[^{18}F]Fluorothymidine Positron Emission Tomography before and 7 Days after Gefitinib Treatment Predicts Response in Patients with Advanced Adenocarcinoma of the Lung

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Abstract

Purpose: To evaluate the usefulness of 3′-deoxy-3′-[^{18}F]fluorothymidine (FLT)-positron emission tomography (PET) for predicting response and patient outcome of gefitinib therapy in patients with adenocarcinoma of the lung.

Experimental Design: Nonsmokers with advanced or recurrent adenocarcinoma of the lung were eligible. FLT-PET images of the thorax were obtained before and 7 days after the start of gefitinib (250 mg/d) therapy, the maximum standardized uptake values (SUVmax) of primary tumors were measured, and the percent changes in SUVmax were calculated. After 6 weeks of therapy, the responses were assessed by computed tomography of the chest.

Results: Among 31 patients who were enrolled, we analyzed 28 patients for whom we had complete data. Chest computed tomography revealed partial response in 14 (50%), stable disease in 4 (14%), and progressive disease in 10 (36%) after 6 weeks of treatment. Pretreatment SUVmax of the tumors did not differ between responders and nonresponders. At 7 days after the initiation of therapy, the percent changes in SUVmax were significantly different (-36.0 $\pm$ 15.4% versus 10.1 $\pm$ 19.5%; $P < 0.001$). Decrease of >10.9% in SUVmax was used as the criterion for predicting response. The positive and negative predictive values were both 92.9%. The time to progression was significantly longer in FLT-PET responders than nonresponders (median, 7.9 versus 1.2 months; $P = 0.0041$).

Conclusion: FLT-PET can predict response to gefitinib 7 days after treatment in nonsmokers with advanced adenocarcinoma of the lung. The change in tumor SUVmax obtained by FLT-PET seems to be a promising predictive variable.

Morphologic imaging techniques such as computed tomography (CT) have been standard methods for assessing tumor response to treatment. Changes in size, however, are often delayed; hence, morphologic imaging is usually repeated after at least 6 weeks of therapy. This causes difficulties in assessing the early treatment response and hinders rapid decisions by clinicians regarding a change in therapy for nonresponders. Moreover, in the case of cytostatic agents, tumors may not regress radiologically despite effective treatment. These limitations could be overcome by using functional imaging techniques such as positron emission tomography (PET), because metabolic and physiologic changes in the tumor are likely to precede changes in size (1). The most widely used PET tracer is [^{18}F]fluorodeoxyglucose (FDG), which reflects cell metabolism. However, FDG is not highly tumor specific and is also taken up by inflammatory cells such as macrophages (2).

Recently, 3′-deoxy-3′-[^{18}F]fluorothymidine (FLT) was introduced as a PET tracer for imaging tumor proliferation. FLT is phosphorylated by thymidine kinase 1, the key enzyme of the salvage pathway of DNA synthesis, and then trapped in the cell with little further metabolism (3). Thymidine kinase 1 is selectively up-regulated during the S phase of the cell cycle (4). Therefore, FLT uptake is dependent on cell proliferation. In lung tumors, FLT uptake correlated better than FDG uptake with the proliferation activity (Ki-67; ref. 5), and the decrease in FLT uptake after treatment is more rapid than that in FDG uptake in preclinical models (6–8). Clinical studies have reported that FLT uptake in lung cancer was lower than FDG uptake but was specific for malignant tumors (9, 10). Several studies have reported that FLT-PET is useful for the early evaluation of tumor response to anticancer drugs (11, 12).

Gefitinib is an inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase that yielded objective response rates of 9% to 19% in patients with previously treated advanced non-small cell lung cancer (13, 14). Higher response rates were

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Received 2/5/08; revised 7/23/08; accepted 8/1/08.

Grant support: National Cancer Control R&D Program 2003, Ministry of Health & Welfare, Republic of Korea grant 0320280-2.

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Note: H-J. Sohn and Y-J. Yang contributed equally to the work as the first authors.

Previous presentation: Presented in part at the 11th World Conference on Lung Cancer, Barcelona, Spain, July 3-6, 2005.

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doi:10.1158/1078-0432.CCR-08-0312

Translational Relevance

This article is to see whether the FLT-PET scan examined before and 7 days after gefitinib treatment has a role of predicting response to gefitinib early during treatment in patients with non-small cell lung cancer. As already known, gefitinib is a targeted agent that works much better in selective patients who harbor some molecular markers such as EGFR mutation, etc. Because the detection of such molecular markers requires sufficient biopsy specimens and test time in practice, not all patients are fitted to such examinations. We expect FLT-PET scan may replace such procedures and helps the clinicians decide the right treatment for patients with non-small cell lung cancer, as it can detect proliferation status of tumor early during treatment. Nowadays, as so many new targeted agents are being developed, these methods using FLT-PET scan may help such translational research and development and save the time.

observed in a subset of patients with female gender, Asian ethnicity, no smoking history, and adenocarcinoma histology (13–15). Other markers such as mutations in EGFR tyrosine kinase (16–19), EGFR gene amplification (20, 21), EGFR overexpression on immunohistochemistry (20), and Akt activation (22) have also been reported to be associated with therapeutic benefit. However, the therapeutic effect of gefitinib is not confined to patients whose tumors harbor EGFR mutations and other predictors of efficacy of this agent (16, 20–22). For instance, the positive predictive values of EGFR mutation were only 53% to 82% (16, 20, 21). These tests require time and sufficiently large specimens for processing, whereas many patients with advanced non-small cell lung cancer are diagnosed based on cytology alone.

This study was prospectively done to evaluate FLT-PET usefulness in the early assessment of treatment response and in predicting patient outcome after gefitinib monotherapy for nonsmokers with advanced adenocarcinoma of the lung. Changes in tumor FLT uptake 7 days after the initiation of treatment were compared between responders and nonresponders based on subsequent CT scans, and a cutoff value was proposed for response prediction.

Patients and Methods

Patients. Eligibility criteria included lifetime nonsmoker, pathologically confirmed adenocarcinoma of the lung, stage IIIB (with malignant pleural effusion) or IV disease, bidimensionally measurable lesion(s), age 18 to 80 years, and Eastern Cooperative Oncology Group performance status of 0 to 2. Patients were also required to have adequate bone marrow, hepatic, and renal functions defined as WBC $>4.0 \times 10^9$/L, neutrophils $>1.5 \times 10^9$/L, platelets $>100 \times 10^9$/L, hemoglobin >10 g/dL, alanine aminotransferase or aspartate aminotransferase <2 times the upper normal limit, serum bilirubin <1.2 mg/dL, and serum creatinine <1.5 mg/dL. Patients with prior chemotherapy or radiotherapy were eligible if there was a treatment-free interval of at least 1 month. The study protocol was approved by the Institutional Review Board of Asan Medical Center, and written informed consent was obtained from all patients.

Treatment. Gefitinib in a dosage of 250 mg/d was administered orally 30 min after breakfast until disease progression, unacceptable toxicity, or patient refusal. Each cycle consisted of 3 weeks of therapy, and administration could be interrupted for a maximum of 14 days.

FLT-PET imaging. Baseline FLT-PET was done 1 day before initiation of gefitinib therapy, and second FLT-PET was repeated at 7 days after initiating therapy. FLT was prepared from two-step synthesis method. We used 40 mg (5′-*O*-DMTr-2′-deoxy-3′-*O*-nosyl-β-D-threo-pentofuranosyl)-3-*N*-BOC-thymidine as precursor for [^{18}F]fluorination. After hydrolysis, we had high-performance liquid chromatography purification with ethanol/H_2O (1:9) solvent condition. All procedures were done with TracerLab MX (GEMS Benelux) FDG module as described previously (23). Decay-corrected radiochemical yield was 45.7 ± 5.7% with radiochemical purity of 98.2 ± 1.2% and specific activity of 3,225 to 7,672 Ci/mmol from the end of bombardment. PET images of the thorax were obtained using a PET-CT scanner (Biograph Sensation 16; Siemens) 1 h after intravenous injection of ~555 MBq FLT. CT images for attenuation correction were acquired during shallow breathing in a spiral mode. PET images of the chest field were acquired with 5 min of emission scan per bed for 4 bed positions, corrected for attenuation based on the CT data, and reconstructed by Fourier rebinning followed by attenuation-weighted ordered subset expectation maximization reconstruction with 2 iterations and 16 subsets.

For quantitative image analyses of tumor FLT uptake, the volume of interest was drawn semiautomatically over the main lung mass by using the vendor's software (Esoft 3.5; Siemens). The maximum standardized uptake value (SUVmax) was calculated using the single maximum pixel count within the volumes of interest, and the SUV75 was calculated using the average counts within threshold-defined volumes of interest that only included pixels greater than 75% of the maximum value within a lesion. All SUVs were normalized to the injected dose and patient body weight. Then, the percent changes in the SUVs between baseline and second PET images were calculated.

Response evaluation and follow-up. Chest CT scans were done within 4 weeks before enrollment and repeated after 6 weeks of gefitinib therapy. None of the patients received additional diagnostic CT at day 7. Tumor response was assessed according to the WHO criteria (24) without knowledge of the results of FLT-PET studies. We correlated the results with the changes in FLT uptake.

Patients with no tumor progression underwent further therapy, and chest CT was done every 6 weeks. Survival times were measured from the date of the therapy to the first occurrence of an important event (documented disease progression or death). If a patient was lost to follow-up, that patient was censored at the last date of contact.

Statistical analysis. The primary endpoint of the study was the comparison between early changes in FLT uptake of the primary tumor at 7 days after initiating gefitinib therapy and subsequent CT response at 6 weeks. All quantitative data were expressed as mean ± SD. Mann-Whitney *U* and Wilcoxon signed rank tests were used for unpaired and paired observations, respectively. Spearman's rank correlation coefficient (ρ) was used to describe the correlation between quantitative variables. We performed receiver operating characteristic curves analysis (25) for FLT-PET with regard to predicting the response to gefitinib therapy. Median overall survival (OS) and time to progression (TTP) were estimated according to the Kaplan-Meier method. Survival of FLT-PET responders and nonresponders, as determined according to the set cutoff value, was compared by the log-rank test. Cox proportional hazards model was used to see whether there is a quantitative relationship between the change in SUVmax and survival. $P \leq 0.05$ was considered to indicate a statistically significant difference. Statistical computations were done using the software SPSS for Windows version 12K (SPSS).

Results

Patient characteristics and response assessment by CT. Between August 2003 and March 2005, a total of 31 patients

Table 1. Patient characteristics and CT response to gefitinib

	Patients, *n* (%)
Total no. patients	28
Age, y	
Median	58
Range	40-76
Sex	
Female	23 (82)
Male	5 (18)
Histology	
Adenocarcinoma only	22 (79)
Adenocarcinoma with bronchioloalveolar carcinoma features	6 (21)
Stage	
IV	28 (100)
No. prior chemotherapy	
0	17 (61)
1	3 (11)
2	8 (28)
CT response to gefitinib	
Complete response	0 (0)
Partial response	14 (50)
Stable disease	4 (14)
Progressive disease	10 (36)

were enrolled in this study and underwent baseline and follow-up PET scanning. Among them, 3 patients were not included in this analysis due to the following reasons: misregistration of PET-CT with error in quantitation due to respiratory motion error in 1 patient and no follow-up PET examination in 2 patients who did not attend after treatment. The time interval between FLT injection and acquisition of PET transmission scans was 64 ± 10 min (range, 50-91 min). The acquisition time difference between baseline and follow-up PET scan after FLT injection in the same patient was 12 ± 10 min (range, 0-35 min). Patient characteristics are shown in Table 1. There were 23 (82%) women and 17 (61%) previously untreated patients. CT responses of the patients were partial response in 14 (50%), stable disease in 4 (24%), and progressive disease in 10 (36%). We considered patients with partial response as responders (n = 14) and all the others as nonresponders (n = 14) to gefitinib.

Early therapy response assessment by FLT-PET. The mean size of primary tumor was 4.7 ± 2.1 cm in greatest diameter. There was no relation between tumor size and ability to detect difference in SUV. Pretreatment SUVmax and SUV75 of the tumor did not differ between responders and nonresponders. As there was a good correlation (r = 0.99) between SUVmax and SUV75, we used the SUVmax as representative variable for further analysis. During treatment, SUVmax measured at 7 days after gefitinib therapy revealed a clear difference between responders and nonresponders on subsequent CT scans (Fig. 1). In responders by CT scan, tumor SUVs decreased significantly after 7 days of treatment (SUVmax = 3.2 ± 1.0 versus 2.0 ± 0.7; P < 0.001). In nonresponders by CT scan, however, there were no significant changes in tumor SUVs before and during gefitinib treatment (SUVmax = 4.0 ± 1.9 versus 4.3 ± 1.9; P = NS). Percent changes in SUVmax were significantly different between responders and nonresponders (-36.0 ± 15.4% versus 10.1 ± 19.5%; P < 0.001). Images of representative cases are shown in Fig. 2. Baseline SUVmax of the 4 patients with stable disease was not different from patients with partial response or progressive disease (3.0 ± 0.7 versus 3.2 ± 1.1 versus 4.3 ± 2.0; P = NS). Percent changes in SUVmax were not significantly different between stable disease and progressive disease (20.9 ± 10.8% versus 6.0 ± 18.9%; P = 0.169; Fig. 3).

Receiver operating characteristic curve (Fig. 3A) showed that the percent decrease in SUVmax was a good variable for distinguishing between responders and nonresponders to gefitinib. A threshold of >10.9% decrease of SUVmax from

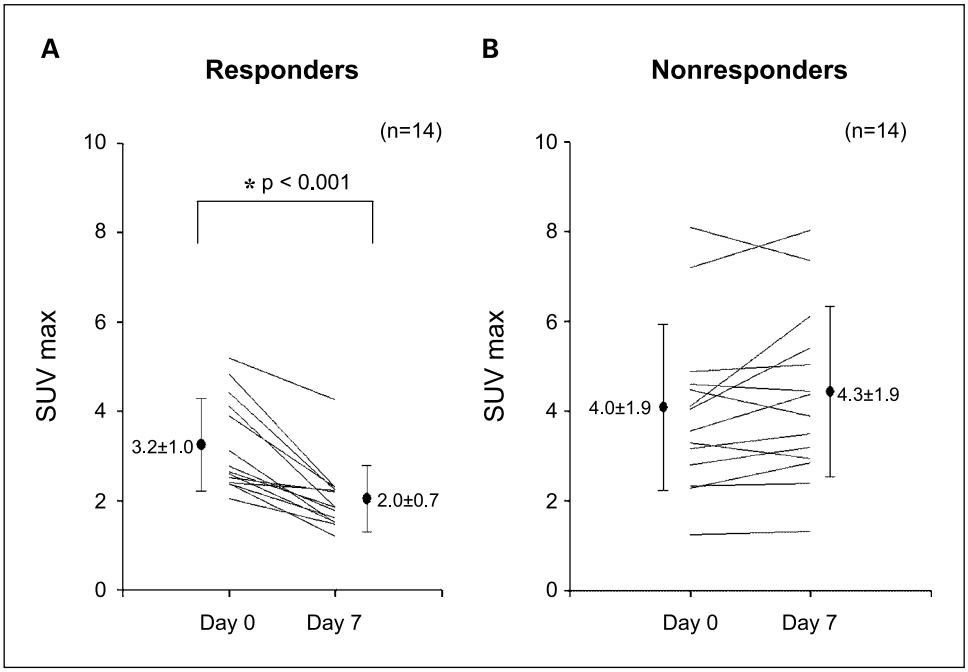

Fig. 1. *A* and *B,* changes in the SUVmax of a primary tumor 7 d after initiating gefitinib therapy. Significant decrease in the SUVmax of the responders (*A*) but no difference in the SUVmax of the nonresponders (*B*).

the baseline tumor FLT uptake would be optimal for differentiation between responders and nonresponders, resulting in 92.9% [95% confidence interval (95% CI), 66.1-98.8] sensitivity and 92.9% (95% CI, 66.1-98.8) specificity (Fig. 3B). Using this cutoff value, 14 patients were grouped as FLT-PET responders and 14 as FLT-PET nonresponders (Table 2). Subsequently, 13 of the 14 FLT-PET responders were classified as responders by using CT. Therefore, positive predictive value was 92.9%. In contrast, only 1 of the 14 FLT-PET nonresponders achieved a partial response, resulting in a high negative predictive value of 92.9%. When we set cutoff value as >15% or 20% decrease of SUVmax from baseline, the positive predictive values improved to 100% each, but the sensitivities deteriorated as 85.7% and 78.6%, respectively.

One FLT-PET responder with SUVmax reduction of 13% was not identified as a responder by CT. In this patient, the diameter of the primary tumor remained unchanged and the pleural lesions progressed. One responder who was not classified as a FLT-PET responder showed a 7.5% decrease in SUVmax.

Survival according to FLT-PET response. Median follow-up time was 26.8 months (range, 23.2-42.1 months). During this period, 20 patients died, and tumor progression has been observed in 27 patients. The median TTP was 4.2 months (95% CI, 1.5-6.9), and the median OS was 10.8 months (95% CI, 4.4-17.2). For patients with FLT-PET response, the median TTP was 7.9 months (95% CI, 4.5-11.3), whereas it was only 1.2 months (95% CI, 1.1-1.2) for patients with a less pronounced decrease in SUVmax ($P = 0.0041$; Fig. 4A). Further analysis using Cox proportional hazards model showed that hazard ratio for TTP was 1.18 (95% CI, 1.02-1.37) with 10% change in SUVmax as a continuous variable ($P = 0.03$). The median OS for patients with and without FLT-PET response was 20.8 months (95% CI, 1.9-39.7) and 8.9 months (95% CI, 2.0-15.7), respectively ($P = 0.26$; Fig. 4B). When we set cutoff value of FLT-PET response as >15% or 20% decrease of SUVmax from baseline, TTP and OS curves showed similar trends.

Discussion

Although the response rate of gefitinib in the patients with advanced non-small cell lung cancer is only 9% to 19% (13, 14), it may be a more effective initial therapy than platinum-based cytotoxic chemotherapy in selected patients. Moreover, it can also be considered as a treatment option for patients who are aged or showing poor performance. We aimed to determine whether FLT-PET imaging could be used to predict clinical responses of advanced adenocarcinoma of the lung to gefitinib. This prospective study showed that it was possible to differentiate between responders and nonresponders only 7 days after initiating gefitinib therapy by using FLT-PET scans.

In our study, patients with adenocarcinoma and nonsmoking history were enrolled to enrich the patient population responsive to gefitinib (26), and the resultant response rate was 50%. When decrease of >10.9% in the baseline SUVmax obtained by FLT-PET was used as the threshold for a FLT-PET

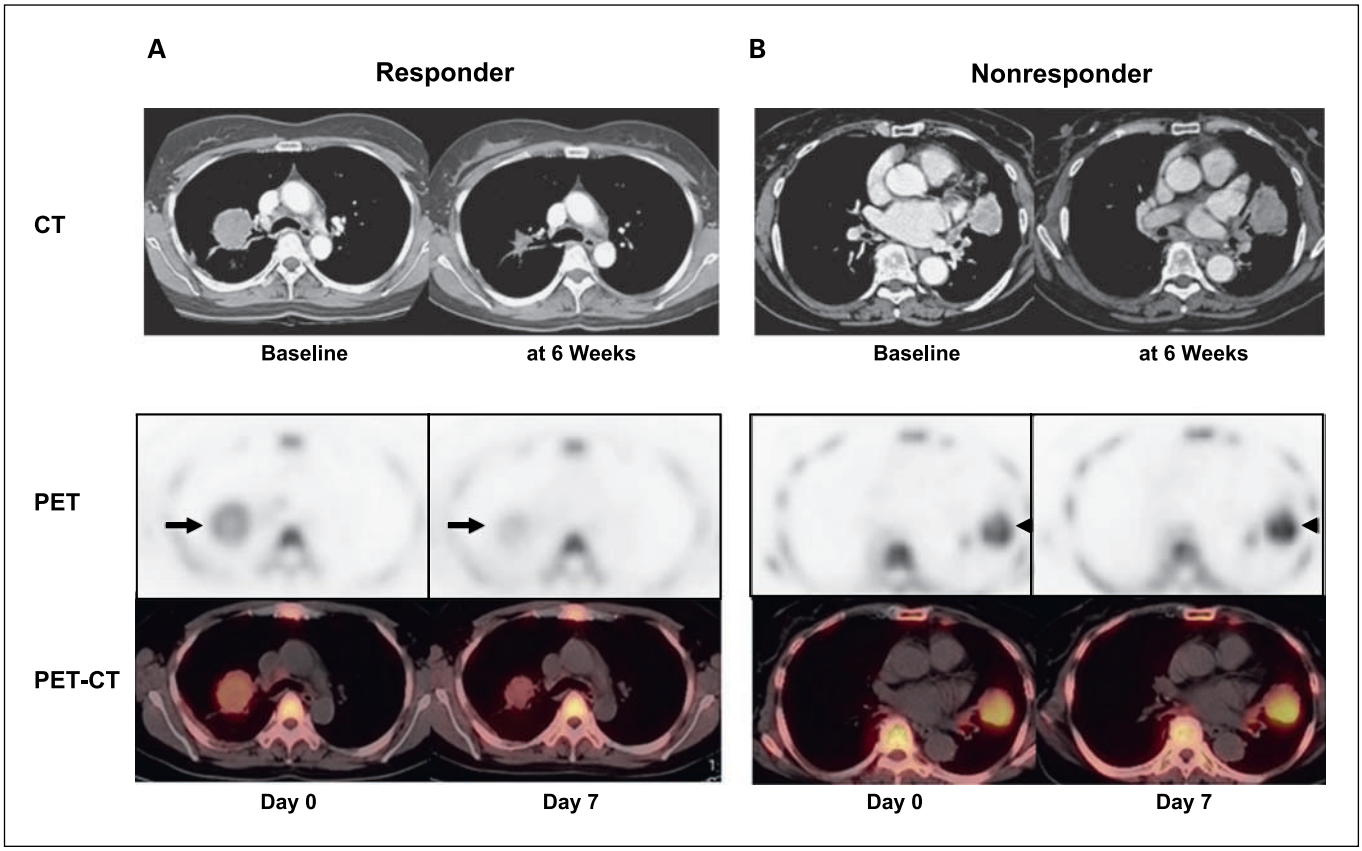

Fig. 2. PET images of a patient (*A*) show markedly decreased FLT uptake (SUVmax = 4.8 → 2.3) at 7 d after gefitinib therapy. The subsequent CT scan at 6 wk reveals tumor shrinkage. PET images of another patient (*B*) show no visible change at 7 days after gefitinib therapy (SUVmax = 7.2 → 8.0) and increase in tumor size at 6 wk.

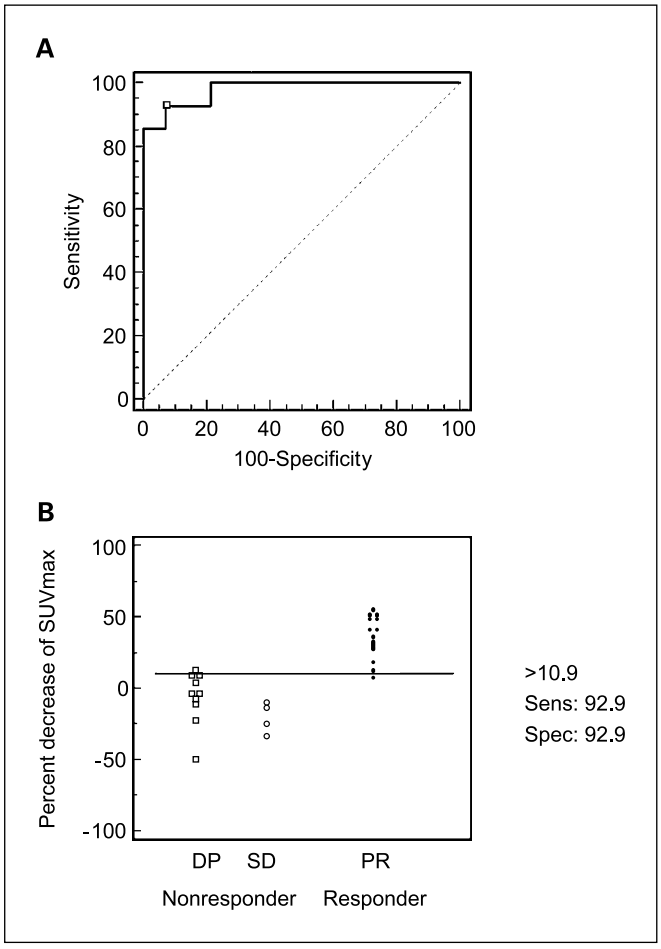

Fig. 3. *A,* receiver operating characteristic curve for predicting the response to gefitinib therapy. Areas under the curve are 0.980 for percent change of SUVmax. *B,* percent decrease in the SUVmax. A decrease in the SUVmax of >10.9% is considered as cutoff value for predicting the response to gefitinib therapy.

response, the positive and negative predictive values for prediction of the CT response were both 92.9%. Moreover, median TTP was significantly longer in FLT-PET responders. These findings indicate that FLT-PET imaging may be used to predict the clinical outcome of gefitinib therapy at an early stage of treatment.

FDG-PET is also used for the diagnosis and staging of malignant tumors and to monitor treatment efficacy in various cancers (27, 28). Because FLT uptake correlates with cellular proliferation (7), FLT-PET may be a superior examination for response assessment than FDG-PET. FDG uptake is influenced not only by tumor glucose metabolism but also by several other factors such as inflammation (2), hypoxia (29), and fasting time or serum glucose level (30). However, tumor FLT uptake is generally lower than FDG uptake (9) and there is a late downward curvature in the FLT uptake curves due to tumor loss of phosphorylated FLT nucleotide (31). Kinetic analysis may allow more accurate measurement of FLT flux (31). A recent study with gefitinib treatment have shown that changes in FDG metabolism preceded changes in cell cycle distribution, thymidine uptake, and apoptosis in cultured cell lines and animal models (32). Although FLT metabolism is potentially more tumor-specific than glucose metabolism and may reflect more directly tumor response to therapy, further studies are needed to determine whether FLT-PET is superior to FDG-PET for monitoring response and predicting survival early after the initiation of therapy for lung cancer.

There are several points that should be clarified. First, we used a post hoc definition of the criterion for predicting the treatment response. Validation studies should be conducted. More than 10.9% decrease of SUVmax after treatment is a significant change. When we checked reproducibility of FLT-PET, the mean percent difference of test-retest values of

Table 2. Correlation between the FLT-PET response and subsequent CT response according to the WHO criteria (n = 28)

CT response	*n*	FLT-PET response	
		Responders	Nonresponders
Responders			
Complete response	0	0	0
Partial response	14	13	1
Nonresponders			
Stable disease	4	0	4
Progressive disease	10	1	9

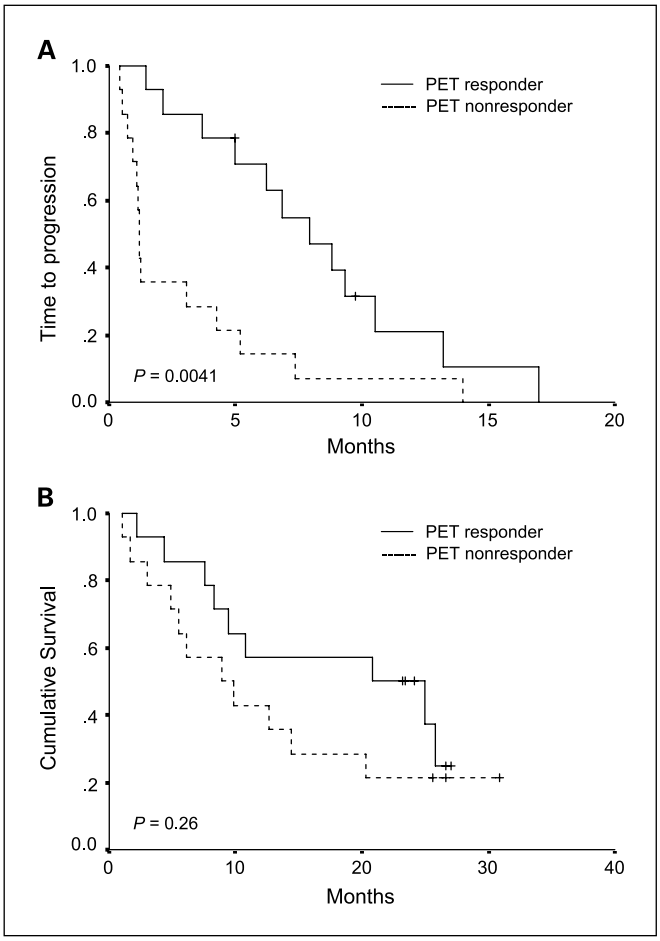

Fig. 4. Kaplan-Meier plots showing (*A*) TTP and (*B*) OS according to FLT-PET response.

SUVmax in the main lung mass was 2.03 ± 8.43% (n = 12; ref. 33). Second, we used SUVmax and SUV75 instead of mean SUV. It was difficult to define accurate tumor boundary on PET image manually. When there was tumor necrosis, it might cause underestimation of mean FLT uptake. We thought the values of mean SUV with manually defined region of interest might result in greater intraobserver and interobserver variation and be inappropriate for response monitoring. These variations in calculation of SUVmax or SUV75 were negligible. Third, the acquisition time difference between baseline and follow-up PET scan after FLT injection in the same patient was 12 ± 10 min. As the SUV of tumor changes with time after FLT injection (31) and the variability in injection time to scan may be the source of variability in SUV measurement, FLT-PET should be done at a constant time interval after FLT injection as like in FDG-PET (34). Fourth, the OS of FLT-PET responders was not statistically longer than that of FLT-PET nonresponders. This may be due to the small number of patients in this study and salvage treatment after failure of gefitinib therapy. In our study, 12 of 28 patients received salvage chemotherapy (7 patients in responders and 5 in nonresponders). Fifth, it was not possible to predict stable disease after 7 days of gefitinib treatment, because only 4 patients showed stable disease and they showed increased mean percent change in SUVmax by 20% (Fig. 3). In Iressa Survival Evaluation in Lung Cancer study, where gefitinib treatment was compared with best supportive care in previously treated patients with non-small cell lung cancer, the proportion of stable disease was 31% in the best supportive care group and 32% in the gefitinib group (35). Therefore, some stable disease might not derive from the effect of gefitinib. Stable disease might be a heterogenous category that depends on the proliferative and apoptotic activity of tumor. However, FLT-PET reflects only the proliferative activity of tumor. In a FDG-PET study for lung cancer, only 7 of 17 patients with stable disease showed a metabolic response (36). Therefore, assessment of disease stabilization may be still insufficient with FLT-PET and further studies with a larger number of patients are required.

To date, only a few preliminary reports have described the use of FLT-PET for monitoring tumor response to anticancer therapy (11, 12, 37). In one study, FLT-PET can detect changes in breast cancer proliferation at 1 week after chemotherapy and discriminate between clinical response and stable disease (12). Similar results reported with high-grade non-Hodgkin's lymphoma (11) and malignant glioma (37). Our data are consistent with the above-mentioned clinical studies and preliminary reports done using animal tumor models (38–40). This study showed the potential of FLT-PET for the early prediction of treatment response and patient outcome in patients with non-small cell lung cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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