Role of ¹⁸F-Fluorodeoxyglucose Positron Emission Tomography in Predicting Epidermal Growth Factor Receptor Mutations in Non-Small Cell Lung Cancer

RAYMOND H. MAK,^a SUBBA R. DIGUMARTHY,^{b,f} ALONA MUZIKANSKY,^c JEFFREY A. ENGELMAN,^{d,f} JO-ANNE O. SHEPARD,^{b,f} NOAH C. CHOI,^{e,f} LECIA V. SEQUIST^{d,f}

^aHarvard Radiation Oncology Program, Boston, Massachusetts, USA; ^bDepartment of Radiology, ^cBiostatistics Center, ^dCenter for Thoracic Cancers, and ^eDepartment of Radiation Oncology, Massachusetts General Hospital Cancer Center, Boston, Massachusetts, USA; ^fHarvard Medical School, Boston, Massachusetts, USA

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ABSTRACT

Purpose. To compare ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) and computed tomography (CT) imaging characteristics in non-small cell lung cancer (NSCLC) with or without epidermal growth factor receptor (*EGFR*) mutations.

Methods. We retrospectively identified NSCLC patients who underwent *EGFR* mutation testing and pretreatment FDG-PET and CT scans. The maximum standard uptake value (SUV_{max}) of the primary tumor and any metastases was measured and normalized to the SUV of blood in the pulmonary artery. We compared normalized SUV_{max} values between *EGFR*-mutant and wild-type patients and modeled radiographic and clinical predictors of *EGFR* mutation status. Receiver operator characteristic (ROC) curves were used to identify potential SUV cutoffs predictive of genotype.

Results. We included 100 patients (24 *EGFR*-mutant and 76 wild-type). There was a trend for higher normalized SUV_{max} in the primary tumors among patients with *EGFR*-wild-type versus mutant (median, 3.4; range, 0.6–12.8; versus median, 2.9; range, 0.4–5.0; *p* = .09). Normalized SUV_{max} of nodal and distant metastases, and CT characteristics were not associated with genotype. On multivariate analysis, low normalized SUV_{max} of the primary tumor was predictive for *EGFR* mutation (odds ratio, 0.72; 95% confidence interval, 0.53–0.98; *p* = .034). ROC curve analyses yielded an area under the curve of 0.62, and identified a potential cutoff of ≥5.0 to distinguish wild-type from mutant tumors.

Conclusions. In this retrospective study, high FDG avidity (normalized SUV_{max} ≥5) correlated with *EGFR*-wild-type genotype. Although genotyping re-

Correspondence: Lecia V. Sequist, M.D., M.P.H., 55 Fruit Street, PO Box 212, Boston, Massachusetts 02144, USA. Telephone: 617-726-7812; Fax: 617-724-3166; e-mail: LVSequist@partners.org Received August 31, 2010; accepted for publication January 4, 2011; first published online in *The Oncologist Express* on February 21, 2011. ©AlphaMed Press 1083-7159/2011/\$30.00/0 doi: 10.1634/theoncologist.2010-0300

mains the gold standard, further work to validate FDG-PET as a surrogate for tumor genotype may provide

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INTRODUCTION

Non-small cell lung cancer (NSCLC) with somatic mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor gene (*EGFR*) are uniquely susceptible to *EGFR*-specific TK inhibitors (TKIs) [1–3]. Three randomized clinical trials have demonstrated a progression-free survival benefit when patients with advanced NSCLC and *EGFR* mutations are treated with upfront TKIs rather than standard chemotherapy [4–6]. However, rapid genotyping remains an obstacle in clinical practice in many settings because of a lack of access to sufficient tumor tissue and logistical constraints of the testing process [7]. Furthermore, the use of computed tomography (CT) tumor characteristics to predict *EGFR* mutation status does not decisively correlate with genotype [8, 9].

Glucose metabolism can be molecularly imaged in vivo with ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET), and uptake of FDG has been correlated with tumor proliferation in NSCLC [10]. FDG-PET scans are gaining an increasing role in NSCLC for initial staging, radiation therapy planning, and restaging after therapy [11–13]. Furthermore, *EGFR*-mutant cancers preferentially activate Akt signaling [14], which in turn regulates glycolysis, glucose metabolism, and FDG avidity [15–17]. Thus, quantification of glucose metabolism with FDG-PET may present a noninvasive method to predict *EGFR* mutation.

We examined a large retrospective cohort of patients with NSCLC who had *EGFR* mutation testing and underwent pretreatment FDG-PET and CT and compared imaging characteristics between mutation-positive *EGFR* and wild-type *EGFR* patients.

METHODS

Study Design and Patient Population

Screening for *EGFR* mutations has been part of routine clinical care at the Massachusetts General Hospital multidisciplinary thoracic oncology clinic since 2004. Under an institutional review board–approved protocol, we retrospectively reviewed the medical records of patients who underwent *EGFR* screening in August 2004 to November 2008 and included all patients with an FDG-PET scan and a CT scan of the chest for anatomical correlation, which were both performed prior to initiation of any therapy. Tumor size had to be a minimum of 1 cm to minimize partial volume averaging effects in FDG-PET interpretation.

EGFR Mutation Analysis

Direct sequencing of *EGFR* exons 18–21 was performed in an internal Clinical Laboratory Improvement Amendments–certified laboratory in 2004–2008, as previously published [18]. In 2009, we adopted an allele-specific polymerase chain reaction–based assay [19].

Covariates

Pretreatment patient characteristics were collected via chart review, including age, gender, race, Eastern Cooperative Oncology Group performance status score, smoking status, and pack-years of smoking. Smoking status was categorized with standard criteria: (a) never-smokers had <100 cigarettes in their lifetime, (b) former smokers had quit >1 year prior to diagnosis, and (c) current smokers were smoking at the time of diagnosis or had quit <1 year prior. Tumor characteristics, including histology, grade, and stage, were collected. Subtypes of adenocarcinoma, according to World Health Organization classification, were abstracted from clinical pathology reports. Patients were staged based on the sixth edition of the *American Joint Committee on Cancer Staging Manual*.

Radiologic Analyses

All PET–CT examinations were performed with an integrated PET–CT scanner (Biograph Sensation 16, Siemens Healthcare, Malvern, PA), which has the capability for 16-multidetector computed tomography and PET with three-dimensional lutetium oxyorthosilicate crystals. According to departmental protocol, patients were instructed to fast for 6 hours before scanning, and blood glucose was measured immediately before injection of an i.v. bolus of 15–20 mCi ^{18}F -FDG. Static emission images were obtained 60 minutes after the injection.

Attenuation correction CT was performed with the following parameters: 40 mA, 120 kVp, 0.5 second per gantry rotation, detector configuration of 16×1.5 mm, and 10-mm slice thickness. PET images were acquired as per scanner instructions, including 3–4 minutes per bed position for patients weighing <77 kg and for up to 7 minutes for those weighing >104 kg. The attenuation correction CT images were then fused with the PET images to yield the PET–CT data. In addition, a diagnostic neck, chest, and abdominal CT examination with administration of 120 ml iodinated i.v. contrast agent (iopamidol, 370 mg, 100 ml; Isovue, Bracco Diagnostics, Inc., Princeton, NJ) was also

performed on the same day or a few days before or after the PET scan, as per our standard clinical practice. The imaging parameters for diagnostic CT examination were 120 kVp, 200 reference mAs, detector configuration of 16×1.5 mm, gantry rotation time of 0.5 second, 2.5-mm slice thickness at 2.5-mm slice interval, and pitch of 1.2.

All scans were independently reviewed in a blinded fashion by a radiologist (S.D.) with expertise in imaging of thoracic malignancies. PET and attenuation correction CT images were registered on a MIRADA work station using REVEAL – MVS 6.2 (CTI Molecular Imaging, Oxford, U.K.). For each involved site, including the primary tumor, mediastinal lymph node metastases, and distant metastases, a region of interest (ROI) was identified and manually drawn into the workstation computer, using images from the fused CT–PET and diagnostic CT to help with anatomic correlation. The maximum standard uptake value (SUV_{max}) and SUV_{mean} were measured within the ROI. Because SUVs may vary throughout different regions in the normal lungs [20], the corrected SUV based on body weight is the most commonly used method and is calculated by the formula:

$$SUV = \text{mean ROI activity (MBq/ml)} / \text{injected dose (MBq/body weight (g))}$$

The maximal pixel activity in the ROI was the SUV_{max} and the value within the entire tumor was the SUV_{mean} . Photopenia resulting from tumor cavitation or necrosis was not included in the ROI. If there were multiple lymph node or distant metastases, the lesion with the highest SUV was selected. Blood pool SUV activity was measured in the main pulmonary artery and was used to control for any differences in technique between scans by calculating the ratio of the SUV_{max} of the tumor ROI to that of the blood pool activity.

The diagnostic CT images were analyzed for tumor morphology and lung masses were classified as either ground glass opacity (GGO) (blood vessels can be seen through the lesion), solid (vessels are obscured behind the lesion), or mixed solid and GGO. Lymph nodes were considered pathologic if they measured >1 cm in short-axis diameter.

Statistical Considerations

Continuous covariates, including the normalized SUV_{max} , were compared by *EGFR* mutation status using the Wilcoxon rank-sum test. Categorical covariates were analyzed using the Fisher's exact test or χ^2 test. Logistic regression was performed to identify significant clinical and radiographic predictors of mutation status. Variables examined included gender, race, tumor histology, smoking status, normalized SUV_{max} , tumor size, and morphology. Multi-

variate analysis was then performed incorporating significantly associated covariates in a model with the normalized SUV_{max} of the primary tumor. Backward selection with a *p*-value for inclusion of $<.10$ was used. Receiver operating characteristic (ROC) curves were generated to obtain a cut-off for the SUV_{max} of the primary tumor. A two-sided *p*-value $<.05$ was considered to be statistically significant. All analyses were performed using SAS, version 9.2.1, software (Cary, NC).

RESULTS

Patient and Tumor Characteristics

There were 427 patients who underwent *EGFR* mutation testing during the study period and 123 were found to be *EGFR* mutation positive. One hundred patients had the requisite radiology studies, including 24 with mutant *EGFR* cancers and 76 with wild-type *EGFR* cancers. The majority of patients in both groups were female, white, and never- or former-smokers (Table 1). There was a significant difference in smoking status and pack-years of smoking between the two groups. Tumor characteristics did not differ significantly by mutation status, and because of clinical referral patterns for genotyping, the majority of patients had stage III or IV adenocarcinoma.

EGFR Mutations

Among the 24 patients with *EGFR* mutations, 10 had an L858R point mutation in exon 21, nine had an exon 19 deletion, one had an exon 19 insertion, one had a G719C point mutation in exon 18, one had an exon 20 insertion, one had a V834L point mutation in exon 21, and one had a L861Q point mutation in exon 21.

CT Characteristics

CT-based assessments of the primary tumor, including size and morphology, were not significantly different between genotype groups (Table 2). The majority of the primary tumors had solid morphology in both groups, and neither solid nor GGO morphology was associated with mutation status.

FDG-PET Characteristics

All patients had SUV_{max} data for their primary lung cancer, whereas 51 had SUV_{max} data for lymph node metastases and 38 had SUV_{max} data for distant metastases. There was a trend toward a higher normalized SUV_{max} in the primary tumor of patients with wild-type *EGFR* than in patients with mutated *EGFR* ($p = 0.09$) (Table 2 and Fig. 1). Nearly all primary tumors with a normalized $SUV_{max} >5$ had wild-type *EGFR* (Fig. 1).

Table 1. Patient characteristics by *EGFR* mutation status

Characteristic	All patients, <i>n</i> (%) (<i>n</i> = 100)	Wild-type <i>EGFR</i> , <i>n</i> (%) (<i>n</i> = 76)	Mutant <i>EGFR</i> , <i>n</i> (%) (<i>n</i> = 24)	<i>p</i> -value
Age, median (range)	64.5 (26–87)	64.5 (30–87)	66.5 (26–85)	.82
Gender				.34
Female	61 (61)	44 (58)	17 (71)	
Male	39 (39)	32 (42)	7 (29)	
Race				.22
White	88 (88)	66 (87)	22 (92)	
Asian	5 (5)	5 (6.6)	0	
Black	3 (3)	3 (4.0)	0	
Other	4 (4)	2 (2.6)	2 (8.3)	
Smoking status				.0004
Current	24 (24)	22 (29)	2 (8.3)	
Former	49 (49)	41 (54)	8 (33)	
Never	27 (27)	13 (17)	14 (58)	
Pack-years, median (range)	20 (0–106)	35 (0–106)	0 (0–60)	<.0001
AJCC stage				.28
IA	18 (18)	14 (18)	4 (17)	
IB	14 (14)	12 (16)	2 (8.3)	
IIA	3 (3)	3 (4.0)	0	
IIB	5 (5)	5 (6.6)	0	
IIIA	6 (6)	4 (5.3)	2 (8.3)	
IIIB	12 (12)	7 (9.2)	5 (21)	
IV	42 (42)	31 (41)	11 (46)	
Tumor histology				.13
Adenocarcinoma NOS	49	41 (54)	8 (33)	
Primarily BAC	5	3 (4.0)	2 (8.3)	
Primarily acinar	7	6 (7.9)	1 (4.2)	
Mixed BAC/adenocarcinoma	23	11 (15)	12 (50)	
Other adenoCA subtype	6	5 (6.6)	1 (4.2)	
Other histology ^a	10	10 (13)	0	

^aIncluding undifferentiated carcinoma (*n* = 8) and adenosquamous carcinoma (*n* = 2).

Abbreviations: adenoCA, adenocarcinoma; AJCC, American Joint Committee on Cancer; BAC, bronchioloalveolar carcinoma; EGFR, epidermal growth factor receptor; NOS, not otherwise specified.

Examining the FDG uptake by type of *EGFR* mutation, the median normalized SUV was 2.0 (range, 0.75–3.9) for tumors with exon 19 deletions and 2.2 (range, 0.33–3.9) for tumors with the exon 21 L858R mutation.

Multivariate Analysis

On univariate analysis, smoking status and pack-years were significantly associated with *EGFR* mutation status, whereas the normalized SUV_{max} of the primary tumor trended toward significance (*p* = .054) (Table 3). On multivariate analysis, after adjusting for pack-years of smoking, a low normalized SUV_{max} of the primary tumor was significantly associated with *EGFR* mutation (*p* = .034).

ROC Curves

An ROC curve was generated using the logistic regression model for the normalized SUV_{max} of the primary tumor (Fig. 2); the area under the curve was 0.62. The predictive probability of the model was plotted against the observed normalized SUV_{max} of the primary tumor (Fig. 3), and a higher normalized SUV_{max} resulted in a greater predictive probability. A cut-off of the normalized SUV_{max} ≥ 5 was identified to have the highest area under the curve of 0.64 (Table 4).

DISCUSSION

In this predominantly white population of NSCLC patients with clinical features enriching for the presence of mutant

Table 2. Radiographic characteristics by *EGFR* mutation status

Radiographic characteristic	All patients (n = 100)	Wild-type <i>EGFR</i> (n = 76)	Mutant <i>EGFR</i> (n = 24)	p-value
SUV _{max} of primary tumor, median (range)	5.0 (0.7–14.2)	5.2 (0.7–14.2)	4.3 (0.8–8.2)	.17
SUV _{max} of LN metastasis, median (range) ^a	4.1 (1.0–29.2)	4.2 (1.0–29.2)	3.0 (1.3–9.9)	.50
SUV _{max} of distant metastasis, median (range) ^b	4.1 (1.0–15.3)	4.8 (1.0–15.3)	3.8 (1.1–15.0)	.69
Normalized ^c SUV _{max} of primary tumor, median (range)	3.3 (0.4–12.8)	3.4 (0.6–12.8)	2.9 (0.4–5.0)	.09
Normalized ^c SUV _{max} of LN metastasis, median (range) ^a	2.7 (1.2–15.4)	2.9 (1.2–15.4)	2.7 (1.2–5.5)	.25
Normalized ^c SUV _{max} of distant metastasis, median (range) ^b	2.7 (0.9–8.3)	2.8 (0.9–8.1)	2.8 (0.9–8.3)	.25
Primary tumor size on CT (cm), median (range)	3.7 (1.0–12.7)	3.7 (1.0–12.5)	3.6 (1.2–12.7)	.74
Primary tumor CT appearance, n (%)				.56
Solid	79 (79)	62 (83)	17 (74)	
GGO	2 (2)	1 (1.3)	1 (4.4)	
Solid and GGO	17 (17)	12 (16)	5 (22)	

^an = 51; 38 wild-type *EGFR* and 13 mutant *EGFR* patients.

^bn = 38; 28 wild-type *EGFR* and 10 mutant *EGFR* patients.

^cSUV_{max} normalized by dividing by SUV blood pool.

Abbreviations: CT, computed tomography; *EGFR*, epidermal growth factor receptor; GGO, ground glass opacity; LN, lymph node; SUV_{max}, maximum standard uptake value.

Figure 1. Box plot of normalized SUV_{max} of primary tumor with median, 25th, 75th, and 95th percentiles highlighted.

Abbreviations: *EGFR*, epidermal growth factor receptor; SUV_{max}, maximum standardized uptake value; WT, wild-type.

EGFR tumors, we demonstrate that lung cancer with FDG-PET findings of a low normalized SUV_{max} within the primary tumor is significantly associated with having an

EGFR mutation. The ROC analysis concluded that this correlation is most useful as a negative predictor. In other words, high FDG avidity (normalized SUV ≥ 5) may be predictive of the wild-type *EGFR* genotype, whereas a low normalized SUV_{max} may predict the presence of *EGFR* mutations less robustly. Importantly, CT-based tumor characteristics were not associated with genotype. On multivariate analysis, pack-years of smoking and the normalized SUV_{max} of the primary tumor were significantly associated with *EGFR* mutation status.

The results of our study build upon the existing literature. Prior studies correlating FDG uptake with *EGFR* mutation status in Taiwan and Korea have had conflicting results [21, 22]. In a Taiwanese study of 77 patients with adenocarcinoma including 49 mutant *EGFR* and 28 wild-type *EGFR* patients, FDG uptake was significantly higher in mutant *EGFR* cancers (mean SUV_{max}, 10.5 ± 4.7) than in wild-type *EGFR* cancers (8.0 ± 3.3) [21]. A cutoff SUV_{max} ≥ 9.5 was identified as predictive of a mutant *EGFR* status. Potential limitations of this study were the inclusion of only stage IV and stage IIIB patients, and exclusion of patients with the bronchioloalveolar subtype of adenocarcinoma (known to have generally lower SUVs), and thus, this study may not be a representative sampling of the full spectrum of tumor biology in patients with *EGFR* mutations. In contrast, the Korean study of 100 NSCLC patients, including 21 patients with *EGFR* mutations, included patients with stage I through IV disease, and demonstrated that patients with low SUVs were more likely to have *EGFR* mutations than those with high SUVs [22].

Table 3. Odds ratio (95% CI) of *EGFR* mutation on univariate and multivariate analyses

Characteristic	Univariate	<i>p</i> -value	Multivariate	<i>p</i> -value
Age	1.0 (0.97–1.0)	.94	–	
Gender				
Female	1.0 ^a	–	–	
Male	0.57 (0.21–1.5)	.26		
Smoking status				
Current	0.47 (0.09–2.4)	.36	–	
Former	1.0 ^a	–		
Never	5.5 (1.9–16.1)	.0017		
Pack-years smoking	0.96 (0.93–0.98)	.0011	0.95 (0.93–0.98)	.0009
AJCC stage				
I	0.65 (0.21–2.0)	.45	–	
II–III	1.0 (0.34–3.1)	.95		
IV	1.0 ^a	–		
Tumor histology				
Adenocarcinoma	1.0 ^a	–	–	
Other	2.3 (0.90–6.2)	.083		
Radiologic characteristics				
Primary tumor size on CT	0.98 (0.82–1.2)	.87	–	
Primary tumor appearance on CT				
Solid	1.0 ^a	–	–	
GGO or solid/GGO	1.7 (0.56–5.1)	.36		
Normalized SUV _{max} ^b				
Primary SUV _{max} ^b	0.79 (0.61–1.0)	.054	0.72 (0.53–0.98)	.034
LN SUV _{max} ^b	0.76 (0.48–1.2)	.24	–	
Metastasis SUV _{max} ^b	0.88 (0.58–1.3)	.53	–	

^aReference group.^bSUV_{max} normalized by dividing by SUV blood pool.Abbreviations: AJCC, American Joint Committee on Cancer; CI, confidence interval; CT, computed tomography; *EGFR*, epidermal growth factor receptor; GGO, ground glass opacity; LN, lymph node; SUV_{max}, maximum standard uptake value.

Using an ROC curve analysis, the Korean study identified an SUV_{max} cutoff <9.2 as predictive of a positive *EGFR* mutation status. The majority of patients in that study were stage I–II (57%). However, the study included squamous cell carcinoma in the wild-type control group, which may represent a cancer with distinct tumor biology and has been shown to have higher FDG uptake than adenocarcinoma [23].

Our study is the first to our knowledge that examines a predominantly white population that is enriched for clinical features of *EGFR*-mutant cancers, because the study was performed among those clinically selected for *EGFR* mutation testing. Hence, our identification of an association between low FDG uptake and *EGFR*-mutant tumors is applicable to patients under consideration for *EGFR* mutation screening in the U.S. Although our own institutional practice is currently to offer genetic testing for *EGFR* and other driver mutations in all patients with NSCLC, the find-

ings of our study have particular utility in centers where genetic testing is limited or for patients from whom tumor tissue is unobtainable. More specifically, in patients with clinical features associated with *EGFR* mutation, such as a low smoking history, our findings demonstrate that high FDG avidity in the primary tumor is associated with a very low chance of harboring an *EGFR* mutation.

Regarding our techniques for analyzing PET scans, Zasadny and Wahl showed that absolute SUVs may vary depending on the method used [24]. Variables that can affect SUV include body size, amount of tracer injected, blood volume, and systemic condition of the body, such as glomerular excretion rate of the contrast [25]. To reduce variability from these factors, we calculated the ratio of the SUV_{max} in the tumor to the SUV_{max} in the mediastinal blood pool as determined in the pulmonary artery. This correction factor enhances the accuracy and increases the sensitivity of our assessments by reduc-

Figure 2. Receiver operator characteristic (ROC) curve of normalized SUV_{max} of the primary tumor (as a continuous variable), illustrating an area under the curve of 0.62.

Figure 3. Predicted probability with 95% confidence limits (blue) of wild-type *EGFR* status on logistic regression plotted against the observed values of normalized maximum standardized uptake value (SUV_{max}) of the primary tumor.

ing the influence of technique variations [26–28]. It also explains the slightly lower mean SUV_{max} in our study than in those reported by other groups [22].

We did not identify any association between CT imaging characteristics and *EGFR* mutation status, including tumor size and morphology. This is concordant with prior retrospective studies showing no clear association between *EGFR* mutation status and CT-based morphology assessments, specifically GGO [8, 9]. Thus, assessment of tumor metabolism using FDG-PET may represent the best widely available radiographical test with the potential to distinguish mutant *EGFR* from wild-type *EGFR* cancers.

Our findings must be interpreted in the context of the study’s retrospective design, which may introduce biases. The ability to generalize our findings to all North American lung cancer patients is limited because our cohort was enriched for clinical features associated with *EGFR* mutations, especially a low smoking history. Therefore the wild-type patients in our cohort were atypical compared with the average lung cancer patient in the U.S., with a higher percentage of females, adenocarcinoma tumors, and never-smokers. However, one would expect that these clinical features would bias toward the null hypothesis in our comparison between FDG avidity in mutant *EGFR* and wild-type *EGFR* tumors. Furthermore, we did not have comprehensive genotyping (such as *KRAS* and *ALK* status) in the majority of patients studied, and so the differing FDG uptake characteristics of these groups may have not been accounted for. Future work will examine the PET characteristics of these and other genotype-defined cohorts, and validation of our *EGFR* findings must be performed among a larger cohort

CONCLUSIONS

In conclusion, a lower normalized SUV_{max} of the primary tumor was associated with *EGFR* mutation in this retrospective analysis of a sample of predominantly white patients with NSCLC. Noninvasive imaging-based prediction of *EGFR* genotype may be limited in tumors with a low normalized SUV_{max}, but using a normalized SUV_{max} cutoff

Table 4. Receiver operator characteristic curves and odds ratio (95% CI) of <i>EGFR</i> mutation status using different cutoff values for normalized SUV _{max}						
Normalized SUV _{max} cutoff	All	Wild-type <i>EGFR</i>	Mutant <i>EGFR</i>	Odds ratio (95% CI)	<i>p</i> -value	AUC
≥3	55	43	12	1.30 (0.52–3.30)	.57	0.53
≥4	44	37	7	2.30 (0.89–6.55)	.10	0.60
≥4.5	32	29	3	4.32 (1.18–15.77)	.027	0.63
≥5	25	24	1	10.6 (1.35–83.2)	.025	0.64

Abbreviations: AUC, area under the curve; CI, confidence interval; EGFR, epidermal growth factor receptor; SUV_{max}, maximum standard uptake value.

≥ 5 appears to be a potential predictor of wild-type tumors. Thus, while genetic testing is the gold standard, further work to validate FDG-PET as a surrogate for tumor genotype and biology may provide useful information in patients without available tumor tissue.

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Raymond H. Mak and Subba R. Digumarthy contributed equally to this manuscript. Noah C. Choi and Lecia V. Sequist contributed equally to this manuscript.

AUTHOR CONTRIBUTIONS

Conception/Design: Raymond H. Mak, Lecia V. Sequist, Subba R. Digumarthy, Noah Choi

Provision of study material or patients: Raymond H. Mak, Lecia V. Sequist, Subba R. Digumarthy, Noah Choi

Collection and/or assembly of data: Raymond H. Mak, Lecia V. Sequist, Subba R. Digumarthy, Noah Choi

Data analysis and interpretation: Raymond H. Mak, Lecia V. Sequist, Subba R. Digumarthy, Alona Muzikansky, Jeffrey A. Engelman, Jo-Anne O. Shepard, Noah Choi

Manuscript writing: Raymond H. Mak, Lecia V. Sequist, Subba R. Digumarthy, Alona Muzikansky, Jeffrey A. Engelman, Jo-Anne O. Shepard, Noah Choi

Final approval of manuscript: Raymond H. Mak, Lecia V. Sequist, Subba R. Digumarthy, Alona Muzikansky, Jeffrey A. Engelman, Jo-Anne O. Shepard, Noah Choi

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