^{18}F-Fluoro-2-Deoxy-Glucose Uptake Predicts Clinical Outcome in Patients with Gefitinib-Treated Non–Small Cell Lung Cancer

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Abstract

Purpose: To evaluate response and survival according to ^{18}F-fluoro-2-deoxy-glucose uptake at presentation in patients with gefitinib-treated non–small cell lung cancer.

Experimental Design: We retrospectively analyzed 84 positron emission tomography/computed tomography findings. Patient characteristics, response rates, and survivals were evaluated according to the maximum standardized uptake value (SUV) of primary tumor. The cutoff value of SUVs was obtained from receiver operating characteristic analysis.

Results: The response rate (RR) was higher for never-smokers (41%) than ever-smokers (9%; $P = 0.001$). Patients with adenocarcinoma showed higher RR than those with other tumor histopathology (35% versus 9%; $P = 0.009$). The SUV was significantly lower in patients who were never-smokers ($P = 0.005$), patients with adenocarcinoma ($P < 0.001$), and female patients ($P = 0.017$). Patients with a low SUV showed higher RR compared with those with a high SUV (53% versus 18%; $P = 0.003$). Prolonged progression-free survival was observed in patients with low SUVs compared with those with high SUVs (median, 33.1 weeks versus 8.6 weeks; $P = 0.003$). While controlling for performance status, smoking history, and pathology, the high SUV conferred unfavorable outcome (hazard ratio, 2.3; $P = 0.012$). In terms of overall survival, a low SUV was associated with favorable outcome in univariate analysis ($P = 0.011$). Patients with a low SUV showed prolonged survival in multivariate analysis ($P = 0.043$).

Conclusions: These results suggest that low SUVs at presentation can predict favorable response and survival in gefitinib-treated non–small cell lung cancer patients.

Lung cancer is the leading cause of cancer mortality worldwide (1, 2). The overall 5-year survival for lung cancer is ~15% and has improved only marginally over decades despite the progress of new agents (3). Therefore, novel treatment strategies are needed to improve the prognosis of this dismal disease.

Several agents designed to inhibit epidermal growth factor receptor tyrosine kinase, such as gefitinib and erlotinib, have shown good tolerability and antitumor activity in non–small cell lung cancer (NSCLC; refs. 4–7). Somatic mutations of epidermal growth factor receptor can predict the sensitivity to these drugs (5). Epidermal growth factor receptor gene copy number is also associated with tyrosine kinase inhibitor (TKI) responsiveness (8). Although such molecular findings can predict TKI responsiveness, it is often difficult to obtain a sufficient sample from patients with advanced NSCLC.

Previous studies have evaluated the role of positron emission tomography (PET) in patients with NSCLC (9, 10). A correlation between the proliferation of NSCLC and the ^{18}F-fluoro-2-deoxy-glucose (FDG) uptake was observed (11). It was also suggested that low FDG uptake may be associated with favorable outcomes among patients with localized disease (9, 10).

Recently, PET/computed tomography (CT) scans have been introduced, and these can provide both anatomic and functional information in a single imaging session in <30 minutes (12). It is believed that PET/CT is a useful tool of staging work-up in NSCLC patients (13). Lee et al. reported that the maximum standardized uptake value (SUV) in patients with advanced NSCLC might be related to a response to platinum-based cytotoxic treatment (14). However, to our knowledge, such findings have not been evaluated in patients receiving TKI treatment. Thus, we investigated the associations between the SUV on PET/CT and clinical outcomes of patients with gefitinib-treated NSCLC.

Patients and Methods

Patients. All PET studies using a PET/CT scanner in NSCLC patients who received gefitinib treatment between April 2003 and April 2007 were evaluated retrospectively. Eighty-six patients met the following entry criteria: pathologically proved stage IIIb (with pleural effusion and/or positive supraclavicular lymph nodes) or stage IV NSCLC; PET/CT was applied before any therapy was given; histopathology was reviewed at Korea Cancer Center Hospital in Seoul. Two patients with diabetes mellitus were excluded from the study. Sixteen of the

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84 patients were chemotherapy-naive, and 68 patients received up to six cycles of initial cisplatin-based or carboplatin-based chemotherapy combined with one agent of paclitaxel, docetaxel, gemcitabine, or vinorelbine. Patients with progressing disease after initial chemotherapy received subsequent chemotherapy at the discretion of primary physician. As a first to fifth line treatment, gefitinib monotherapy (250 mg/d) was delivered, and in most patients, this was continued until disease progression. Three patients discontinued medication due to development of unacceptable adverse events, such as hepatotoxicity (one patient) and diarrhea (one patient) or refusal (one patient). Chest X-rays were taken every 4 wk. CT scans were done at 4 wk after gefitinib treatment and every 8 wk thereafter. In case of response, confirmation required at least 4 wk of interval. Responses to gefitinib were classified into complete response, partial response, stable disease, and progressive disease using the WHO criteria (15). Performance status was defined according to the Eastern Cooperative Oncology Group classification. The study protocol was reviewed and approved by the institutional review board of the Korea Cancer Center Hospital.

^{18}F-FDG PET/CT. Pretreatment whole-body ^{18}F-FDG PET/CT scans were acquired as a part of staging work-up using a Discovery LS PET/CT scanner (GE Medical Systems) with the protocol of PET/CT scanning used at our institution (16). In brief, whole-body CT was done using helical CT, and then an emission scan was done 50 min after injecting 370 MBq of ^{18}F-FDG i.v. All patients fasted for at least 6 h before PET/CT. The PET images were reconstructed with the OSEM algorithm, and attenuation correction was done using a CT scan. Abnormal FDG uptake was defined as that greater than the background activity in the surrounding tissue, and the intensity of FDG uptake was quantified by calculating the SUV. Region of interest was drawn manually around the primary malignancy with abnormal FDG uptake on transaxial images, which were reconstructed using a Gaussian filter. The SUV was calculated from the amount of FDG injected, total body weight, and soft-tissue uptake in the attenuation-corrected regional images: SUV = (activity / unit volume) / (injected dose / total body weight). The maximum SUV was defined as the peak SUV on one pixel with the highest counts within region of interest. The maximum SUV of the primary site, found on PET image, was selected for further analysis.

Statistical analysis. The categorical variables were analyzed using univariate analysis with a Pearson's χ^2 test or Fisher's exact test. To obtain the cutoff value of SUVs, which is a continuous variable, receiver operating characteristic curve analysis was done. Using this value, patients were divided into groups of those with low or high SUV. Multivariate logistic regression was used to test the association between significant variables in univariate analysis and gefitinib responsiveness. Nonparametric Kruskal-Wallis test was used when appropriate. The progression-free survival (PFS) and overall survival (OS) were calculated from start of gefitinib administration. Kaplan-Meier estimates of PFS and OS were calculated as described (17). Log-rank tests were done for univariate analysis. In addition to performance status, significant factors in univariate analysis were evaluated using the Cox model (18). Odds ratios, hazard ratios, and their 95% confidence intervals (95% CI) were calculated. Stata version 8.2 was used for statistical analyses. All P values were derived from two-sided tests, and $P < 0.05$ was considered significant.

Results

Patient characteristics. The baseline characteristics of the patients are shown in Table 1. Forty-eight (57%) patients were male. The median age was 60 years. Never-smokers comprised 49% of patients. The maximum SUV of 84 patients ranged from 1.6 to 40.1 with median value of 11.3. The response rate (RR) was 25% (21 partial response + no complete response), and the disease control rate was 62% (21 partial response + 31 stable disease). Response to gefitinib was associated with smoking history and pathology (Table 2). Never-smokers showed better response than smokers (RR, 41% versus 9%; $P = 0.001$). Patients with adenocarcinoma showed better response than those with other pathologic types (RR, 35% versus 9%; $P = 0.009$). RR in female and male patients was 33% and 19%, respectively ($P = 0.127$). Stages (III versus IV) and performance status (0-1 versus 2-3) were not significantly associated with gefitinib responsiveness.

SUV and other factors. Associations between the SUV and clinical features were evaluated. The SUVs of smokers (median, 14.0; range, 2.7-40.1) were significantly higher than those of nonsmokers ($P = 0.005$; median, 9.6; range, 1.6-25.2). Patients with adenocarcinoma had low SUVs (median, 8.5; range, 1.6-40.1) compared with patients with other types of histopathology ($P < 0.001$; median 15.4; range, 4.5-38.7). Female patients showed lower SUVs (median, 9.8; range, 2.4-29.9) than male patients ($P = 0.017$; median, 13.2; range, 1.6-40.1). Age (<60 years versus ≥60 years), performance status (0-1 versus 2-3), and stage (III versus IV) were not associated with the SUV (data not shown).

SUV and response. We evaluated associations between the SUV and clinical outcomes in gefitinib-treated patients. According to response type (partial response, stable disease, or progressive disease), patients had significantly different SUVs for primary tumor (medians of 6.8, 9.0, and 15.2, respectively; $P = 0.001$; Fig. 1A). To classify SUVs into two subgroups showing different outcomes, receiver operating characteristic analysis was done using overall response (Fig. 1B). Receiver operating characteristic analysis suggested that the SUV was a reasonable predictor of tumor response to gefitinib (area under curve ± SD, 0.74 ± 0.06). A lower cutoff would capture more gefitinib-responsive patients. To select gefitinib-responsive

Table 1. Patient characteristics

Characteristic	No. patients (%)
Age (y)	
Median	60 (range, 35-76)
<60	42 (50)
≥60	42 (50)
Male	48 (57)
Stage	
IIIB	15 (18)
IV	69 (82)
Smoking history	
Never	41 (49)
Ever	43 (51)
Histopathology	
Adenocarcinoma*	52 (62)
Squamous cell carcinoma	21 (25)
Others	11 (13)
Performance status	
0-1	49 (58)
2-3	35 (42)
Prior treatment	
No	16 (19)
Yes	68 (81)
No. regimens	
1	23
2	31
3	12
4	2
SUV of primary tumor: median	11.3 (range, 1.6-40.1)

*One bronchioloalveolar carcinoma.

Table 2. Clinical predictors for patient response to gefitinib

Characteristic	Univariate analysis		Multivariate analysis	
	Responder (*n*, %)	*P*	Odds ratio (95% CI)	*P*
Age (y)				
<60	11 (26)	0.801	—	
≥60	10 (24)			
Sex				
Male	9 (19)	0.127	—	
Female	12 (33)			
Stage				
IIIB	1 (7)	0.101	—	
IV	20 (29)			
Smoking history				
Never	17 (41)	0.001	Reference	0.008
Ever	4 (9)		0.2 (0.0-0.6)	
Histopathology				
Adenocarcinoma	18 (35)	0.009	Reference	0.183
Other	3 (9)		0.4 (0.1-1.6)	
Performance status				
0-1	12 (24)	0.898	—	
2-3	9 (26)			
Prior treatment				
No	7 (44)	0.054	—	
Yes	14 (21)			
SUV				
Low (<6.2)	9 (53)	0.003	Reference	0.018
High (≥6.2)	12 (18)		0.2 (0.1-0.8)	

patients efficiently, cutoff values required sensitivity of >80% with a loss of specificity (19). Among these values, the SUV of 6.2, which gave maximum sensitivity and specificity (87% and 43%, respectively), was chosen for further analysis. Using this value, 17 patients (20%) had tumors with low SUV (<6.2). These patients showed with higher RR than those with high SUV (53% versus 18%, respectively; $P = 0.003$). Multivariate analysis, which was corrected for smoking history and pathology, revealed that a high SUV was associated with reduced gefitinib responsiveness ($P = 0.018$; Table 2).

SUV and survival outcome. The median PFS of all patients was 12 weeks (95% CI, 8.1-16.6 weeks). Predictors for PFS were evaluated in univariate and multivariate analysis (Table 3). Never-smokers had prolonged PFS compared with ever-smokers ($P = 0.002$). Adenocarcinoma was a favorable prognostic factor in terms of PFS ($P = 0.003$). Patients with a low SUV showed longer PFS than those with a high SUV ($P = 0.003$; Fig. 1C). According to performance status (0-1 versus 2-3), the survival difference did not reach statistical significance ($P = 0.175$). Age (≤60 years versus >60 years) and sex did not confer statistically different outcomes in terms of PFS ($P = 0.987$ and 0.427, respectively). When analysis was conducted controlling for smoking history, performance status, and histopathology, patients with a low SUV showed favorable outcomes ($P = 0.012$).

When OS was analyzed, the median survival time was 30 weeks (95% CI, 21.6-43.6 weeks). Never-smokers had prolonged survival compared with smokers ($P = 0.043$). Adenocarcinoma and good performance status (≤1) were favorable factors with statistical significance ($P = 0.009$ and 0.002, respectively). Low SUVs conferred prolonged survival times compared with high SUVs ($P = 0.011$; Fig. 1D). After adjustment for factors, such as smoking history, performance status, and histopathology, patients with a low SUV had favorable survival ($P = 0.043$).

Discussion

We retrospectively evaluated PET/CT findings in patients with gefitinib-treated NSCLC. To our knowledge, this is the first study to evaluate SUVs and their association with clinical outcomes. It seems clear that some subgroups might respond to TKI or show a survival benefit in patients with NSCLC. The current study shows that favorable responses or survival occur in patients with no smoking history, adenocarcinoma, and good performance status. Such findings were observed in previous studies for TKI-treated NSCLC patients (20–23). Although epidermal growth factor receptor mutations or gene copy number could predict responsiveness to TKI (7, 8), genetic testing, frequently unavailable in clinical practice, was beyond the scope of this study.

In our study, PET images using a PET/CT scanner were evaluated at the time of diagnosis. Low SUVs were observed in patients with adenocarcinoma, never-smokers, and are female, which were predictable factors in previous studies (20–23). As expected, we observed that SUVs at presentation were different according to response to gefitinib (Fig. 1A). Patients with low and high SUVs were classified using a cutoff value from receiver operating characteristic analysis, and they showed different clinical outcomes. Importantly, the SUVs remained significant in multivariate analysis of tumor responsiveness and survival. These findings suggest that the SUV may be used as an independent predictor of outcomes along with the clinical features reported previously (20–23).

There are some arguments in terms of changing continuous to categorical variables (24). However, when SUVs were analyzed as a continuous variable, SUVs were significantly associated with RR and survival (odds ratio for objective response 1.17, $P = 0.005$; hazard ratio for PFS 1.04, $P < 0.001$; hazard ratio for OS 1.04, $P = 0.008$). It is believed that patient-related factors

other than statistical methods might explain the clinical outcomes in this study more accurately.

In our data, primary tumors were larger than 1.7 cm on CT. Considering the resolution of PET/CT at our institution (5.4 mm at the full-width at half-maximum), the results of this study are unlikely to have been altered by partial volume effects (25). In addition to tumor-related factors, SUVs can be affected by various factors (e.g., reconstruction methods, blood sugar level, and the dose of FDG; ref. 26). Further studies for standardized methods to obtain SUV, including optimal cutoff values, should be conducted.

There are rare data to suggest that the SUV at presentation is associated with TKI responsiveness. However, our findings are in line with the result of a previous study that reported a low SUV at the time of diagnosis in a pathologic subtype of bronchioloalveloar carcinoma (27), another predictor of TKI responsiveness (20). Interestingly, we observed that the SUV of never-smokers was lower than that of smokers. Toh et al. reported different clinical features according to smoking history (28). Also, previous studies have suggested that cancer cells in patients with a never-smoking history, compared with patients who are smokers, may undergo different genetic changes, including changes in the TKI-binding region (7, 29). Considering the favorable outcomes in patients with a low SUV (9, 10), we speculate that low SUVs might reflect a less aggressive biology of TKI-responsive tumors. However, to our knowledge, there is no published literature to suggest that genetic changes, such as mutations of the TKI-binding domain might be related to FDG uptake of tumors. Further studies, including laboratory tests, are warranted.

Some authors have reported an association between high SUV and favorable response to cytotoxic agents (14). Similarly,

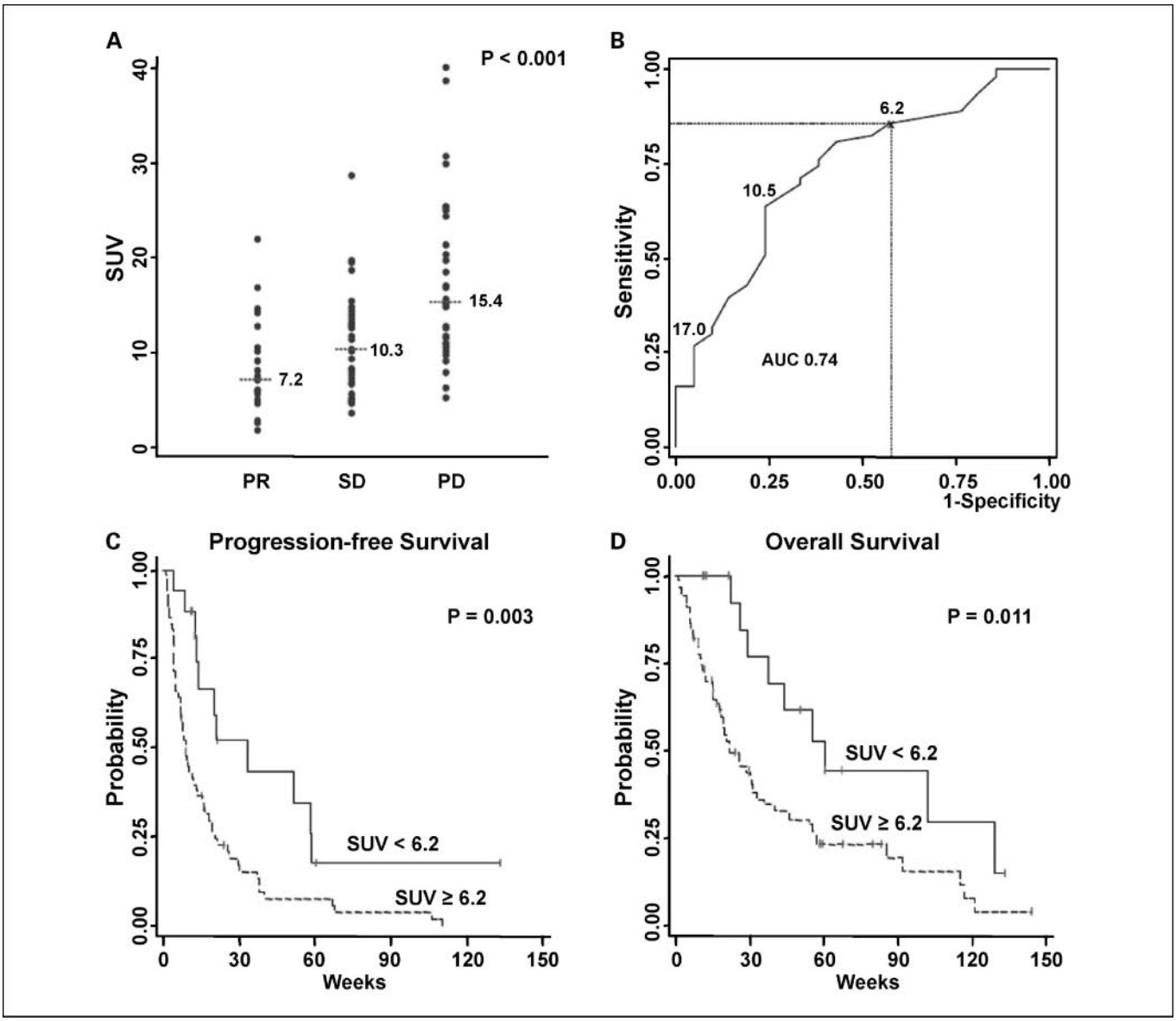

Fig. 1. *A,* the maximum SUV of primary lung lesion according to response to gefitinib. *B,* receiver operating characteristic curve of the SUV predictable for gefitinib-responsiveness. Lower cutoffs indicate a higher probability of response. A cutoff value of 6.2 was selected. *C,* Kaplan-Meier plots of PFS according to the SUV. *D,* Kaplan-Meier plots of OS according to the SUV. Horizontal line, median; AUC, area under curve; CR, complete response; PR, partial response; SD, stable disease.

Table 3. Results of survival analysis

Characteristic	Median PFS (95% CI, wk)	*P*	Hazard ratio (95% CI)	*P*	Median OS (95% CI, wk)	*P*	Hazard ratio (95% CI)	*P*
Age (y)								
≤60	11.1 (7.4-19.0)	0.987	—		30.9 (21.6-55.3)	0.610	—	
>60	12.0 (6.9-19.0)				30.0 (17.4-46.0)			
Sex								
Male	10.1 (6.9-16.6)	0.427	—		25.3 (19.0-36.7)	0.305	—	
Female	13.0 (6.9-38.0)				43.6 (25.6-102.0)			
Stage								
IIIB	7.6 (2.4-15.4)	0.105	—		20.4 (8.7-31.0)	0.120	—	
IV	12.0 (8.3-20.4)				32.9 (22.0-56.6)			
Smoking history								
Never	25.6 (9.6-38.0)	0.002	Reference	0.012	46.0 (25.6-85.4)	0.043	Reference	0.046
Ever	8.6 (4.7-12.3)		1.9 (1.2-3.2)		22.0 (15.3-30.9)		1.9 (1.0-3.4)	
Histopathology								
Adenocarcinoma	18.0 (9.6-29.4)	0.003	Reference	0.061	37.6 (21.6-85.4)	0.009	Reference	0.045
Other	8.1 (4.7-13.0)		1.7 (1.0-2.9)		21.9 (12.1-31.0)		1.9 (1.0-3.7)	
Performance status								
0-1	13.3 (8.6-20.4)	0.175	Reference	0.067	54.1 (26.1-85.4)	0.002	Reference	<0.001
2-3	8.6 (6.3-16.0)		1.6 (1.0-2.5)		18.3 (10.4-28.6)		3.3 (1.8-5.8)	
Prior treatment								
No	15.4 (>4.7)	0.511	—		28.6 (>12.1)	0.911	—	
Yes	11.1 (7.6-16.6)				30.9 (21.6-43.6)			
SUV								
Low (<6.2)	33.1 (13.0-58.9)	0.003	Reference	0.012	60.4 (29.1-128.9)	0.011	Reference	0.043
High (≥6.2)	8.6 (6.7-13.0)		2.3 (1.2-4.5)		21.9 (17.4-32.9)		2.2 (1.0-4.5)	

when response to initial chemotherapy was analyzed in 68 patients, objective tumor RRs with initial cytotoxic chemotherapy were higher among patients with a high SUV (56%; 30 of 54 patients) than patients with a low SUV (29%; 4 of 14 patients); however, this difference was not statistically significant ($P = 0.072$). It seems contradictory that cytotoxic chemoresponsiveness, a favorable prognostic factor (30), may be associated with high SUV, which has been reported as an unfavorable prognostic factor (10) Comprehensive studies need to evaluate that outcomes according to types of chemotherapeutic agents may be affected by SUVs.

In this study, the SUV of primary site was selected for analysis according to the method as previous studies for localized disease was done (10). In fact, we evaluated the SUVs of all cancerous lesions on CT (longest diameter, >1 cm) and in the majority of cases (77 cases), the SUV of primary lesion was the highest one in each patient, as has been observed elsewhere (14). Even when the highest one was used for statistical analysis, clinical significance of the SUV remained (data not shown). However, the SUV of primary site seems to be easily evaluated in clinical practice.

Besides being retrospective with a small sample size, there are some limitations in our study. Timing of gefitinib delivery, another limitation of this work, differed between patients because of various courses of cytotoxic treatment, which has also been reported in previous studies (21, 23). In the current study, groups of chemonaive and chemotherapy-pretreated patients did not show statistically different outcomes. It should be considered that different outcomes according to types of previous treatment were not suggested in previous studies (21, 23).

In conclusion, the present study suggests that low SUVs at presentation can predict favorable response and survival in patients with NSCLC treated with gefitinib. Thus, SUVs might help identify patients who benefit from TKI treatment, but a large prospective study is required to confirm this.

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