High Fluorodeoxyglucose Uptake on Positron Emission Tomography in Patients with Advanced Non–Small Cell Lung Cancer on Platinum-Based Combination Chemotherapy

Kyung-Hun Lee,[1] Se-Hoon Lee,[1,3] Dong-Wan Kim,[1,3] Won Jun Kang,[2] June-Key Chung,[2] Seock-Ah Im,[1,3] Tae-You Kim,[1,3] Young Whan Kim,[1] Yung-Jue Bang,[1,3] and Dae Seog Heo[1,3]

Abstract

Purpose: To evaluate response and survival for platinum-based combination chemotherapy in chemonaive patients with non–small cell lung cancer (NSCLC) according to pretreatment standardized uptake values (SUV) by fluorodeoxyglucose positron emission tomography.

Experimental Design: Patients with advanced NSCLC who had not previously received chemotherapy were eligible. Response rates and survivals were analyzed according to maximal SUVs [low (≤7.5) versus high (>7.5), where 7.5 was the median value] before the first cycle of chemotherapy.

Results: Eighty-five consecutive patients were included in the retrospective study. Patients with high SUV tumors exhibited significantly higher response rates (34.1% for low SUVs versus 61.0% for high SUVs; $P = 0.013$). Other factors, including sex, age, histology, performance status, number of involved organs, regimens used, and disease stage, did not affect response. However, high SUVs were related with a shorter response duration (279 days for low SUVs versus 141 days for high SUVs; $P = 0.003$) and time to progression (282 days for low SUVs versus 169 days for high SUVs; $P = 0.015$). Overall survival was unaffected by maximal SUVs (623 days for low SUVs versus 464 days for high SUVs; $P = 0.431$).

Conclusions: Patients having NSCLC with high maximal SUVs showed a better response to platinum-based combination chemotherapy but had a shorter time to progression. Tumor glucose metabolism, as determined by SUVs on fluorodeoxyglucose positron emission tomography, was found to discriminate NSCLC subsets with different clinical and biological features.

Primary lung cancer is the leading cause of cancer deaths in Korea as well as in the United States (1, 2). Two thirds of patients with newly diagnosed non–small cell lung cancer (NSCLC) have inoperable disease, including locally advanced or metastatic tumors, and many patients who undergo curative surgery suffer from recurrent NSCLCs (3). Platinum-based chemotherapy is a well-established first-line therapy in the palliative setting for patients with advanced disease, as it improves the quality of life and prolongs overall survival (4, 5).

High glucose metabolism is a unique feature of tumor cells, which is reflected by standardized uptake values (SUV) as measured by positron emission tomography (PET) using [^{18}F]-fluorodeoxyglucose (FDG). NSCLC also shows increased glucose metabolism, and FDG-PET has improved the management of NSCLC in several ways. The detection of lymph nodes and distant metastases by FDG-PET are more sensitive and specific than by conventional methods (6). In addition, reduced metabolic activity during chemotherapy as measured by FDG-PET is correlated with response to chemotherapy and allows the early prediction of treatment outcome and patient survival (7).

Previous reports have shown that high FDG uptake as measured by SUVs is correlated with tumor proliferative rates in NSCLC (8) as well as in other various types of malignancies (9–11). On the other hand, FDG-PET imaging has been shown to provide a highly reproducible measure of metabolism (12, 13). Therefore, it is likely that tumor metabolism measured by PET is related to response to chemotherapy in patients with NSCLC because chemotherapeutic agents are directed against dividing cells. The relation between initial SUV before treatment and subsequent response to chemotherapy, however, has not been well investigated. Most previous studies about PET and chemotherapy focus rather on the early prediction of response using differences between SUVs before and after treatment.

Thus, we retrospectively investigated response and survival for platinum-based chemotherapy in chemonaive patients with advanced NSCLCs according to pretreatment SUVs on FDG-PET.

Authors' Affiliations: [1]Department of Internal Medicine and [2]Nuclear Medicine, Seoul National University Hospital; and [3]Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea

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Requests for reprints: Dae Seog Heo, Department of Internal Medicine, Seoul National University Hospital, 28 Yongon-dong, Chongno-gu, Seoul 110-744, Korea. Phone: 82-2-2072-2857; Fax: 82-2-742-6689; E-mail: heo1013@plaza.snu.ac.kr.

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Table 1. Patient characteristics

	No. patients (%)
No. patients	85
Age, median (y)	62
Sex	
Male	66 (77.6)
Female	19 (22.4)
Tumor stage	
III	21 (24.7)
IV	47 (55.3)
Recurrent	17 (20.0)
Histopathology	
Adenocarcinoma	47 (55.3)
Squamous cell carcinoma	22 (25.9)
Large cell carcinoma	3 (3.5)
Others	13 (15.3)
Performance status	
0	6 (7.0)
1	72 (84.7)
2	7 (8.3)
Maximal SUV	
≤7.5	44 (51.8)
>7.5	41 (48.2)
Location of maximal SUV	
Primary tumor	69 (81.2)
Locoregional lymph node	11 (12.9)
Distant metastasis	5 (5.9)
Tumor response to first-line chemotherapy	
Partial response	40 (47.1)
Stable disease	29 (34.1)
Progressive disease	16 (18.8)

Patients and Methods

Patients. Among the patients with pathologically proven NSCLC at Seoul National University Hospital (Seoul, Korea) from September 1999 to June 2005, those who had undergone an FDG-PET scan and had received platinum doublets as first-line chemotherapy were analyzed. Patients with locally advanced or metastatic disease, including brain metastases, or recurrence after curative surgery were eligible, but patients who had received neoadjuvant or adjuvant chemotherapy were excluded. The full list of patients with NSCLC who underwent PET scan was retrospectively drawn from the electronic archive of the institution, and 85 patients met the inclusion/exclusion criteria. The main purpose of PET scan was staging work-up for possible resection and identification of recurrence after surgery. The PET scan results did not influence selection of chemotherapy regimens.

Initial staging work-ups of the patients included computed tomography of the chest and upper abdomen and bone scintigraphy. Cerebral magnetic resonance imaging was done if clinical symptoms suggested the presence of brain metastases. Previous palliative radiation therapy at symptomatic sites was permitted, including whole-brain radiotherapy, provided that the indicator sites (the sites that were followed to determine maximal SUVs or whether there was a response) had not been irradiated and that the radiation therapy had been completed before chemotherapy was initiated. Patients with recurrent disease after curative radiotherapy were not included in this study. Three patients had received adjuvant radiotherapy after curative surgery, but the indicator sites had not been irradiated. The median time from the date of PET scan to the date of the first chemotherapy was 8 days. The performance statuses of the patients were 0 to 2 on the Eastern Cooperative Oncology Group scale.

Chemotherapy and response evaluation. The chemotherapy regimens used in the present study included paclitaxel (145 mg/m^2) and cisplatin (60 mg/m^2) in 42 patients, paclitaxel (135 mg/m^2) and carboplatin (area under the curve, 5) in 18, gemcitabine (1,250 mg/m^2) and cisplatin (60 mg/m^2) in 9, vinorelbine (25 mg/m^2) and cisplatin (80 mg/m^2) in 6, docetaxel (75 mg/m^2) and cisplatin (70 mg/m^2) in 6, gemcitabine (1,200 mg/m^2) and carboplatin (area under the curve, 5) in 3, and etoposide (100 mg/m^2) and cisplatin (75 mg/m^2) in 1. Dose reductions were allowed at the discretion of the treating physician. Chest X-rays and serum tumor markers, if elevated, were taken every cycle of chemotherapy, and computed tomography scans were taken every two cycles if other means showed no disease progression. Tumor response was evaluated by the treating physician according to WHO criteria and independently reviewed by another diagnostic radiologists (14). Time to progression (TTP) was calculated from the date of the initiation of chemotherapy to the date of progression or death. Response duration was calculated from the date of confirmation of response to the date of progression. Overall survival was calculated from the date of initiation of chemotherapy until the date of death or the date when the patient was last known to be alive. Forty-six patients received second-line chemotherapy, seven patients palliative radiotherapy, and one patient palliative surgery followed by chemotherapy, after the first chemotherapy.

FDG-PET imaging. Whole-body FDG-PET was done using the same scanner, ECAT-EXACT 47 PET scanner (CTI/Siemens, Knoxville, TN). For attenuation correction, transmission scanning with triple germanium-68 ring sources was done for 2 minutes for each bed. After the

Table 2. Univariate analysis of response rates according to clinical factors, including the maximal SUV

	Total patients	Responding patients	Response rate (%)	*P*
Maximal SUV				
≤7.5	44	15	34.1	0.013
>7.5	41	25	61.0	
Sex				
Male	66	28	42.4	0.111
Female	19	12	64.2	
Histopathology				
Adenocarcinoma	38	18	47.4	0.959
Others	47	22	46.8	
Performance status				
0 or 1	78	38	48.7	0.439
2	7	2	28.6	
Location of the maximal SUV				
Primary tumor	69	32	46.4	0.794
Other sites	16	8	50.0	
Disease status				
Locally advanced (stage III)	21	8	38.1	0.613
Metastatic (stage IV)	47	24	51.1	
Recurrent after surgery	17	8	47.1	
Chemotherapy regimens				
Cisplatin based	64	28	43.8	0.286
Carboplatin based	21	12	57.1	

Table 3. Multivariate analysis of response rates by logistic regression

	Odds ratio (95% CI)	*P*
Maximal SUV (≤7.5)	0.220 (0.076-0.638)	0.005
Histopathology (adenocarcinoma)	0.743 (0.280-1.973)	0.551
Chemotherapy regimens (cisplatin based)	0.434 (0.143-1.318)	0.141
Chemotherapy setting (recurrent)	1.829 (0.531-6.301)	0.339

patient had fasted for at least 6 hours, [^{18}F]-FDG (370-555 MBq) was injected i.v. After 60 minutes, whole-body images were obtained for 6 minutes for each bed. Transaxial images were reconstructed using a Shepp-Logan filter (cutoff frequency, 0.35 cycles per pixel) and corrected for attenuation using the attenuation map obtained from the transmission images.

The SUV was calculated from the amount of FDG injected, body weight, and soft tissue uptake in the attenuation-corrected regional images: SUV = (activity / unit volume) / (injected dose / body weight).

Region of interest was drawn manually around tumor area on transaxial section of FDG-PET image. Because maximal SUV showed higher reproducibility than that of mean SUV, maximal SUV was chosen for analysis. Maximal SUV was defined as the peak SUV value on one pixel with the highest counts within region of interest.

We measured maximal SUVs of all the lesions, such as lymph nodes or distant metastasis, found on FDG-PET images, but the lesion chosen for analysis was the one with the highest SUV. Therefore, maximal SUV was the highest SUV in the patient. Patients with brain metastases were included in this study, but brain metabolism was not chosen for the analysis.

Statistical analysis. The statistical analyses of categorical variables were done using Pearson's χ^2 test or Fisher's exact test, as appropriate. Median durations of TTP and overall survival were calculated using the Kaplan-Meier method, and comparisons between groups were made using log-rank tests. Multivariate logistic regression analysis was carried out using the Cox proportional hazards model. A significance level of 0.10 was used for covariate entry. Two-sided *P*s < 0.05 were considered significant. All analyses were done using SPSS for Windows, version 12.0 (SPSS, Inc., Chicago, IL).

Ethics. The study protocol was reviewed and approved by the institutional review board of Seoul National University Hospital. The recommendations of the Declaration of Helsinki for biomedical research involving human subjects were also followed.

Results

Patient characteristics. A total of 85 patients were included in the study, and they were divided into two groups according to maximal SUVs; ≤7.5 and >7.5, where 7.5 was equal to the median value of the maximal SUVs of 85 patients studied. Forty-four patients had tumors of low SUV (≤7.5) and 41 had tumors of high SUV (>7.5). Patient characteristics are presented in Table 1.

Response rates according to maximal SUVs. Forty of 85 patients responded to first-line chemotherapy with an overall response rate of 47%. Patients with high SUV tumors exhibited significantly higher response rates to first-line platinum-based chemotherapy (34.1% for low SUV versus 61.0% for high SUV; $P = 0.013$). Other factors, including sex, age, histology, performance status, number of involved organs, regimens used, and whether in an advanced or recurrent setting, did not affect response (Table 2). Maximal SUV and other factors that might influence the response were included in the multivariate analysis, and high SUV was an independent factor with a higher response rate (Table 3). The separate analysis of 68 patients excluding 17 recurrent cases also revealed higher response rate for high SUV tumors (33.3% for low SUV versus 57.9% for high SUV; $P = 0.044$).

The response to chemotherapy according to initial maximal SUVs are presented in Table 4. Sixty-one percent of patients with a high SUV showed response to chemotherapy. Interestingly, half of the patients with a low SUV had stable disease after first-line chemotherapy.

TTP and overall survival according to maximal SUVs. Median TTP for the 85 patients was 200 days [95% confidence interval (95% CI), 132-268]. TTP was significantly shorter in patients with tumors with a high SUV (169 days; 95% CI, 135-203) than in patients with a low SUV (282 days; 95% CI, 203-361; $P = 0.015$; Fig. 1). Multivariate analysis showed that a high SUV was a predictor of shorter TTP (hazard ratio, 0.429; 95% CI, 0.224-0.822). Interestingly, differences according to SUV were significant in both responder and nonresponder subgroups. Of those patients that responded to first-line chemotherapy, median TTPs were 351 days (95% CI, 304-398) for patients with a low SUV and 181 days (95% CI, 149-213) for those with a high SUV ($P = 0.004$). Of those that did not respond, median TTPs were 193 days (95% CI, 86-300) for patients with a low SUV and 71 days (95% CI, 66-76) for those with a high SUV ($P = 0.006$; Fig. 2).

Response duration also was significantly shorter in patients with high SUVs. Median response durations were 279 days (95% CI, 214-344) for patients with a low SUV and 141 days (95% CI, 102-180) for those with a high SUV ($P = 0.003$). Overall survival was not affected by initial maximal SUV (623 days for low SUV versus 464 days for high SUV; $P = 0.431$; Fig. 1).

Discussion

The present study shows that tumors with a high pretreatment SUV respond better to first-line platinum-based doublet chemotherapy in chemonaive patients with NSCLC. But, responses were rather transient, and TTPs and response durations were significantly shorter for those with a high SUV.

Table 4. Response to platinum-based combination chemotherapy according to the maximal SUV

Response to chemotherapy	Partial response (%)	Stable disease (%)	Progressive disease (%)	Total
Maximal SUV				
≤7.5	15 (34.1)	22 (50.0)	7 (15.9)	44
>7.5	25 (61.0)	7 (17.0)	9 (22.0)	41
Total	40 (47.1)	29 (34.1)	16 (18.8)	85

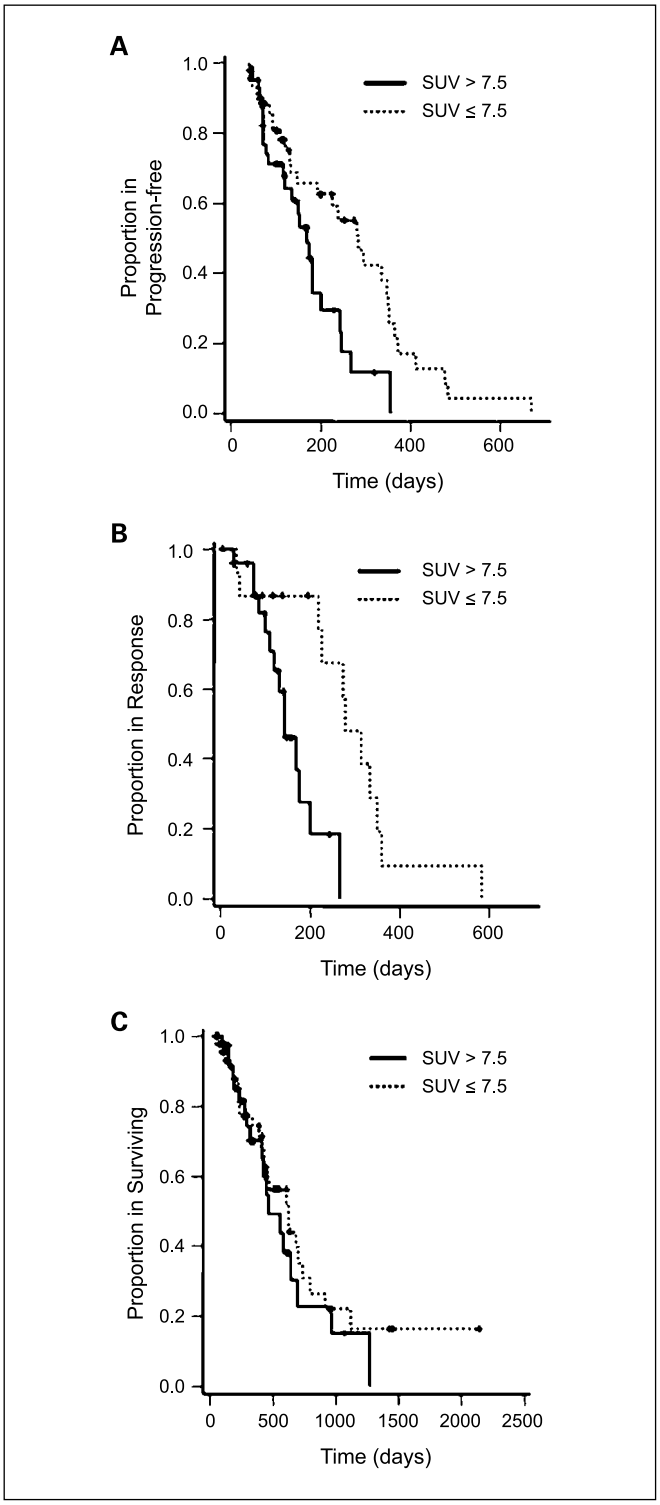

Fig. 1. Kaplan-Meier plots of TTP (*A*), response duration (*B*), and overall survival (*C*) according to pretreatment maximal SUVs.

Generally, tumors responding to chemotherapy are believed to be associated with a longer TTP. However, our data suggest that tumors with a high SUV respond to chemotherapy initially but then rapidly progress. In contrast, tumors with a low SUV did not show a marked response but progressed rather slowly. Table 4 provides an explanation of this phenomenon. Half of our patients with a low SUV had stable disease, which have been a consequence of the slow growth. On the other hand, the higher response rate of tumors with a high SUV may have been the result of rapid proliferation.

It has been shown that SUV, measured by FDG-PET, correlates with the immunohistochemistry of Ki-67 (a proliferation index marker) in NSCLC and lesion doubling time in lung tumors (8, 15). Moreover, higher Ki-67 was associated with better response to chemotherapy in early or locally advanced breast cancer (16–18). Thus, higher response rates in patients with higher SUVs can be explained in terms of the rapid proliferation of tumor cells and the effectiveness of the chemotherapy against proliferating cells. However, other biological factors influencing chemosensitivity, such as apoptosis, are not evaluated in this study and should be included together in the future study.

Response rates are often considered as a surrogate end point for survival in patients with advanced cancers, such as NSCLC (19). However, our results show that patients who show response to chemotherapy do not necessarily have a longer TTP or overall survival. Instead, it should be pointed out that patients who responded were heterogeneous, and some had relatively short TTPs and overall survivals. However, FDG-PET can aid in identifying patients who shows discordance between response rate and survival.

Previous reports about SUVs and responses to chemotherapy have focused on changes in the glucose metabolism before and after chemotherapy. Early prediction of response was found to be possible from SUV changes in various types of cancers

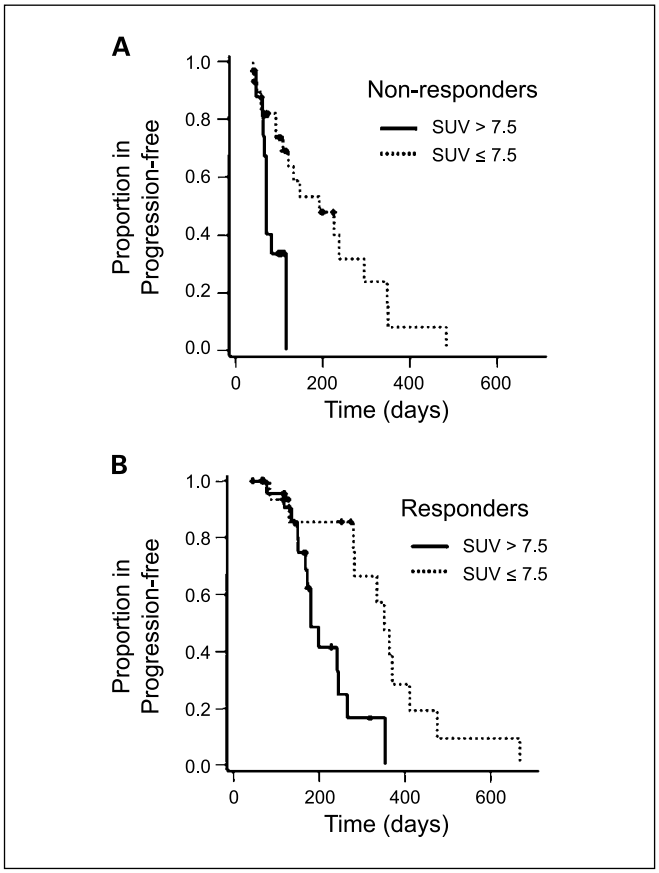

Fig. 2. Kaplan-Meier plots of TTP (*A*) and overall survival (*B*) for responder and nonresponder subgroups to first-line chemotherapy.

(7, 20–26). However, the relationship between pretreatment SUVs and subsequent response seems to be uncertain based on this series of studies.

An interesting example is provided by the study of Wieder et al. (25), which included 38 patients with esophageal squamous cell carcinoma. An analysis of the raw data presented in the report produced results that agreed with those of the present study. Excluding 5 patients not evaluable for histopathologic response, 12 of 16 patients with high SUVs (>9.08, where 9.8 is the median) responded histopathologically (response rate, 75.0%), whereas 7 of 17 patients with low SUVs (≤9.08) did (response rate, 41.2%; $P = 0.08$, Fisher's exact test). Considering the relatively small number of patients, this finding is in clear accordance with our results.

The raw data in the study by Smith et al. (20), which included 31 tumors in 30 patients with locally advanced breast cancer, can be similarly analyzed. Taking the higher dose uptake ratio value from breast lesions or axillary lymph nodes, the median dose uptake ratio was 0.0904. Six of 15 (40.0%) tumors with a high dose uptake ratio (>0.0904) showed microscopic complete pathologic response, whereas only 1 of 16 (6.3%) tumors with a low dose uptake ratio (≤0.0904) did ($P = 0.037$, Fisher's exact test).

In another report about colorectal carcinoma, it was concluded that pretreatment SUV was predictive with respect to therapy outcome (96% for progressive disease and 47% for stable disease), although partial remission could not be predicted exactly (24). These results support the possibility that pretreatment glucose metabolism measured by FDG-PET is related to subsequent response to chemotherapy in NSCLC.

In our analysis, the overall response rate was 47% (40 of 85), and median TTP was 200 days (95% CI, 132-268), which seems better than those of previously reported clinical trials (4, 19). One possible explanation is that not all patients who had been diagnosed in the hospital where this study was conducted underwent a PET scan. The main purpose of PET scan was staging work-up for possible resection and identification of recurrence after surgery. In addition, PET might have upstaged patients more so than conventional studies, such as chest computed tomography scan or bone scintigraphy, and early detection of metastases by PET might have led to apparently better survival in NSCLC patients, perhaps due to potential bias like lead-time bias.

The cutoff point of the maximal SUV used in the present study is 7.5, which was the median value of SUVs of the patients. Previous reports about the prognostic significance of SUVs in NSCLC have used various cutoff values from 7 to 10 (27, 28). Analysis using the cutoff point of 10 also gave similar results from the 85 patients (response rate, 38.3% for SUV ≤10.0 versus 68.0% for SUV >10.0; $P = 0.013$; TTP, 267 days versus 149 days; $P = 0.009$; response duration, 272 days versus 141 days; $P = 0.005$; overall survival, 626 days versus 419 days; $P = 0.064$). Appropriate cutoff values, however, remains to be investigated in future research.

In conclusion, patients having NSCLC with high maximal SUVs showed a better response to platinum-based combination chemotherapy but had a shorter TTP. Tumor glucose metabolism, as determined by SUVs on FDG-PET, was found to discriminate NSCLC subsets with different clinical and biological features.

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