.001[b] |
| Male | 48 (34.8) | 118 (74.2) | 166 (55.9) | |
| Female | 90 (65.2) | 41 (25.8) | 131 (44.1) | |
| Smoking status, n (%) | | | | <0.001[b] |
| Never smoker | 105 (76.1) | 63 (39.6) | 168 (76.1) | |
| Ever smoker | 33 (23.9) | 96 (60.4) | 129 (43.4) | |
| pSUVmax, mean ± SD | 8.24±4.51 | 10.64±5.77 | 9.53±5.35 | <0.001[a] |
| nSUVmax, mean ± SD | 5.64±3.77 | 7.25±4.53 | 6.58±4.29 | 0.009[a] |
| mSUVmax, mean ± SD | 7.20±3.86 | 7.32±4.72 | 7.27±4.37 | 0.870[a] |
| Tumor size, mean ± SD | 2.89±1.46 | 3.54±1.90 | 3.24±1.74 | 0.001[a] |
| Nodal metastasis, n (%) | | | | 0.141[b] |
| Negative | 51 (37.0) | 46 (28.9) | 97 (32.7) | |
| Positive | 113 (71.7) | 87 (63.0) | 200 (67.3) | |
| Distant metastasis, n (%) | | | | 0.293[b] |
| Negative | 77 (55.8) | 79 (49.7) | 156 (52.5) | |
| Positive | 61 (44.2) | 80 (50.3) | 141 (47.5) | |
| Stage, n (%) | | | | 0.138[b] |
| I | 38 (27.5) | 28 (17.6) | 66 (22.2) | |
| II | 16 (11.6) | 15 (9.4) | 31 (10.4) | |
| III | 23 (16.7) | 36 (22.6) | 59 (19.9) | |
| IV | 61 (44.2) | 80 (50.3) | 141 (47.5) | |
| TTF-1, n (%) | | | | 0.001[b] |
| Negative | 2 (4.0) | 24 (24.5) | 26 (17.6) | |
| Positive | 48 (96.0) | 74 (75.5) | 122 (82.4) | |
| Napsin A, n (%) | | | | <0.001[b] |
| Negative | 2 (4.2) | 33 (37.5) | 35 (25.7) | |
| Positive | 46 (95.8) | 55 (82.5) | 101 (74.3) | |
| CK7 (n, %) | | | | 0.548[b] |
| Negative | 0 (0.0) | 3 (4.9) | 3 (3.3) | |
| Positive | 30 (100.0) | 58 (95.1) | 88 (96.7) | |
| Ki67 score, mean | 35.95±19.07 | 49.08±23.96 | 44.60±23.19 | 0.003[a] |
| *EGFR* mutations, n (%) | | | | |
| Exon 18 | 3 (2.2) | | | |
| Exon 19 | 69 (50.0) | | | |
| Exon 20 | 4 (2.9) | | | |
| Exon 21 | 62 (44.9) | | | |

[a], *t*-test calculation; [b], Chi-Square calculation. EGFR, epidermal growth factor receptor; SD, standard deviation; pSUVmax, maximal standard uptake value of primary tumor; nSUVmax, maximal standard uptake value of lymph node; mSUVmax, maximal standard uptake value of distant metastasis; TTF-1, thyroid transcription factor 1.

**Table 2** Univariate and multivariate analysis of various predictive indicators for *EGFR* status

| Characteristics | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | OR (95% CI) | P value | OR (95% CI) | P value |
| Age | | 0.230 | | |
| <60 years | Reference | | | |
| ≥60 years | 1.323 (0.838–2.090) | | | |
| Sex | | <0.001 | | 0.002 |
| Male | Reference | | Reference | |
| Female | 5.396 (3.276–8.888) | | 2.853 (1.451–5.611) | |
| Smoking status | | <0.001 | | 0.012 |
| Never | 4.848 (2.929–8.026) | | 2.414 (1.217–4.789) | |
| Ever | Reference | | Reference | |
| Tumor size | | <0.001 | | 0.010 |
| <3.5 cm | 3.314 (1.881–5.222) | | 2.170 (1.205–3.908) | |
| ≥3.5 cm | Reference | | Reference | |
| pSUVmax | | <0.001 | | 0.022 |
| <8.2 | 2.322 (1.454–3.706) | | 1.904 (1.098–3.302) | |
| ≥8.2 | Reference | | Reference | |
| Nodal metastasis | | 0.142 | | |
| Negative | Reference | | | |
| Positive | 0.694 (0.427–1.130) | | | |
| Distant metastasis | | 0.293 | | |
| Negative | Reference | | | |
| Positive | 0.782 (0.495–1.236) | | | |
| Stage | | 0.046 | | |
| I | Reference | | | |
| II | 0.786 (0.334–1.852) | 0.582 | | |
| III | 0.471 (0.230–0.963) | 0.039 | | |
| IV | 0.562 (0.311–1.015) | 0.056 | | |

EGFR, epidermal growth factor receptor; OR, odds ratio; CI, confidence interval; pSUVmax, maximal standard uptake value of primary tumor.

A (95.8% *vs.* 4.2%, P<0.001). In addition, the Ki67 scores were lower in the EGFR-mutant group (35.95±19.07) than in the wild-type group (49.08±23.96, P=0.003; *Table 1*). The means of the pSUVmax (8.24±4.51 *vs.* 10.64±5.77; P<0.001) and lymph node SUVmax (5.64±3.77 *vs.* 7.25±4.53; P=0.009) of PET/CT were lower, respectively, in the mutant group compared to the wild-type group. The mean tumor size of the primary mass (2.89±1.46 *vs.* 3.54±1.90; P=0.001) was smaller in the mutant group than that in the wild-type group. There were no statistical differences in the parameters of PET/CT among the *EGFR*-mutation subtypes.

A ROC curve was plotted to calculate the cut-off point (8.20) of the pSUVmax with 64.8% sensitivity, 55.8% specificity, a 62.8% positive predictive value, a 57.9% negative predictive value, and 60.6% accuracy; the AUC was 0.623 (95% CI: 0.560–0.686; P<0.001). The cut-off point for tumor size was 3.5 cm with 46.5% sensitivity,

 

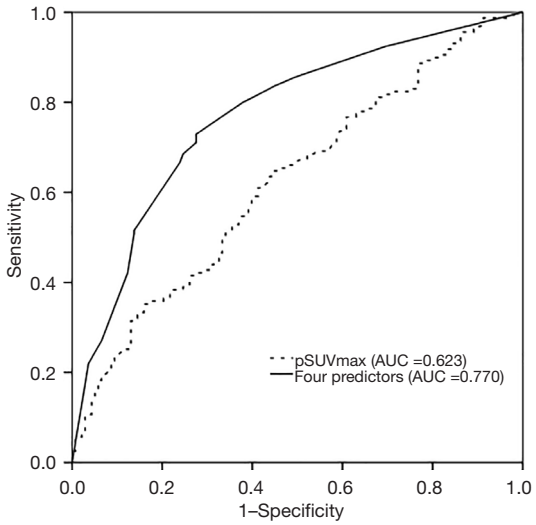


**Figure 1** ROC curves of *EGFR* mutation. pSUVmax gained 0.623 (continuous line) of AUC, and the value increased to 0.770 when combined with all predictive factors (gender, smoking status, tumor size, and pSUVmax, dotted line). P value <0.05. AUC, area under curve; ROC, receiver operating characteristic; EGFR, epidermal growth factor receptor; pSUVmax, maximal standard uptake value of primary tumor.

71.2% specificity, 71.2% positive predictive value, 56.0% negative predictive value, and 61.3% accuracy; the AUC was 0.600 (95% CI: 0.536–0.665; P=0.003). Thus, even though *EGFR* mutations were detected more frequently in individuals with a pSUVmax <8.2 (P<0.001) and tumor size <3.5 cm, the 2 indicators had a marginal predictive value for *EGFR* mutations.

### *Prediction of EGFR mutations*

To confirm the predictive factors of *EGFR* mutations, univariate and multivariate logistic regression analyses were used. Univariate regression analysis indicated that sex, smoking status, tumor size, pSUVmax, and stage were correlated with *EGFR* mutations. Multivariate regression indicated that sex, smoking status, tumor size, and pSUVmax remained independent factors for predicting *EGFR* mutation. Women (OR =2.853; 95% CI: 1.451–5.611; P=0.002), never smokers (OR =2.414; 95% CI: 1.217–4.789; P=0.012), tumor size <3.5 cm (OR =2.170; 95% CI: 1.205–3.908; P=0.010), and pSUVmax <8.2 (OR =1.904; 95% CI: 1.098–3.302; P=0.022) were effective predictors of *EGFR* mutation (*Table 2*). In addition, the AUCs of the pSUVmax and tumor size were 0.623 and 0.600, respectively. When using pSUVmax combined with tumor size to calculate the ROC curve, the AUC was 0.656. Combined with clinical characteristics, including sex and smoking status, the AUC of the 4 predictors increased to 0.770 (*Figure 1*).

## Discussion

TKIs have played an important role in improving the outcomes of a particular group of patients and enabled a significant paradigm shift in the therapeutic agent management of NSCLC (1-5). *EGFR* mutations are mostly found in lung adenocarcinoma, which is the predominant subtype of lung cancer (24). Nevertheless, due to the deficiency of biopsy samples and the physical condition of patients, obtaining sufficient high-quality tumor tissues for *EGFR* testing remains challenging in many situations. Therefore, a noninvasive, simple, and convenient method to detect the presence of *EGFR* mutations is needed for managing treatment strategies, especially when making initial treatment decisions. In this study, we showed that lung adenocarcinoma patients harboring *EGFR* mutations had lower pSUVmax and smaller tumor size than wild-type cases according to $^{18}$F-FDG PET/CT. As a noninvasive method, pSUVmax and tumor size based on PET/CT together with clinical characteristics such as gender and smoking status could enhance *EGFR* status discriminability in those patients for whom *EGFR* detection is not feasible.

Previous studies have revealed a relationship between *EGFR* mutations and $^{18}$F-FDG uptake, but the results have been conflicting (18-29). The majority of studies demonstrated that a lower pSUVmax was an indicator for predicting *EGFR* mutations in either lung adenocarcinomas or NSCLC, regardless of tumor stage (18-25). The present study also showed a lower pSUVmax was an independent indicator in lung adenocarcinoma. Our results were consistent with the findings of multiple studies (18-25) but contradicted with 2 studies (26,27). Notably, one of the 2 studies that showed a higher pSUVmax was a predictor of *EGFR* mutations involved 132 advanced adenocarcinoma (ADC) cases regardless of tumor stage (26), while the other study included 77 stage III and IV ADC patients (27). Further, retrospective analyses conducted by Lee *et al.* (28) and Caicedo *et al.* (29) found there was no relationship between pSUVmax and *EGFR* mutations, which also differed from our results. Further studies of ADC patients in stage IV demonstrated that there was no difference in

 

pSUVmax between *EGFR*-mutant patients and wild-type patients (21,28).

Several possible factors may have contributed to these contradictory results. First, these studies involved either NSCLC or lung adenocarcinomas with different tumor stages. Thus, the histological type and tumor stage of the included cases could have influenced the results. Second, of the 2 studies showing results that were contrary to ours (26,27), one included 132 ADC cases regardless of tumor stage and also required pretreatment serum indicator and CT assessments (26). The other study, which involved 77 cases of stage III and IV ADC patients, reported an *EGFR*-mutation rate of 64% (27). The pretreatment requirement, small sample size, and high *EGFR* mutation rate of both studies may reflect the bias in patient selection. Moreover, although pSUVmax was significantly related to *EGFR* mutation in univariate regression analysis, no relationship was found in multivariate regression analysis in the study conducted by Lee *et al.* (28). In our study, despite the fact that pSUVmax showed predictive value in both univariate and multivariate regression analysis, the AUC was only 0.623, which was consistent with the results of Lv *et al.* (AUC =0.557) (21). Hence, the marginal discriminating ability of pSUVmax could have led to discrepancy among results.

The results of tumor size as a predictive indicator for *EGFR* mutations were also conflicting and there are several possible reasons for this (21,28,30). The studies performed by Lee *et al.* (28) and Guan *et al.* (30) showed a smaller tumor size could predict *EGFR* mutations in both univariate and multivariate regression analysis, which was consistent with our study. The results from Lv *et al.* (21) revealed no relationship between tumor size and *EGFR* status in a separate analysis of an ADC-only group. However, tumor size was smaller in *EGFR*-mutant individuals than that in wild-type patients when ADC and non-ADC cases were analyzed as a whole in Lv's study. In our study, the rate of *EGFR* mutations was 46.5%, and a smaller tumor size was weakly associated with *EGFR* mutations (AUC =0.600). Further, due to the limited availability of testing technology, the detection rate of *EGFR* mutation was only 9.6% in China about a decade ago (31). One large-sample survey reported the *EGFR*-mutation rate was 42.5% in a noninterventional, real-world study of IIIB/IV NSCLC patients in northern China (32). However, patients with early-stage disease and a sound economic background were more likely to undergo genetic detection. Therefore, the modest discriminating power of tumor size and genetic-testing patient selection bias may have affected the results.

Although detecting *EGFR* mutations from tissue is the gold standard for therapeutic agent management using *EGFR*-TKIs for first-line treatment, sufficient tissue for *EGFR*-mutation detection is not available in many situations. Previous randomized head-to-head data (33,34) have demonstrated the potential benefit of *EGFR*-TKIs in patients who did not undergo *EGFR*-status detection and were selected based on clinical characteristics only. More and more diagnoses of NSCLC rely on cytologic specimens or small biopsies which result in insufficient quality and quantity of tumor cells for *EGFR* detection. A retrospective study including 11 Asian Pacific countries showed 71.4% (53.8% in China) of samples used for detecting *EGFR* mutations were cytology samples and/or small biopsies (35). Overall failure rates for *EGFR* testing using cytology samples and/or small biopsies have been reported to be 5–30% (36,37). Therefore, *EGFR*-mutation detection from tissue rather than cytology samples and/or small biopsies is highly recommended before first-line treatment with *EGFR*-TKIs. In addition to the limitations of clinical resources and testing technology mentioned above, the subjective willingness of patients also restrict invasive examination and obtainment of sufficient high-quality tumor tissues for *EGFR* testing.

While *EGFR*-mutation testing from tissue is important, noninvasive methods to predict *EGFR* mutations is also necessary when tissue detection is not available in order to identify patients likely to benefit from *EGFR*-TKIs. This study aimed to investigate the predictive value of pSUVmax for *EGFR* mutations in those patients for whom *EGFR* testing was not feasible. The results showed that a lower pSUVmax and a smaller tumor size could be helpful for distinguishing *EGFR* mutations from wild type. Although both indicators had marginal predictive value for *EGFR* mutations, they could be combined with other clinical characteristics to enhance patient stratification in cases where *EGFR* detection is not feasible. Reasonable application of clinical factors and parameters of PET/CT could be used to manage therapeutic strategies in lung adenocarcinomas without available *EGFR* detection.

Our study had several limitations. Above all, the retrospective nature of the study may have led to sample availability bias and patient selection bias. The nature of a single-center study can also induce bias in the results. Thus, larger samples and multicenter prospective studies should be performed to validate the results. In addition, maximal standard uptake value of lymph node (nSUVmax) and maximal standard uptake value of distant metastasis

 

(mSUVmax) were not included in this study for patients without lymph node and distant metastasis. Hence, individuals with a similar background (stage of disease, race, gender, smoking status, etc.) should be compared to verify the results. Finally, the study did not detect all mutations, and several drive mutations may exist in a patient concurrently. Each driver mutation may influence the glucose metabolism process through different signaling pathway activations. Therefore, more comprehensive genetic detection is needed to confirm the results.

## Conclusions

This study aimed to reveal whether pSUVmax could be a noninvasive indicator to predict *EGFR* mutations in untreated primary lung adenocarcinomas. The results identified that pSUVmax <8.2 was an independent predictor of *EGFR* mutations, and the AUC was 0.629. When using all the predictors, including female, never smoker, tumor size <3.5 cm, and pSUVmax <8.2, the AUC increased to 0.770. Other biomarkers could be integrated with the parameters of PET/CT to predict *EGFR* status and efficiency of TKI treatment in the future in cases where genetic detection is not feasible.

## Acknowledgments

*Funding:* This work was supported by the Youth Foundation of Health Commission of Shanxi Province (No. 2020058) and the Youth Foundation of Science and Technology Commission of Shanxi Province (No. 202103021223447).

## Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1726/rc

*Data Sharing Statement:* Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1726/dss

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1726/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 committee of Shanxi Province Cancer Hospital (No. 201835). Individual consent for this retrospective analysis was waived.



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(English Language Editor: A. Muylwyk)

**Cite this article as:** Wang J, Wen X, Yang G, Cui Y, Hao M, Qiao X, Jin B, Li B, Wu J, Li X, Ren X. The predictive value of $^{18}$F-FDG PET/CT in an *EGFR*-mutated lung adenocarcinoma population. Transl Cancer Res 2022;11(7):2338-2347. doi: 10.21037/tcr-22-1726

 