Total Lesion Glycolysis Determined per RECIST 1.1 Criteria Predicts Survival in *EGFR* Mutation-Negative Patients With Advanced Lung Adenocarcinoma

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Objective: The aim of this retrospective study was to investigate the clinical impact of ^{18}F-FDG PET in patients with advanced lung adenocarcinoma stratified according to the epidermal growth factor receptor (*EGFR*) mutation status.

Patients and Methods: A total of 56 patients with advanced lung adenocarcinoma were included in the study. Thirty-one patients (55%) were *EGFR* mutation-positive, whereas the remaining 25 (45%) participants tested negative for *EGFR* mutations. All of the patients underwent ^{18}F-FDG PET/CT for pretreatment planning. The main outcome measure was overall survival (OS) at 24 months. The following ^{18}F-FDG PET/CT-derived variables were tested for their associations with OS: main tumor SUV_{max}, main tumor total lesion glycolysis, and target lesions TLG determined per RECIST (Response Evaluation Criteria In Solid Tumors) 1.1 criteria (TLG_{RECIST}). We also investigated the clinical characteristics in relation to OS and *EGFR* mutation status.

Results: In *EGFR* mutation-positive patients, neither the clinical characteristics nor ^{18}F-FDG PET/CT-derived parameters were significantly associated with OS. In contrast, univariate analysis identified male sex, a positive history of smoking, and TLG_{RECIST} greater than or equal to 412 g as adverse prognostic factors for OS in *EGFR* mutation-negative patients. After adjustment for potential confounders in multivariate analysis, TLG_{RECIST} was the sole independent predictor of OS in this subgroup.

Conclusions: TLG determined per RECIST 1.1 criteria is an independent predictor of OS in *EGFR* mutation-negative patients with advanced lung adenocarcinoma. Further studies are needed to investigate whether this parameter may be a promising tool for stratifying such patients for risk-adapted therapies.

Key Words: lung cancer, adenocarcinoma, epidermal growth factor receptor mutations, ^{18}F-FDG PET, total lesion glycolysis, RECIST 1.1

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Lung cancer remains a leading cause of cancer-related mortality worldwide. It is not only the most commonly diagnosed but also ranked first in terms of cause of cancer deaths globally.[1] In addition, the majority of lung cancer patients are diagnosed at advanced stage.[2] The main prognostic factors in lung cancer include clinical variables and the presence of epidermal growth factor receptor (*EGFR*) mutations.[3] Importantly, the prevalence of EGFR mutations is ethnicity dependent, with a higher proportion in Asian (51.4%) than in whites (13.7%).[4,5]

To date, little is known about the prognostic significance of ^{18}F-FDG PET/CT-derived variables in relation to *EGFR* mutations among patients with lung cancer. We therefore designed this retrospective study to investigate the clinical impact of ^{18}F-FDG PET-derived parameters in patients with advanced (≥ stage IIIB) lung adenocarcinoma stratified according to the *EGFR* mutation status.

PATIENTS AND METHODS

Patients

A total of 56 patients with histology-proven lung adenocarcinoma in advanced stage (≥ stage IIIB) were included in the study. Thirty-one patients (55%) were *EGFR* mutation-positive, whereas the remaining 25 (45%) participants tested negative for *EGFR* mutations. All of the participants were followed up for at least 24 months or censored at the date of the last follow-up. Staging was performed using the *Seventh Edition of the American Joint Committee on Cancer Staging System* published in 2010. Each patient's stage was determined by the consensus reached in our tumor board conference. The study protocol was approved by the institutional review board of the Chang Gung Memorial Hospital (IRB: 102-2413B).

^{18}F-FDG PET/CT Imaging

All ^{18}F-FDG PET/CT scans were performed on either Discovery ST 16 PET/CT scanner (GE Healthcare, Milwaukee, Wis) or Siemens Biograph mCT PET/CT scanner (Siemens Healthcare Molecular Imaging, Hoffman Estates, Ill). After 6 hours of fasting, patients were injected intravenously with 370 to 444 MBq (10–12 mCi) ^{18}F-FDG. Patients were scanned at 50 minutes from the mid thigh to the skull vertex. CT data were used for both attenuation correction and fusion with attenuation-corrected PET images. Images were reconstructed using ordered subsets expectation maximization (4 iterations and 10 subsets). All PET, CT, and PET/CT images were displayed in axial, coronal, and sagittal views. PET data were also displayed in a rotating MIP. Two nuclear medicine physicians independently reviewed all PET imaging results. Abnormal ^{18}F-FDG uptake was defined as focal increased activity higher than the background activity. Regions of interest were measured over lesions visible on PET images. The SUV was calculated according to the following formula: SUV = radioactivity concentration in tissue [becquerel/gram]/(injected dose [becquerel]/patient weight [gram]).

EGFR Mutation Analysis

Exons 18 to 21 of the *EGFR* gene were amplified and subjected to direct sequencing as previously described.[6]

Lesion Analysis per RECIST 1.1 Criteria

The following lesions were selected using the RECIST (Response Evaluation Criteria In Solid Tumors) 1.1 criteria: pulmonary main tumor with longest diameter greater than or equal to 10 mm, lymph nodes with longest diameter greater than or equal to 15 mm in short axis, and solid metastatic lesions with longest diameter greater than or equal to 10 mm. All measurable lesions up to a maximum of 5 lesions per patient and 2 lesions per organ were included in the analysis.[7]

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TABLE 1. General Characteristics of the Study Patients (n = 56)

Variable	n (%)
Age, y	
≥63	28 (50)
<63	28 (50)
Sex	
Male	33 (59)
Female	23 (41)
History of smoking	
Yes	23 (41)
No	33 (59)
EGFR mutations	
Yes	31 (55)
No	25 (45)
SUV_{max}, main tumor	
≥12	28 (50)
<12	28 (50)
TLG_{MT}, g	
≥170	28 (50)
<170	28 (50)
TLG_{RECIST}, g	
≥342	28 (50)
<342	28 (50)
M status	
M0	7 (12)
M1a	6 (11)
M1b	43 (77)
Radiotherapy	
Yes	33 (59)
No	23 (41)

TLG_{RECIST}, sum of TLG values of lesions selected per RECIST 1.1 criteria.

Total Lesion Glycolysis

The metabolic tumor volume (MTV) was measured from attenuation-corrected ^{18}F-FDG PET/CT fusion images. A segmentation algorithm implemented in the TrueD software (Siemens Healthcare) was used for tumor segmentation. The boundaries were drawn to include all of the lesions identified using the RECIST 1.1 criteria on axial ^{18}F-FDG PET/CT images. Lesion contours were delineated automatically by a threshold SUV of 2.5. All voxels presenting SUV intensity greater than 2.5 within the contouring margin were incorporated to define the MTV. The mean SUV value within each volume of interest was acquired simultaneously. Total lesion glycolysis (TLG) was then calculated according to the following formula: TLG = mean SUV × MTV. The main tumor total lesion glycolysis (TLG_{MT}) was defined as TLG from the largest primary pulmonary lesion. Finally, TLG_{RECIST} was calculated as the sum of all TLG values of the lesions selected using the RECIST 1.1 criteria.

Data Analysis

The main outcome measure was overall survival (OS) at 24 months. ^{18}F-FDG PET-derived parameters were expressed as continuous variables, and univariate Cox proportional hazards regression analysis was used to identify their associations with OS. Receiver operating characteristic curves were used to determine the optimal cutoff values that maximized the sum of sensitivity and specificity. Kaplan-Meier survival estimates compared with the log-rank test were used in the univariate analysis. Multivariate Cox regression models were constructed to identify the independent predictors of OS. Two-tailed *P* values less than 0.05 were considered statistically significant.

RESULTS

Patient Characteristics

Between November 2007 and May 2012, a total of 56 patients (33 men and 23 women; median age, 63 years) with advanced (≥ stage IIIB) lung adenocarcinoma were included in the study. The general characteristics of the study participants are reported in Table 1.

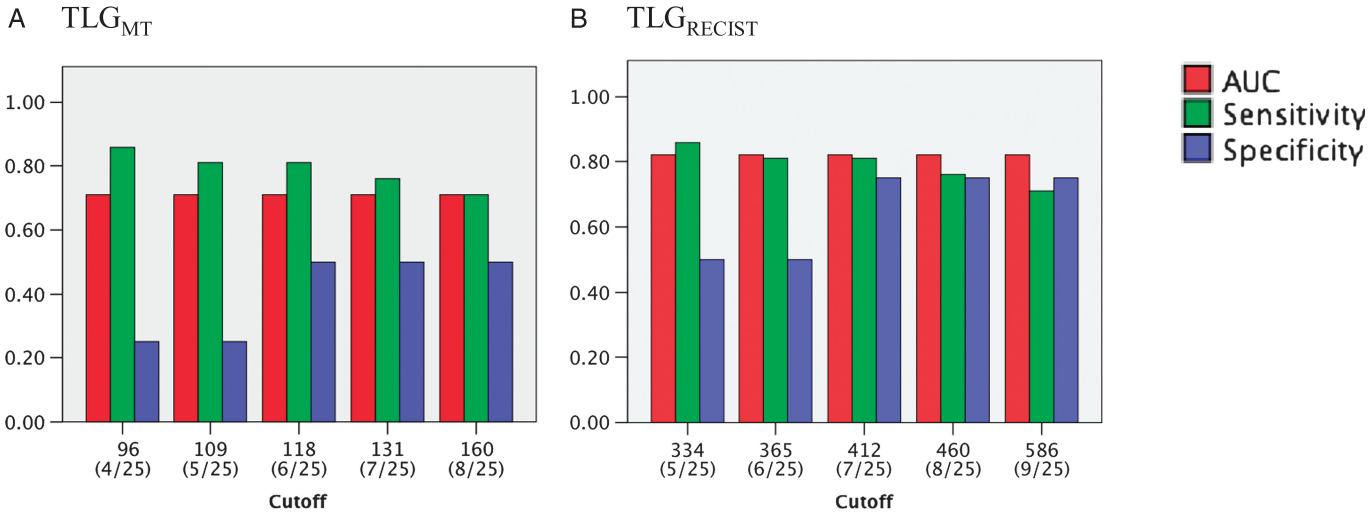


FIGURE 1. ROC curve analysis for identifying the optimal cutoff values of ^{18}F-FDG PET/CT-derived parameters in *EGFR* mutation-negative patients. The optimal cutoff points were identified by determining the values where the area under the curve and the sum of sensitivity and specificity were maximal. The parentheses under each cutoff value indicate the number of patients with measured values under the cutoff value out of the total number of patients per group. The optimal cutoff values for TLG_{MT} and TLG_{RECIST} in *EGFR* mutation-negative patients were 118 g and 412 g, respectively.

TABLE 2. Univariate and Multivariate Analyses of OS in *EGFR* Mutation-Negative Patients

		Univariate Analysis			Multivariate Analysis	
Parameter		**n vs n**	**OS (months ± SD)**	***P***	**HR (95% CI)**	***P***
Age, y	≥63 vs < 63	14 vs 11	15.0 ± 3.3 vs 12.7 ± 2.9	0.487		
Sex	M vs F	19 vs 6	10.5 ± 2.1 vs 24.3 ± 4.0	0.022	6.13 (0.77-48.67)	0.087
History of smoking	Yes vs no	14 vs 11	9.4 ± 2.2 vs 19.8 ± 3.5	0.022	2.67 (0.66-10.82)	0.168
M1b	M1b vs non-M1b	18 vs 7	13.3 ± 2.9 vs 15.6 ± 2.7	0.749		
TLG_{MT}, g	≥118 vs < 118	19 vs 6	12.6 ± 2.5 vs 18.0 ± 4.0	0.315		
TLG_{RECIST}, g	≥412 vs < 412	18 vs 7	10.0 ± 2.0 vs 24.7 ± 4.4	0.006	8.72 (1.20-63.22)	0.032
Radiotherapy	Yes vs no	17 vs 8	13.0 ± 2.8 vs 15.7 ± 3.7	0.490		
Use of TKIs	Yes vs no	17 vs 8	15.9 ± 2.9 vs 8.9 ± 2.2	0.201		

M, Male; F, Female; TLG_{RECIST}, sum of TLG values of lesions selected per RECIST 1.1 criteria; TKIs, tyrosine kinase inhibitors.

Survival Analysis

Information on age, sex, history of smoking, SUV_{max} of the main tumor, TLG_{MT}, TLG_{RECIST}, M1 status, radiotherapy, *EGFR* mutation status, and use of tyrosine kinase inhibitors was available for all participants. Thirty-one patients (55%) were *EGFR* mutation positive, whereas the remaining 25 participants (45%) tested negative for *EGFR* mutations. The mean OS of patients who were positive for *EGFR* mutations was marginally higher than that of patients who tested negative (21.5 ± 2.6 months vs 14.1 ± 2.3 months, respectively, $P = 0.057$). Among *EGFR* mutation-positive patients, no associations between ^{18}F-FDG PET-derived parameters and OS were identified in univariate Cox regression analysis. By contrast, TLG_{RECIST} was significantly associated with OS in *EGFR* mutation-negative patients ($P = 0.041$). Similarly, TLG_{MT} showed a marginally significant association with OS in patients without *EGFR* mutations ($P = 0.054$). Receiver operating characteristic curve analysis was then performed to identify the optimal cutoff values for TLG_{RECIST} and TLG_{MT}. Figure 1 shows the identified optimal cutoff points (412 g and 118 g for TLG_{RECIST} and TLG_{MT}, respectively) and their corresponding sensitivity, specificity, and areas under the ROC curve. Such values were used for subsequent survival analyses.

Among *EGFR* mutation-positive patients, Kaplan-Meier estimates failed to identify significant associations of OS with clinical variables (eg, age, sex, history of smoking, M1 status, and radiotherapy). However, there were significant univariate associations of OS with sex, history of smoking, and TLG_{RECIST} in *EGFR* mutation-negative patients (Table 2). After allowance for potential confounders in multivariate Cox regression analysis, a TLG_{RECIST} greater than or equal to 412 g was identified as the only independent predictor of OS in *EGFR* mutation-negative patients (hazards ratio [HR], 8.72; 95% confidence interval [CI], 1.20–63.22; $P = 0.032$), whereas male sex showed a marginally significant association (HR, 6.13; 95% CI, 0.77–48.67; $P = 0.087$; Table 2). As expected, Kaplan-Meier plots for OS were significantly different in *EGFR* mutation-negative patients who had a TLG_{RECIST} greater than or equal to 412 g versus TLG_{RECIST} less than 412 g (Fig. 2). However, no such association was seen for *EGFR* mutation-positive patients (Fig. 3).

DISCUSSION

The results of the present study demonstrate that TLG_{RECIST} is an independent predictor of OS in *EGFR* mutation-negative patients with advanced lung adenocarcinoma. Specifically, significantly shorter OS time characterized *EGFR* mutation-negative patients who had a TLG_{RECIST} greater than or equal to 412 g. However, neither the clinical characteristics nor ^{18}F-FDG PET/CT-derived parameters were significantly associated with OS in *EGFR* mutation-positive patients.

The results obtained in our *EGFR* mutation-negative patients are generally in line with those of previous studies demonstrating the prognostic significance of whole-body TLG in non-Asian patients undergoing nonsurgical treatment for advanced non–small cell lung cancer.[8,9] However, it should be noted that the prognostic significance of TLG_{RECIST} found in our study was limited to patients without *EGFR* mutations. The low frequency of *EGFR* mutations in whites[5] may explain the comparable findings. Notably, our data also suggest that TLG_{RECIST} may reliably reflect the whole-body metabolic tumor burden. Because EGFR mutation-positive lung cancer cases are common in Asia (~50% of all patients), we stratified our study population according to the *EGFR* mutation status. Our results indicated that *EGFR* mutation-positive patients had marginally better OS than those without *EGFR* mutations. The lack of statistical significance may be explained by the smaller sample size as compared with previous studies.[3] Among *EGFR* mutation-positive patients, neither clinical variables nor ^{18}F-FDG PET/CT-derived parameters were found to be

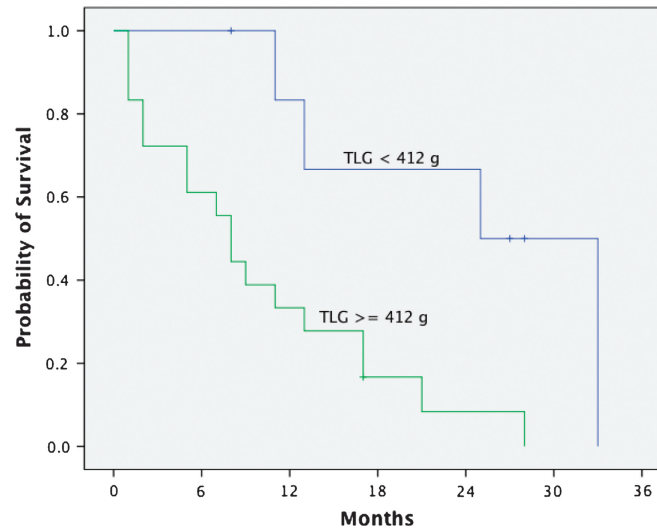
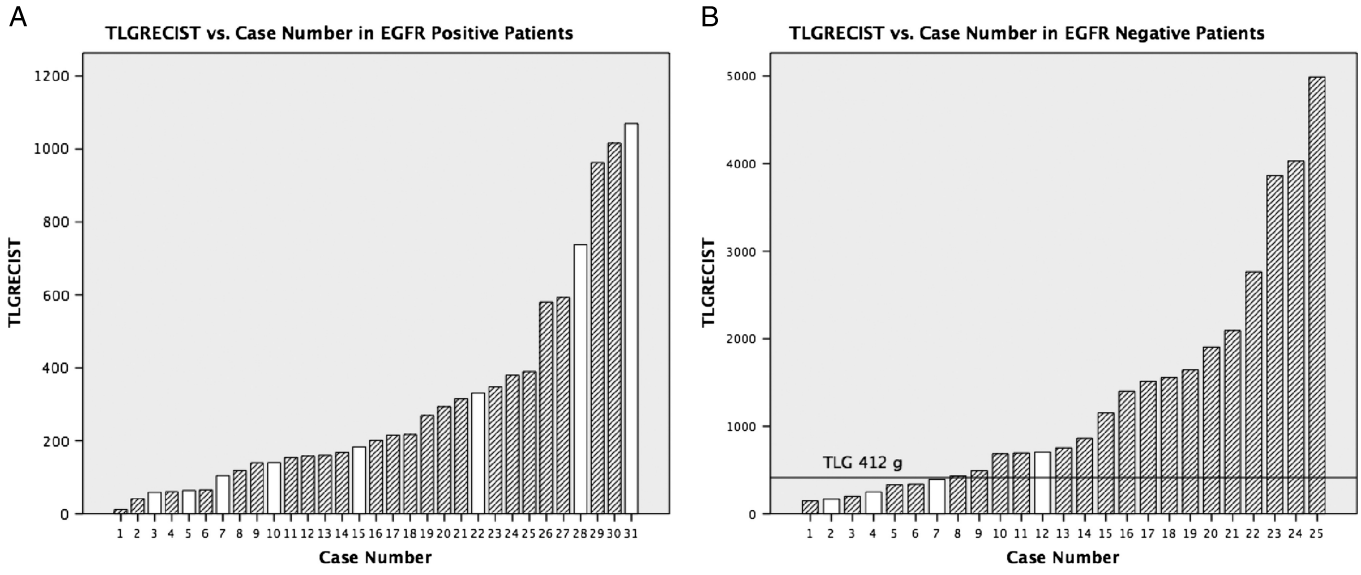


FIGURE 2. Kaplan-Meier curves for OS according to TLG_{RECIST} in *EGFR* mutation-negative patients. In *EGFR* mutation-negative patients, subjects with a TLG_{RECIST} greater than or equal to 412 g showed a shorter OS than those with a TLG_{RECIST} less than 412 g (10.0 ± 2.0 vs 24.7 ± 4.4 months, respectively; $P = 0.006$).



died, alive;

There was no association between TLG_{RECIST} and overall survival status in patients with EGFR mutation. Patients without EGFR mutation were more likely to die if their TLG_{RECIST} were equal to or higher than the cutoff value 412 g.

FIGURE 3. TLG_{RECIST} in relation to OS in patients with advanced lung adenocarcinoma stratified according to the *EGFR* mutation status. *EGFR* mutation-negative patients with a TLG_{RECIST} greater than or equal to 412 g had poor OS. In contrast, TLG_{RECIST} did not predict OS in *EGFR* mutation-positive patients.

significantly associated with OS. These results suggest that genetics is the most important prognostic determinant of OS in patients bearing *EGFR* mutations.

The National Comprehensive Cancer Network guidelines recommend that patients with advanced (≥ stage IIIB) lung cancer should be treated with nonsurgical approaches.[10] In this context, the baseline tumor metabolic burden (as measured by MTV and TLG of the main tumor) is considered an important predictor of progression-free survival and OS rates in patients with advanced non–small cell lung cancer treated with chemotherapy.[11] In our study, we have used TLG_{RECIST} as an expression of total metabolic tumor burden by selecting lesions per RECIST 1.1 criteria and summing up TLG values of selected lesions. In other words, we used TLG and the RECIST 1.1 criteria instead of MTV and the PET Response Evaluation Criteria in Solid Tumors (PERCIST) criteria, respectively. Notably, TLG is considered to reflect the primary metabolic tumor burden more closely than MTV.[12,13] Moreover, the RECIST 1.1 criteria currently represent the standard by which the efficacy of therapeutic agents is determined among patients with systemic diseases.[14] In contrast, the clinical usefulness of the PERCIST 1.0 criteria may be limited for geographical areas characterized by a high incidence of hepatitis (such as Taiwan) because PERCIST 1.0 relies on FDG uptake of liver as its reference tissue value.[15] An important finding of this study is that the prognostic significance of ^{18}F-FDG PET in patients with advanced lung adenocarcinoma was found to be dependent on the *EGFR* mutation status. Moreover, we demonstrate for the first time that TLG determined per RECIST 1.1 criteria predicts survival in this group of patients. Compared with the sum of TLG values from all measurable lesions, TLG_{RECIST} from a maximum of 5 selected lesions is compatible with the widely accepted RECIST 1.1 criteria and can be more practical to perform.

Our findings should be interpreted in the context of some limitations. First, our report has a retrospective nature and represents only a single-center experience. Most patients did not undergo follow-up ^{18}F-FDG PET scans, and longitudinal changes in TLG_{RECIST} values were not examined in relation to treatment response. Further prospective studies are needed to investigate whether this parameter may be a promising tool for stratifying patients with advanced lung cancer for risk-adapted therapies.

These limitations notwithstanding, our current data demonstrate that TLG_{RECIST} is an independent predictor of OS in *EGFR* mutation-negative patients with advanced lung adenocarcinoma. In contrast, ^{18}F-FDG PET/CT-derived parameters did not predict OS in *EGFR* mutation-positive patients.

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