Cancer Management and Research

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ORIGINAL RESEARCH

Diagnostic and Predictive Values of ^{18}F-FDG PET/CT Metabolic Parameters in *EGFR*-Mutated Advanced Lung Adenocarcinoma

This article was published in the following Dove Press journal:
Cancer Management and Research

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Purpose: The clinical implications of the metabolic parameters of ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) in epidermal growth factor receptor (*EGFR)*-mutated lung cancer are not fully understood. The aim of this study was to evaluate the diagnostic and prognostic utility of the parameters in *EGFR*-mutated lung cancer patients.

Patients and Methods: We retrospectively enrolled 134 patients with advanced lung adenocarcinoma (72 *EGFR*-negative and 62 *EGFR*-positive). We evaluated the correlation between *EGFR* mutational status and the maximum standardized uptake value (SUVmax), as well as the associations between treatment outcomes in *EGFR*-mutated patients and various metabolic parameters of primary tumors. For the best predictive parameters, we calculated the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) using two SUV cutoffs: 1.5 ($MTV_{1.5}$, $TLG_{1.5}$) and 2.5 ($MTV_{2.5}$, $TLG_{2.5}$).

Results: Mean SUVmax was lower for *EGFR*-mutated tumors compared with *EGFR* wild-type (6.11 vs 10.41, $p < 0.001$) tumors. Low SUVmax was significantly associated with positive *EGFR* mutation (odds ratio = 1.74). Multivariate analysis for survival demonstrated that high $MTV_{1.5}$, $TLG_{1.5}$, $MTV_{2.5}$, and $TLG_{2.5}$ were independently associated with shorter progression-free survival (PFS) and overall survival (OS), and the highest hazard ratios were found in $TLG_{1.5}$ (3.26 for PFS and 4.62 for OS).

Conclusion: SUVmax may be predictive for *EGFR* mutational status, and MTV and TLG of primary tumors may be promising prognostic parameters; ^{18}F-FDG PET/CT has potential utility for the risk stratification of *EGFR*-mutated patients treated with targeted therapy.

Keywords: lung cancer, ^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography, epidermal growth factor receptor mutation, survival, metabolic parameters

Introduction

Lung cancer is the most common cause of cancer mortality globally. In 2013, the estimated global lung cancer incidence was 1.8 million, and the estimated number of fatal cases was 1.6 million.[1] According to the Korean National Lung Cancer registry data, the crude incidence rate of lung cancer was 43.9 per 100,000, and the age-standardized mortality rate was 19.8 per 100,000 in 2012.[2,3] Adenocarcinoma is the most frequent histologic subtype, and it accounts for 50% of all lung cancers.[4] Although new treatment modalities, including molecular-targeted therapy and immune checkpoint inhibitors, have demonstrated remarkable survival benefits in patients with advanced lung adenocarcinoma,[4,5] the prognosis is still poor, and

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http://doi.org/10.2147/CMAR.S259055

more individualized therapeutic strategies should be established to improve clinical outcomes.

^{18}F-fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F-FDG PET/CT) is a functional imaging modality that measures the glucose metabolism of tumors. Due to its advantages over conventional techniques such as CT scan, it is widely used in lung cancer management; its uses include staging at diagnosis, response evaluation after systemic treatment, re-staging after neoadjuvant treatment, and surveillance after curative resection or stereotactic radiosurgery.[6,7] To extend its application in practice, numerous studies have evaluated the possible utility of the semi-quantitative metabolic parameters obtained from ^{18}F-FDG PET/CT images. Standardized uptake value (SUV) is the most widely investigated across various human malignancies; some studies reported the association between maximal SUV (SUVmax) and poor survival of non-small-cell lung carcinoma (NSCLC) patients,[8–10] while others showed no association.[11–14] These conflicting data partially result from the limitation of SUVmax; it is vulnerable to statistical noise, as it is measured using a single voxel analysis.[15] Thus, recent studies have focused on the volumetric parameters, including metabolic tumor volume (MTV) and total lesion glycolysis (TLG), which reflect metabolic tumor burden.

Most of the studies that have evaluated the prognostic values of the volumetric parameters were conducted on early-stage, operable NSCLC. According to a meta-analysis, high SUVmax, MTV, and TLG were significantly associated with a high risk of recurrence and death in patients who received surgical resection.[10] However, studies on the clinical utility of those parameters in advanced diseases are rare, and only 3 studies have been reported to date.[12,16,17] One study reported that high whole-body MTV and TLG, rather than SUVmax, were associated with poor survival in stage IV NSCLC, suggesting that global metabolic tumor burden is associated with prognosis.[16] In contrast, the two other studies simultaneously evaluated MTV and TLG from whole-body and primary tumors and reported that the MTV of a primary tumor was independently associated with progression-free survival (PFS)[17] and overall survival (OS).[12,17] The latter suggests the prognostic utility of the volumetric parameters measured in primary tumors, not in all the target lesions, even in advanced NSCLC.

EGFR mutations are major driver mutations occurring in lung adenocarcinomas.[18] Approximately 15% of Caucasian and 30%–40% of Asian patients with lung adenocarcinoma have tumors with *EGFR* mutations.[19] Although these patients have shown prolonged PFS when treated with *EGFR*-tyrosine kinase inhibitors (TKIs), the response rate is no more than 70%–80%, and resistance inevitably occurs after approximately 11 months of treatment in most patients.[20–22] Thus, it is important to determine predictive and prognostic factors before TKI treatment to improve clinical outcomes.

To address this issue, we conducted this study to determine whether metabolic parameters of ^{18}F-FDG PET/CT can discriminate between *EGFR*-mutated lung adenocarcinomas and *EGFR* wild-types and predict treatment response and survival in patients treated with first-line *EGFR*-TKIs.

Patients and Methods

Study Subjects and Data Collection

We retrospectively recruited patients who received systemic treatment for histologically confirmed, locally advanced, or metastatic lung adenocarcinoma at the Kyung Hee University Hospital, a tertiary referral hospital in South Korea, between March 2016 and November 2019. Patients who did not have available follow-up data, initial ^{18}F-FDG PET/CT images, a history of other cancers, other driving genetic alterations including *ROS1* and *ALK* fusions, and previous history of chemotherapy or radiotherapy were excluded. *EGFR*-negative patients were all treated with pemetrexed/platinum doublet with or without pemetrexed continuation maintenance chemotherapy, while *EGFR*-mutant patients were treated with *EGFR*-TKIs, including gefitinib, erlotinib, or afatinib as a first-line treatment.

All patients underwent staging workup, including chest computed tomography (CT), brain magnetic resonance imaging, and ^{18}F-FDG PET/CT. TNM staging was performed according to the 8th edition of the International Association for the Study of Lung Cancer TNM staging system.[23] Tumor response was examined by CT after every two cycles of systemic treatment and evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.[24] For *EGFR*-TKIs, a single cycle comprised 4 weeks of treatment. We reviewed electronic medical records to obtain demographic information, past medical or social history, and clinical data of all participants. This study protocol was approved by the Clinical Research Ethics Committee of the Kyung Hee University Hospital (KHUH2020-03-088), and written informed consent was obtained from all patients who were alive, but it

was waived for patients who had died. All research was carried out in compliance with the Declaration of Helsinki.

EGFR Mutation Testing

All the *EGFR* tests were performed using the tumor tissues. Genomic DNA was extracted from formalin-fixed, paraffin-embedded, 5-μm-thick tissue sections using the High Pure Template Preparation Kit (Roche Applied Science, Mannheim, Germany). The extracted DNA was stored at −20°C until analysis. EGFR Pyro Kit (QIAGEN Korea Ltd., Seoul, Korea) and PyroMark Q24 System (QIAGEN Korea Ltd., Seoul, Korea) were used to detect *EGFR* mutations by real-time polymerization chain reaction (PCR). The primer sets covered mutations or deletions spanning exons 18 to 21 of the genes encoding the tyrosine kinase domain of *EGFR*. The results were interpreted according to the manufacturer's instructions.

Acquisition of PET/CT Images and Calculation of Metabolic Parameters

All patients underwent PET/CT scanning with Gemini TF16 PET/CT scanners (Philips Medical Systems, Cleveland, OH) before the initiation of systemic treatment. After fasting for at least 6 hours, 5–6 MBq/kg of ^{18}F-FDG was administered intravenously, and scanning was performed after 60 minutes. Low-dose unenhanced CT scans were first obtained for attenuation correction, and then PET scans (1 min per bed) were obtained. The values of the metabolic parameters were assessed by two experienced nuclear medicine physicians (I.K.H and C.K) using MIRADA XD3 software (MIRADA Medical, Oxford, UK). Physicians dragged the cursor from the center of the primary tumor to a point near the edge of the lesion, and the software automatically outlined a three-dimensional volume of interest (VOI) on the tumor. MTV and TLG were calculated using two SUV cutoff values of 1.5 and 2.5 for this semi-automated contouring system to exclude physiologic FDG uptake of the non-tumor tissue. MTV was defined as the total tumor volume inside the boundaries of the VOI. TLG was calculated as the product of MTV and the mean SUV of the lesion.

Statistical Analyses

Baseline characteristics between groups were compared using Fisher's exact test. The optimal cutoff for SUVmax for the discrimination of *EGFR* mutation was identified using receiver operating characteristic (ROC) curve analysis. The optimal cutoff values of SUVmax, MTV, and TLG for survival analysis were defined using the point with the lowest *p*-value on the Log rank test for progression-free survival (PFS) for all possible values of each parameter. PFS and OS were defined as the periods from the first day of treatment to disease progression/death and death from any cause, respectively. Data on patients without tumor recurrence or death were censored at the last follow-up. Associations between clinical parameters and *EGFR* mutational status or survival were evaluated by univariate analysis using the Log rank test, and subsequently, the multivariate Cox's proportional hazard regression was conducted with adjustment for parameters with p-values < 0.3 from the univariate analysis. Survival curves were generated using the Kaplan–Meier method. P-values < 0.05 were considered significant. All analyses were performed using SPSS version 20.0 (IBM Corporation, Armonk, NY, USA) and MedCalc (MedCalc Software Ltd, Ostend, Belgium).

Results

Patient Characteristics

During the study period, 372 patients were newly diagnosed with NSCLC. Of them, 160 underwent first-line treatment with platinum-based doublet for those without *EGFR* mutation or *EGFR*-TKIs for those with *EGFR* mutation. Eleven patients who had only external ^{18}F-FDG PET/CT images, 5 without unavailable survival data, 3 with history of other cancers, 4 with genetic alterations other than *EGFR* mutation, and 3 who received other cancer treatments were excluded. Finally, a total of 134 (72 *EGFR*-negative and 62 *EGFR*-positive) patients were eligible for analysis.

The clinical characteristics of the study population are summarized in Table 1. All subjects were Korean, and their median age was 69 years (range, 39–81 years). Forty-five (34%) patients were female. Sixty-seven (50%) patients were aged ≥ 65 years. Seventy-six (57%) patients were current or former smokers. One hundred and eight (80%) patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Nine (7%) patients had stage IIIB, and 125 (93%) patients had stage IV. Twenty-eight (20%) patients had metastases at > 3 organs. Thirty-nine (29%) and 22 (16%) patients had brain and liver metastasis, respectively. Thirty-five (57%) patients had exon 19 deletions, 25 (47%) patients had L858R point mutations, and 2 patients had uncommon mutations (G719X and S768I, respectively) among *EGFR*-mutated patients. Compared with *EGFR*-negative patients, the proportions of females (52% vs 18%,

Table 1 Characteristics of Patients with Advanced Lung Adenocarcinomas

	No. of Patients (%)	*EGFR* Mutational Status		*p* value
		Negative	Positive	
All	134 (100)	72 (54)	62 (46)	
Gender				0.046
Female	45 (34)	13 (18)	32 (52)	
Male	89 (66)	59 (82)	30 (47)	
Age, yrs				0.883
<65	67 (50)	39 (54)	28 (45)	
≥65	67 (50)	33 (46)	34 (55)	
Smoking				0.017
Never	58 (43)	20 (28)	38 (61)	
Ever	76 (57)	52 (72)	24 (39)	
ECOG performance status				0.829
0,1	108 (80)	57 (80)	51 (82)	
≥2	26 (20)	15 (20)	11 (18)	
Tumor size, cm				0.747
<3	67 (50)	32 (44)	35 (56)	
≥3	67 (50)	40 (56)	27 (44)	
Stage				1.000
IIIB	9 (7)	4 (6)	5 (8)	
IV	125 (93)	68 (94)	57 (92)	
Metastatic organs				0.937
0–2	106 (80)	58 (81)	48 (79)	
≥3	28 (20)	16 (19)	14 (21)	
Brain metastasis				0.776
No	95 (71)	47 (65)	48 (79)	
Yes	39 (29)	25 (35)	14 (21)	
Liver metastasis				0.641
No	112 (84)	57 (79)	55 (88)	
Yes	22 (16)	15 (21)	7 (12)	
EGFR subtype				–
Exon19 deletion	35 (26)	–	35 (57)	
L858R mutation	25 (18)	–	25 (47)	
Other sites	2 (1)	–	2 (3)	
First-line regimen				-
Pemetrexed/platinum	72 (54)	72 (100)	-	
Gefitinib	3 (2)	-	3 (5)	
Erlotinib	4 (3)	-	4 (6)	
Afatinib	55 (41)	-	55 (81)	
SUVmax				0.010
Low (<9.6)	40 (30)	30 (42)	52 (84)	
High (≥9.6)	94 (70)	42 (58)	10 (16)	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; SUVmax, maximal standardized uptake value.

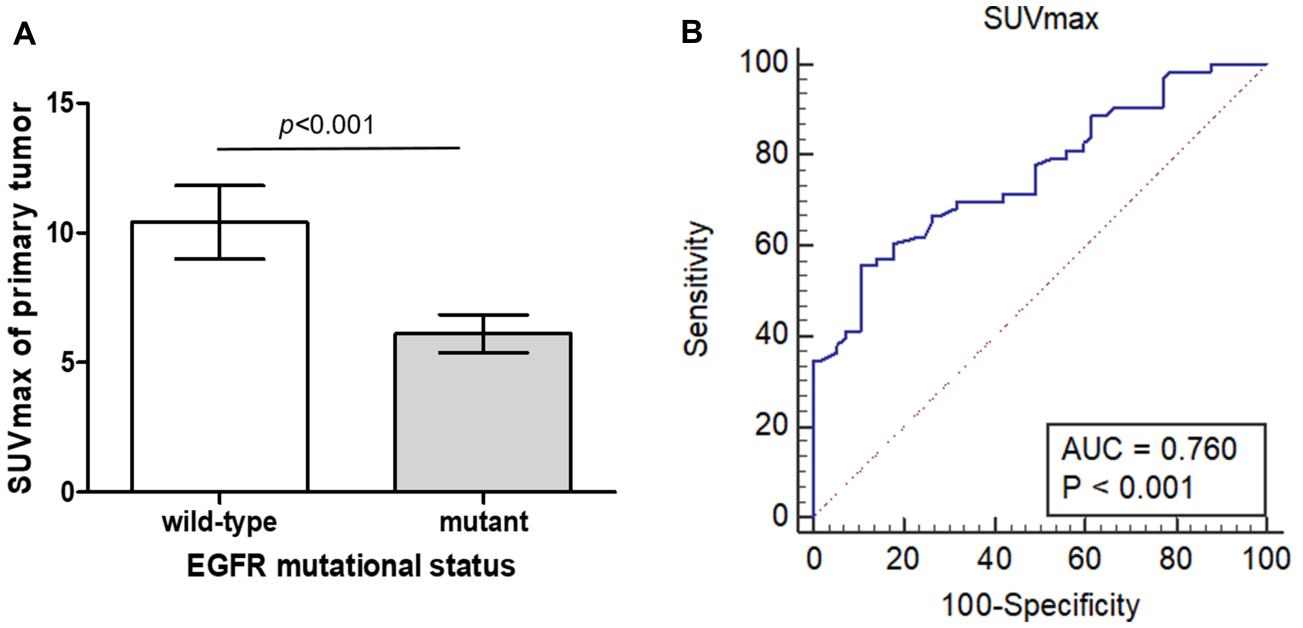

Figure 1 (**A**) Box plot of SUVmax of the primary tumor. Mean SUVmax was significantly lower in *EGFR*-mutated tumors than in *EGFR* wild-type (6.11 vs 10.41, $p < 0.001$). Bars indicate 95% confidence interval of mean values. (**B**) The receiver operating characteristic (ROC) curve of SUVmax for discriminating *EGFR* mutational status. At the cutoff of 9.6, the AUC was 0.760 (95% CI: 0.673–0.833, p < 0.001).

$p = 0.046$) and those who had never smoked (61% vs 28%, $p = 0.017$) were higher in the *EGFR*-mutated group.

Association Between SUVmax and *EGFR* Mutational Status

The SUVmax was significantly lower in the *EGFR*-mutated group (mean, 6.11 ± 2.77) than in the *EGFR*-negative group (mean, 10.41 ± 5.61, $p < 0.001$) (Figure 1A). ROC curve analysis was performed to determine the optimal cutoff for discriminating *EGFR* mutational status. At the cutoff of 9.6, the AUC was 0.760 (95% CI: 0.673–0.833, p < 0.001), with a sensitivity of 55.6% and a specificity of 89.5% (Figure 1B). The proportion of tumors with low SUVmax (< 9.6) was significantly higher in the *EGFR*-mutated group than in the *EGFR* wild-type group (84% vs 42%, $p = 0.010$) (Table 1).

Analysis of Predictive Factors of *EGFR* Mutational Status

In the univariate analysis, the female gender, no history of smoking, and low SUVmax were significantly associated with positive *EGFR* mutation (all p < 0.05). In the multivariate analysis, the female gender (HR = 2.65, 95% CI: 1.13–5.19), no history of smoking (HR = 1.28, 95% CI: 1.05–4.12), and low SUVmax (HR = 3.14, 95% CI: 1.23–5.57) were independently associated with *EGFR* positivity (Table 2).

Survival Analysis for the Patients Receiving *EGFR*-TKIs as a First-Line Treatment

The optimal cutoff values for the survival analysis, as determined by the Log rank test, were 3.54 for SUVmax, 14.08 for $MTV_{1.5}$, 69.86 for $TLG_{1.5}$, 4.28 for $MTV_{2.5}$, and 12.64 for $TLG_{2.5}$ (Figure S1). Survival analysis results on clinical and metabolic parameters are summarized in Table 3. The median PFS for all study subjects was 15.3 months (range, 2.2–30.4 months). The univariate analysis showed metastases in 3 or more organs, gefitinib/erlotinib use, and high SUVmax showed a trend of association with shorter PFS. In addition, smoking, high MTV, and TLG, regardless of SUV cutoffs, were significantly associated with shorter PFS (all $p < 0.05$). Multivariate analysis showed that smoking (HR = 2.08, 95% CI: 1.02–4.26), $MTV_{1.5}$ (HR = 3.12, 95% CI: 1.35–6.67), $TLG_{1.5}$ (HR = 3.26, 95% CI: 1.45–7.32), $MTV_{2.5}$ (HR = 2.16, 95% CI: 1.05–4.44), and $TLG_{2.5}$ (HR = 2.19, 95% CI: 1.10–4.68) were independently associated with shorter PFS. Kaplan–Meier survival curves showed that patients with high values of metabolic parameters were likely to have poor survival in terms of PFS (Figure 2).

The median OS for all study subjects was 28.5 months (range, 2.2–56.0 months). Univariate analysis showed that male sex, poor performance status, and low SUVmax showed a trend of association with OS. Metastases in 3 or more organs and high MTV and TLG, regardless of

Table 2 Analysis Results for the Variables Associated with *EGFR* Mutational Status

	No. of Patients (%)	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	*p*	OR (95% CI)	*p*
All	62 (100)				
Gender			0.004		0.014
Female	32 (52)	2.26 (1.08–4.93)		2.65 (1.13–5.19)	
Male	30 (47)	Reference		Reference	
Age			0.163		0.521
<65	28 (45)	1.14 (0.78–2.96)		1.08 (0.64–2.13)	
≥65	34 (55)	Reference		Reference	
Smoking			0.008		0.044
Never	38 (61)	1.82 (1.13–2.17)		1.28 (1.05–4.12)	
Ever	24 (39)	Reference		Reference	
SUVmax			0.005		0.017
Low (<9.6)	52 (84)	2.26 (1.11–4.25)		3.14 (1.23–5.57)	
High (≥9.6)	10 (16)	Reference		Reference	

Abbreviations: SUVmax, maximal standardized uptake value; OR, odds ratio; CI, confidence interval.

SUV cutoffs, were significantly associated with shorter OS (all $p < 0.05$). Multivariate analysis showed that metastases in 3 or more organs (HR = 2.11, 95% CI: 1.04–3.61), $MTV_{1.5}$ (HR = 4.18, 95% CI: 1.28–10.85), $TLG_{1.5}$ (HR = 4.62, 95% CI: 1.26–12.11), $MTV_{2.5}$ (HR = 2.04, 95% CI: 1.08–6.25), and $TLG_{2.5}$ (HR = 1.87, 95% CI: 1.02–6.33) were independently associated with shorter OS. Kaplan–Meier survival curves showed that patients with high values of metabolic parameters were likely to have poor survival in terms of OS (Figure 3).

Representative cases of *EGFR*-mutant patients with different PFS and OS according to different MTV and TLG of the primary tumors are presented in Figure 4.

Discussion

The present data demonstrate that SUVmax is significantly lower in *EGFR*-mutated lung adenocarcinoma than in the *EGFR* wild-type, and low SUVmax (< 9.6) may be predictive of *EGFR* mutation. In addition, volumetric parameters such as high MTV and TLG measured in the primary tumor were associated with shorter PFS and OS in *EGFR*-mutant patients treated with first-line *EGFR*-TKIs, even after adjusting for the effects of clinical parameters. To the best of our knowledge, this is the first report identifying that ^{18}F-FDG PET/CT parameters of primary tumors may have predictive and prognostic values in advanced *EGFR*-mutated lung adenocarcinoma.

Although mutational analysis using tumor tissue or body fluid is the standard method for determining *EGFR* mutational status, it is sometimes limited by issues such as invasiveness of the tissue acquisition procedures and inaccessibility or insufficiency of sample tissues. Thus, metabolic parameters obtained from the ^{18}F-FDG PET/CT data have been evaluated for non-invasive predictions of *EGFR* mutation.[25–28] SUVmax, representing the most active metabolic location of the tumor, is the most studied, and several studies have shown that low SUVmax is associated with *EGFR* mutation.[26,28,29] Previous studies have demonstrated that glucose transporter 1 (GLUT1), which serves important functions in glucose transport, may be regulated by reactive oxygen species (ROS).[30,31] Chen et al recently observed that ROS activity was lower in *EGFR*-mutant lung cancer cells than in wild-type cells, and identified the role of NADPH oxidase 4 (NOX4)/ROS/GLUT1 axis in glucose metabolism; downregulated NOX4 expression led to a decrease in ROS activity resulting in decreased GLUT1 expression. The decreased FDG uptake in *EGFR*-mutant cells can partially be explained by this mechanism.[29] However, the data on the value of SUVmax in predicting *EGFR* mutation are still conflicting, as some studies have failed to prove associations.[25,27,32,33] One of the reasons for the conflicting results among studies is the differences in the study design and patient characteristics across the studies. All the aforementioned studies enrolled *EGFR*-mutated patients of all clinical

Table 3 Survival Analyses Results According to Clinicopathologic and Metabolic Parameters in *EGFR*-Mutated Patients

	No. of Patients (%)	Progression-Free Survival (PFS)			Overall Survival (OS)		
		Median PFS (Months)	Univariate Analysis *p*	Multivariate Analysis Adjusted HR (95% CI)	Median OS (Months)	Univariate Analysis *p*	Multivariate Analysis Adjusted HR (95% CI)
All	62 (100)	15.3			28.5		
Gender			0.145			0.091	
Female	32 (52)	17.4		Reference	34.3		Reference
Male	30 (47)	14.1		1.57 (0.98–3.14)	21.0		1.69 (0.74–2.85)
Age, yrs			0.179		0.252		
<65	28 (45)	17.9		Reference	32.4		Reference
≥65	34 (55)	14.2		1.14 (0.57–2.26)	26.3		1.28 (0.73–1.93)
Smoking			0.049			0.409	NA
Never	38 (61)	17.3		Reference	30.2		
Ever	24 (39)	12.2		2.08 (1.02–4.26)	26.1		
ECOG performance status			0.320	NA		0.078	
0, 1	51 (82)	16.7			29.9		Reference
≥2	11 (18)	13.4			26.2		1.08 (0.22–2.74)
Stage			0.236			0.548	NA
IIIB	5 (8)	15.6		Reference	28.3		
IV	57 (92)	13.2		1.23 (0.56–2.73)	24.5		
Metastatic organs			0.088			0.011	
0–2	48 (79)	17.3		Reference	31.3		Reference
≥3	14 (21)	11.8		1.98 (0.35–3.14)	17.0		2.11 (1.04–3.61)
Brain metastasis			0.199			0.273	
No	48 (79)	16.3		Reference	29.5		Reference
Yes	14 (21)	14.4		1.20 (0.35–2.63)	27.6		1.37 (0.65–3.41)
Liver metastasis			0.362	NA		0.674	NA
No	55 (88)	16.9			28.6		
Yes	7 (12)	14.4			29.5		
EGFR subtypes*			0.459	NA		0.449	NA
19del	35 (57)	15.3			30.3		
L858R	25 (47)	16.9			23.3		
First-line treatment			0.063			0.316	NA
Gefitinib/erlotinib	22 (35)	12.2		1.82 (0.92–3.56)	24.3		
Afatinib	40 (65)	15.8		Reference	29.3		
SUVmax			0.057			0.070	
Low (<3.54)	12 (20)	16.1		Reference	32.3		Reference
High (≥3.54)	50 (80)	12.4		1.15 (0.92–3.46)	25.9		1.61 (0.89–3.17)
$MTV_{1.5}$						0.015	
Low (<14.08)	26 (42)	20.8	0.010	Reference	36.1		Reference
High (≥14.08)	36 (58)	13.1		3.12 (1.35–6.67)	24.3		4.18 (1.28–10.85)
$TLG_{1.5}$						0.018	
Low (<69.86)	31 (50)	20.2	0.008	Reference	34.9		Reference
High (≥69.86)	31 (50)	13.0		3.26 (1.45–7.32)	23.7		4.62 (1.26–12.11)

(*Continued*)

Table 3 (Continued).

	No. of Patients (%)	Progression-Free Survival (PFS)			Overall Survival (OS)		
		Median PFS (Months)	Univariate Analysis *p*	Multivariate Analysis Adjusted HR (95% CI)	Median OS (Months)	Univariate Analysis *p*	Multivariate Analysis Adjusted HR (95% CI)
$MTV_{2.5}$			0.023			0.036	
Low (<4.28)	25 (47)	19.8		Reference	35.5		Reference
High (≥4.28)	37 (53)	13.6		2.16 (1.05–4.44)	24.6		2.04 (1.08–6.25)
$TLG_{2.5}$			0.026			0.041	
Low (<12.64)	22 (35)	20.1		Reference	35.6		Reference
High (≥12.64)	40 (65)	13.9		2.19 (1.10–4.68)	26.5		1.87 (1.02–6.33)

Note: *Two patients harboring rare mutation were excluded.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; *EGFR*, epidermal growth factor receptor; SUV, standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; HR, hazard ratio; CI, confidence interval; NA, not applicable.

stages. Some studies enrolled all NSCLC histologic subtypes,[25,28] while others did not.[26,27,33] *EGFR* mutation is dominant in adenocarcinomas, and tumors harboring this mutation become heterogeneous as they progress due to the clonal evolution.[34,35] Thus, their metabolic characteristics could vary with the clinical stages. In addition, the detection of *EGFR* mutation is more important in advanced than in early-stage lung cancer because the presence or absence of the mutation determines treatment strategy; whether TKIs should be used for frontline treatment or not. Thus, we ensured that our population was more homogenous, consisting of advanced *EGFR*-mutated

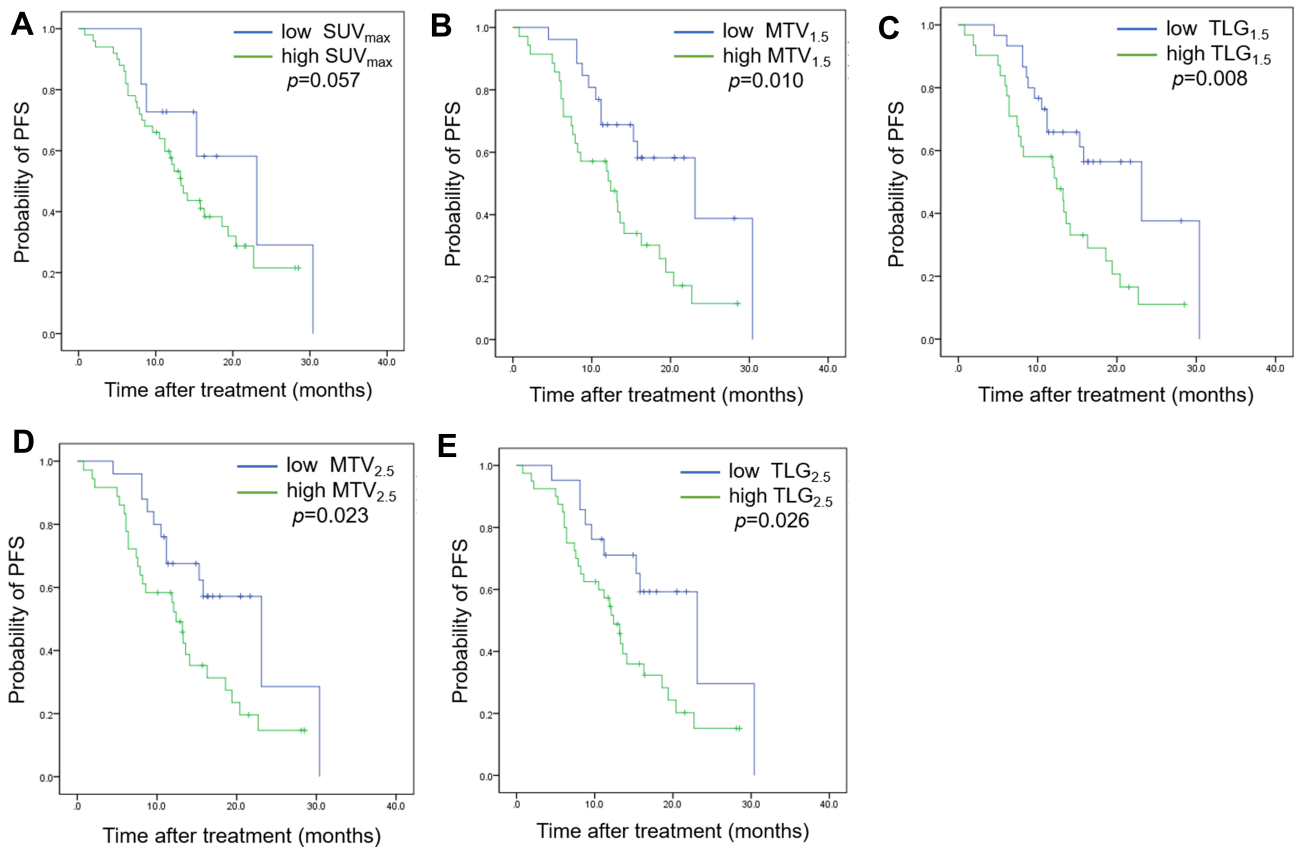

Figure 2 Kaplan–Meier survival curves for progression-free survival (PFS). (**A**) SUVmax, (**B**) $MTV_{1.5}$, (**C**) $TLG_{1.5}$, (**D**) $MTV_{2.5}$, (**E**) $TLG_{2.5}$. *P*-values were determined using the Log rank test.

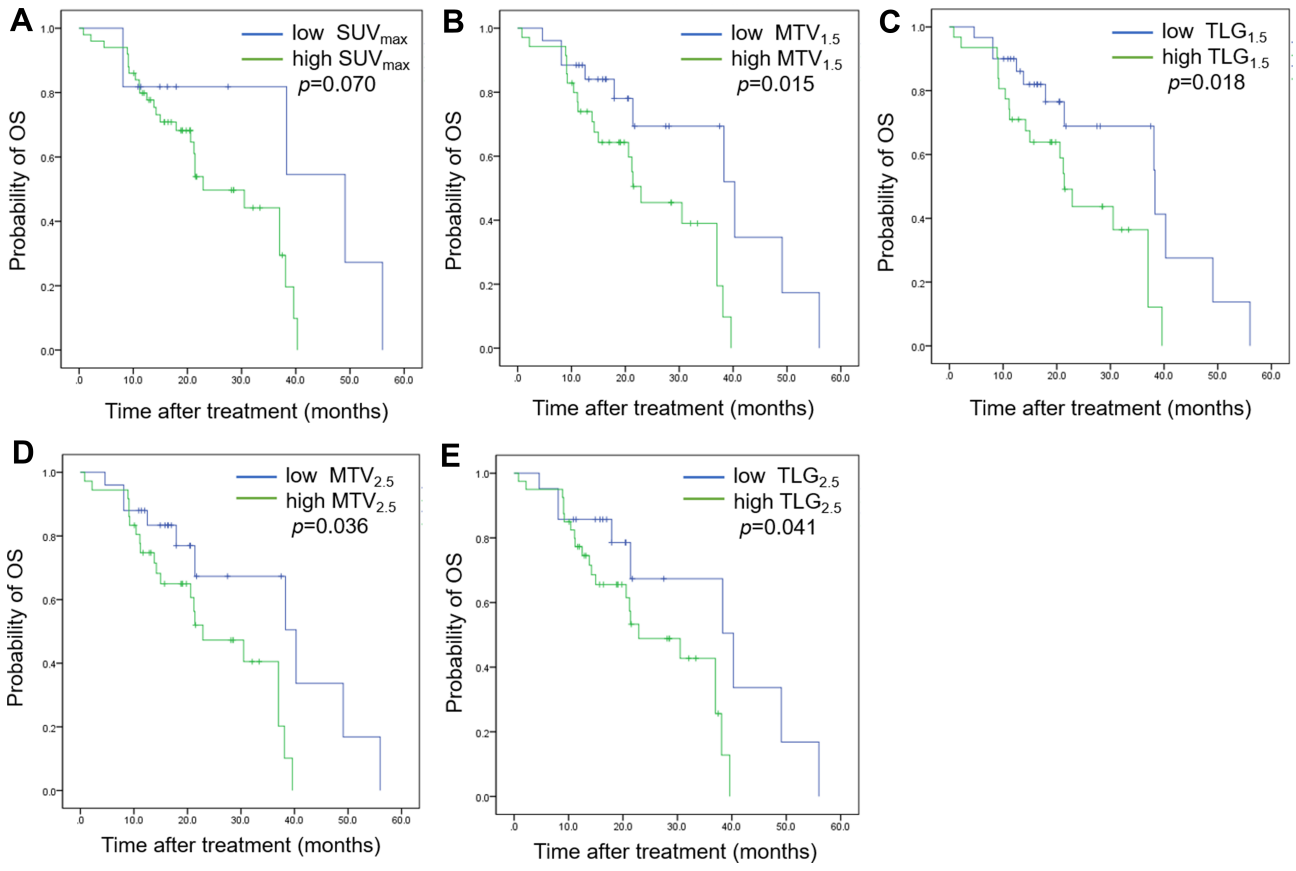

Figure 3 Kaplan–Meier survival curves for overall survival (OS). (**A**) SUVmax, (**B**) $MTV_{1.5}$, (**C**) $TLG_{1.5}$, (**D**) $MTV_{2.5}$, (**E**) $TLG_{2.5}$. *P*-values were determined using the Log rank test.

adenocarcinomas, and we successfully demonstrated that SUVmax, even in advanced stages, can predict *EGFR* mutational status at the cutoff of 9.6. Our data are consistent with those from previous studies,[28,36] and they suggest that PET/CT may be a helpful non-invasive modality for predicting *EGFR* mutation. Our results should be validated and the optimal cutoff should be determined in further large-scale investigations. In addition, the clinical significance of other metabolic parameters as predictors for *EGFR* mutations need to be evaluated, as a recent study has demonstrated that MTV could discriminate the *EGFR*-positive patients from those without the mutation.[37]

In contrast to SUV, which reflects the high metabolic lesion of the tumor, MTV and TLG incorporate metabolic burden and disease extent, and they may have better predictive values than SUV. Several studies have demonstrated that volumetric parameters have prognostic values in advanced NSCLC treated with chemotherapy.[12,16,17] However, the clinical significance of those parameters in *EGFR*-mutated patients receiving TKIs may differ in wild-type patients treated with chemotherapy since the mechanism by which TKIs induce cancer cell death is different from that of cytotoxic agents. In addition, tumors with *EGFR* mutations are metabolically indolent, as shown in previous studies and our present study. To date, only 3 studies have investigated the predictive value of the various metabolic parameters in advanced *EGFR*-mutated NSCLC.[11,38,39] We have summarized their results in Table 4. One study reported that high SUVmax (> 12) was independently associated with PFS.[38] Other studies reported that high whole-body TLG was significantly associated with poor survival in patients treated with *EGFR*-TKIs.[11,39] However, the latter two studies evaluated MTV and TLG from whole-body lesions.

Although it may be ideal to calculate whole-body volumetric information to ascertain the exact metabolic tumor burden, it is time-consuming, especially in patients with extensive metastasis; thus, it may be impractical despite its proven significance. We aimed at finding simpler, image-based markers that could be readily used in clinical practice, and hypothesized that volumetric parameters of the primary tumor have prognostic values. To determine the best

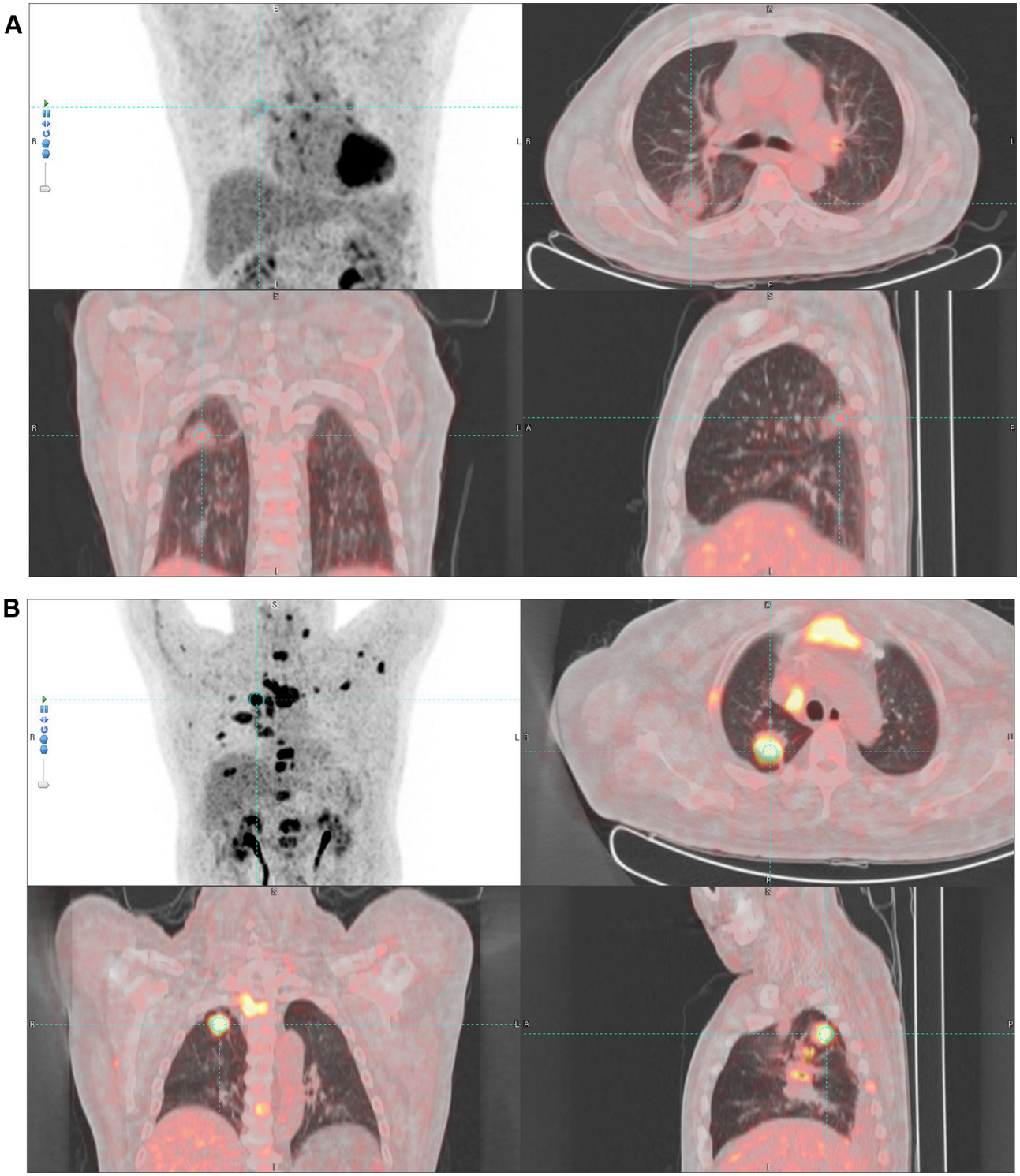

Figure 4 Representative examples of PET/CT images of *EGFR*-mutated patients with different metabolic parameters showing different clinical outcomes. (**A**) A case of a 75-year-old man having a primary tumor in the right upper lobe. $MTV_{1.5}$ is 8.6 and $TLG_{1.5}$ is 14.5. His PFS and OS are 12.6 and 18.7 months, respectively. (**B**) A case of a 76-year-old man having a primary tumor in the right upper lobe. $MTV_{1.5}$ is 22.7 and $TLG_{1.5}$ is 71.8. His PFS and OS are 5.4 months and 9.7 months, respectively.

parameters, we used two SUV cutoffs to calculate MTV and TLG. The present data showed that high MTV and TLG, regardless of the SUV cutoffs, were independently associated with poor PFS and OS. The HRs of $MTV_{1.5}$ (3.12 for PFS and 4.18 for OS) and $TLG_{1.5}$ (3.26 for PFS and 4.62 for OS) were higher than those of $MTV_{2.5}$ (2.16 for PFS and 2.04 for OS) and $TLG_{2.5}$ (2.19 for PFS and 1.89 for OS), suggesting that the predictive performance of volumetric parameters

Table 4 Summary of Published Data and the Present Study on the Association Between ^{18}F-FDG PET/CT Metabolic Parameters and Clinical Outcome of Advanced *EGFR*-Mutated Lung Adenocarcinoma

Author, Year	Pathology	No. of Patients	Metabolic Parameters Analyzed	Results	TKIs Used
Keam et al,[36] 2015	ADC, NSCC NOS	75	SUVmax and TLG of all lesions	High whole-body TLG (third quartile) is significantly associated with PFS and OS.	Gefitinib
Wang et al,[11] 2016	ADC	91	SUVmax and TLG of the primary tumor and target lesions*	High whole-body TLG of (>260) is significantly associated with PFS but not OS.	Gefitinib
Sing et al,[35] 2020	ADC	41	SUVmax	High SUVmax (>12) independently associated with PFS.	Erlotinib, Gefitinib
Present study	ADC	60	SUVmax, MTV, and TLG of the primary tumor	High TLG and MTV of the primary tumor were independently associated with PFS and OS.	Gefintib, Erlotinib, Afatinib

Note: *Target lesions were selected in accordance with the RECIST 1.1 criteria.
Abbreviations: TKIs, tyrosine kinase inhibitors; ADC, adenocarcinoma; NSCC NOS, non-small-cell carcinoma not otherwise specified, SUV, standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PFS, progression-free survival; OS, overall survival.

may be better at the cutoff SUV of 1.5 than 2.5. The exact reason for the better performance of the volumetric parameters with low SUV cutoff is not clear; however, we postulate that the low cutoff permits an MTV that is reflective of a more exact metabolic burden of primary tumors compared with a high cutoff because *EGFR*-mutant tumors are metabolically indolent.[26,28,29] Our results are supported by a previous report demonstrating that MTV and TLG of the primary tumor, rather than SUVmax, were associated with clinical outcomes in NSCLC patients treated with chemotherapy.[12]

Although SUV has been extensively studied and was proven to be related with prognosis in NSCLC patients across all stages, it has several limitations as an optimal metabolic parameter; it depends on various patient-related (body size, blood glucose levels) and technical (reconstruction method, partial volume effect) factors,[40] and does not account for tumor volume, which can be related to the T descriptor in the staging system that is associated with prognosis. Especially, SUVmax is the value of a single voxel in the region of interest that is subject to statistical variability due to noise in a reconstructed PET/CT image.[15] The clinical usefulness of volumetric parameters and optimal SUV cutoffs in calculating metabolic tumor burden should be validated in large-scale studies.

This study has several limitations. First, it is a retrospective study and selection bias is inevitable. Second, it was performed in a single institution and the sample size was small. To compensate for the small sample size and to collect relevant data, we analyzed various metabolic parameters at the various SUV cutoffs simultaneously, and two nuclear medicine specialists assessed the PET/CT images. Third, patients with other genetic alterations such as *ROS1* and *ALK* fusion were not assessed because of the rarity of the alterations among lung adenocarcinoma patients (1%-5%). Finally, we focused on the baseline metabolic parameters rather than follow-up data after treatment. As suggested in a study on NSCLC patients treated with concurrent chemoradiation, the change in metabolic parameters from the baseline to the subsequent study may also have valuable clinical implications.[41]

Conclusion

In conclusion, SUVmax may be useful in predicting *EGFR* mutational status, while MTV and TLG, measured in the primary tumor, may be useful for predicting treatment response and survival in lung adenocarcinomas treated with TKIs. Our results highlight a practical, image-based method for the discrimination of *EGFR*-mutated tumors from wild-types and risk stratification before TKI use. If large-scale prospective studies confirm our results, PET/CT metabolic parameters, either alone or combined with other clinical parameters, can be used to select patients with TKI resistance and modify treatment strategy or prompt more rigorous follow-up. Our data also suggest the possible application of the parameters in other clinical settings, such as immunotherapy, which may facilitate the

clinical utilization of PET/CT as a non-invasive predictive and prognostic modality in lung cancer management.

Acknowledgments

This research was supported by a grant from the Basic Research Program through the National Research Foundation funded by the Ministry of Science and ICT (2019R1F1A1041812) of the Republic of Korea.

Disclosure

The authors declare that they have no competing interests.

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