Early $[^{18}F]$Fluorodeoxyglucose Positron Emission Tomography at 2 days of Gefitinib Treatment Predicts Clinical Outcome in Patients with Adenocarcinoma of the Lung

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Running title: PET at 2 days of gefitinib predicts outcome in NSCLC

Keywords: Lung cancer; PET scans; Gefitinib; Molecularly targeted therapy; EGFR-TKI

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Translational Relevance

It remains difficult to accurately predict clinical benefit of gefitinib in patients with nonsmall cell lung cancer (NSCLC). A recent basic study using a mouse model has shown that gefitinib induces a decrease of fluorodeoxyglucose (FDG) uptake within 48 hours in sensitive NSCLC tumors. We performed a pilot study to validate the utility of early FDG-positron emission tomography (PET) in clinical settings. Assessment of FDG uptake only after 2 days of gefitinib treatment was able to predict tumor response and progression-free survival. This early assessment could help to identify patients who will benefit from gefitinib therapy, while allowing for rapid initiation of alternative strategies and minimizing critical adverse effects such as interstitial lung disease when gefitinib is ineffective.
Abstract

**Purpose:** Positron emission tomography (PET) with $[^{18}\text{F}]$fluorodeoxyglucose (FDG) is increasingly used in early assessment of tumor response after chemotherapy. We investigated if a change in $[^{18}\text{F}]$FDG uptake at 2 days of gefitinib treatment predicts outcome in patients with lung adenocarcinoma.

**Experimental Design:** Twenty patients were enrolled. $[^{18}\text{F}]$FDG-PET/computed tomography (CT) scan was performed before and 2 days after gefitinib treatment. Maximum standardized uptake values (SUVs) were measured, and post-gefitinib percent changes in SUV were calculated. Early metabolic response (SUV decline < -25%) was compared with morphologic response evaluated by CT scan and with progression-free survival (PFS).

**Results:** At 2 days of gefitinib treatment, 10 patients (50%) showed metabolic response, 8 were metabolic stable disease, and 2 had progressive metabolic disease. Percent changes of SUV at 2 days were correlated with those of tumor size in CT at 1 month ($R^2 = 0.496; P = 0.0008$). *EGFR* gene was assessable in 15 patients and, of 12 patients with *EGFR* mutations, 8 showed metabolic response at 2 days and 6 showed morphologic response at 1 month. None of 3 patients with wild-type *EGFR* showed metabolic or morphologic response. Metabolic response at 2 days was not statistically associated with PFS ($P = 0.095$), but when a cutoff of -20% in SUV decline was used, metabolic responders had longer PFS ($P < 0.0001$).

**Conclusion:** Early assessment of $[^{18}\text{F}]$FDG tumor uptake with PET at 2 days of gefitinib treatment could be useful to predict clinical outcome earlier than conventional CT evaluation in patients with lung adenocarcinoma.
Treatment of nonsmall cell lung cancer (NSCLC) has made remarkable progress in the last decade; the epidermal growth factor receptor (EGFR), which is expressed more than 60% of metastatic NSCLC and correlates with poor prognosis (1), has emerged as an important molecular target for advanced or recurrent NSCLC. Reversible EGFR tyrosine kinase inhibitors (TKIs), gefitinib and erlotinib, were found to have anti-tumor activities in second- or third-line therapy (2-4). Objective responses with these agents were limited to a subpopulation of patients, which included never-smokers, women, East Asians, and patients with adenocarcinoma histology (4, 5). It was later demonstrated that most of these responders harbor specific mutations or increased copy number in the gene encoding EGFR that enhances tyrosine kinase activity (6, 7). Indeed, gefitinib as first-line and single agent therapy improved progression-free survival (PFS) of NSCLC patients with the \textit{EGFR} mutations when compared with standard chemotherapy (8-10). Although these genetic markers may be used to predict therapeutic response, they do not guarantee successful treatment since a portion of marker-positive patients did not respond to the EGFR TKIs, whereas a portion of marker-negative patients did respond (11). Moreover, a secondary mutation in the \textit{EGFR} gene or amplification of \textit{c-Met} negates the sensitizing effect, leading to acquired resistance to the EGFR TKIs (12). Thus, it appears difficult to predict clinical benefit accurately only with these genetic biomarkers.

Positron emission tomography (PET) with \textsuperscript{18}Ffluorodeoxyglucose (FDG) plays a role in the diagnosis and staging of lung cancer. It is based on high glucose metabolism in tumor cells that have an increased level of glucose-transport protein expression and hexokinase activity. In addition to diagnosis and staging, \textsuperscript{18}FFDG-PET is increasingly used to assess tumor response and to predict outcome. A decrease in FDG uptake in sensitive tumor cells can be detected earlier than structural changes occur (13). This is the case especially in tumors treated with molecularly targeted drugs rather than with cytotoxic agents. In gastrointestinal stromal tumors (GIST), FDG-PET has been shown to be
highly sensitive in detecting early response to imatinib mesylate, a small molecule that inhibits c-KIT. Decreases in FDG uptake were observed after 1 week of treatment, whereas volume responses evaluated on computed tomography (CT) scan were small and developed more slowly (14) (15). In NSCLC, it has remained unknown how EGFR TKIs down-regulate FDG uptake after initiation of treatment in sensitive tumors. Recently, using a mouse xenograft model, Su et al. showed rapid decreases of tumor FDG uptake in sensitive xenografts within 48 hours of gefitinib treatment (16). They also found a decline in FDG uptake 24 to 48 hours before inhibition of proliferation and induction of apoptosis in a gefitinib-sensitive NSCLC cell line. A more recent preliminary study, which evaluated [18F]FDG-PET in five advanced NSCLC patients treated with gefitinib, suggested that FDG-PET may be able to predict the response. Patients exhibiting a partial response on CT evaluation already showed a mean of 61% decrease in FDG uptake at 2 days of therapy (17). Thus, further prospective studies are needed to confirm that [18F]FDG-PET provides an early sensitive marker of the effectiveness of gefitinib in NSCLC patients.

In the present study, we prospectively evaluated FDG-PET only after 2 days of gefitinib treatment in patients with lung adenocarcinoma to predict response and outcome. We utilized a combined PET/CT scans to provide correct anatomic registration of PET data.

Patients and Methods

Patients

Twenty patients with lung adenocarcinoma who received gefitinib treatment were enrolled from November 2007 to November 2009. Diagnosis was made either histologically or cytologically. Gefitinib at a dose of 250 mg once a day was administered orally 30 min after breakfast as the first
EGFR tyrosine kinase inhibition therapy, until disease progression, unacceptable toxicity, or patient refusal. Eligibility criteria included an age of 20 years or more, unresectable stage or relapse after surgery, measurable disease, and Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2. The study protocol was approved by the Institutional Review Board of Osaka University Hospital, and written informed consent was obtained from all patients.

**EGFR mutation analysis**

Mutation analysis of *EGFR* in exons 18, 19, 20, and 21 was performed using biopsy specimens obtained at diagnosis. Genomic DNA was extracted and analyzed by peptide nucleic acid-locked nucleic acid polymerase chain reaction (PNA-LNA PCR) cramp method manufactured in Mitsubishi Chemical Medience Co. (Tokyo, Japan), as previously described (18).

**FDG-PET/CT**

[^18F]FDG-PET/CT was performed before (at baseline), 2 days and 1 month after gefitinib administration using a GEMINI GXL scanner (Philips Medical Systems, Best, The Netherlands). Baseline scan was done within 14 days prior to the treatment. All patients were fasted for at least 4 hours before scanning. Their serum glucose levels were < 150 mg/dl before FDG injection. One hour after the injection of 3.7 MBq/kg[^18F]FDG, patients were scanned from the head to the thigh. We calculated accurate[^18F]FDG uptake time for each patient and confirmed that there was no significant difference between any metabolic responders and nonresponders. After a 50-mAs low dose CT scan for attenuation correction, emission scan was obtained in a 3-demensional acquisition mode at 11-12 bed positions with 2 min/bed speed. In-plane and axial field-of-view (FOV) of the scanner was 576 mm and 180 mm, respectively. In-plane spatial resolution was 6.31 mm full width at half maximum (FWHM) at the center with 144 x 144 pixel size (4 x 4 x 4 mm³/pixel). Images were reconstructed by
line-of-response row-action maximum likelihood algorithm (LOR-RAMLA) method. After acquisition of the PET images, a diagnostic chest CT was conducted by a 16-row multi-detector scanner in a helical mode with 120 kV of the tube voltage and 200 mAs of the effective tube current. CT gantry rotation time was 0.5 sec with an axial FOV of 600 mm, producing 5 mm-thick slices with a 512 x 512 matrix. Regions of interest (ROIs) were placed over the highest accumulation area, corresponding to tumor sites on the PET images. The maximal standardized uptake value (SUV) was determined as previously described (19).

Response assessment and follow-up

Among measurable lesions according to the Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST 1.0) (20) in fused mode of dual modality PET/CT, up to 5 lesions in order of \[^{18}F\]FDG uptake level were defined as target lesion on the baseline scan. \[^{18}F\]FDG uptake was evaluated as the maximal standardized uptake value (SUV) of the target lesions (21). The lowest SUV of target lesions was 1.6, which was still higher than the background (Table 1). On PET/CT at 2 days and 1 month of gefitinib administration, percent changes in the sum of these SUVs of the target metabolic lesions were determined on the basis of the baseline scan, and time point metabolic response was defined according to the recommendations of the European Organization for Research and Treatment of Cancer (EORTC) PET study group (22). Complete metabolic response (CMR) was achieved when SUVs of all lesions were decreased to uptake equivalent to background. Partial metabolic response (PMR) was defined as percent change of the sum of SUVs (\(\Delta\)SUV\%) < -25\%, stable metabolic disease (SMD) was -25\% ≤ \(\Delta\)SUV\% < +25\%, and progressive metabolic disease (PMD) was defined as +25\% ≤ \(\Delta\)SUV\% or when the extent of \[^{18}F\]FDG increased > 20\% in the longest dimension or when new \[^{18}F\]FDG uptake appeared in metastatic lesions. In analysis of PFS, a cut-off value of -20\%, instead of -25\%, was also used to separate responders from nonresponders. Changes in tumor size of the same target lesions as
[\textsuperscript{18}F]FDG uptake analysis and nontarget lesions were quantified on CT images from PET/CT data at 1 month by two of the authors blinded to the PET data, and time point overall response was classified according to RECIST 1.0. Percent changes in the sum of the longest dimension (\( \Delta \text{CTsize}\% \)) of the target lesions were also determined and compared with \( \Delta \text{SUV}\% \). On CT images at 2 days of gefitinib administration, all patients were with stable disease. Chest CT or radiograph was repeated every 4 weeks until disease progression, which was determined by RECIST 1.0. The overall responses classified at 1 month were not confirmed by the repeat assessments in this study.

**Statistical analysis**

Data were analyzed using JMP statistical discovery software version 8.0.2 (SAS Institute, Cary, NC). Correlation between \( \Delta \text{SUV}\% \) at 2 days and \( \Delta \text{CTsize}\% \) at 1 month was evaluated by Fisher’s analysis of variance. Agreement between the EORTC-recommendations-based metabolic response at 2 days and RECIST-based morphologic overall response at 1 month was evaluated using kappa statistic (23). PFS was measured from the first administration of gefitinib to documented progression or death of any cause. Overall survival (OS) was from the first administration of gefitinib to death of any cause. PFS and OS were estimated using the Kaplan-Meier method and compared by the two-sided log-rank test (24). Hazard ratios were calculated using the Cox proportional hazards model. In multivariate Cox model analysis, metabolic response at 2 days and morphologic response at 1 month, significance of which was \( P < 0.15 \) in univariate analysis, were chosen as variable in addition to smoking history, which was previously shown to be a prognostic factor for gefitinib-treated NSCLC patients (5). \textit{EGFR} mutation status was not included because it was not determined or tested in 5 patients and the number of patients with wild-type \textit{EGFR} was only three.
Results

Patient characteristics

A total of 20 patients (15 females, 5 males) were enrolled in this study, underwent PET/CT for baseline assessment, and received gefitinib treatment. Nineteen were patients with adenocarcinoma, and one with adenosquamous carcinoma. Fifteen patients (75%) had clinical stage IV disease. Five patients at clinical stage III were not treated with surgery or radiation due to the presence of malignant pleural effusion and complicating diseases. Ten were previously untreated, and 10 had been treated with 1 to 4 chemotherapy regimens. Detailed patient characteristics are shown in Table 1. Median time between the baseline PET/CT and the start of gefitinib treatment was 4 days (range, 0 day to 13 days), and no chemotherapy was administered during this period. A 77-year-old male patient did not complete PET/CT at 1 month because ground-glass opacity appeared on chest radiograph and gefitinib administration was discontinued at 6 days of treatment; this patient was excluded from later assessment. In all the other patients, gefitinib was continued to documented disease progression, and none of them received additional treatment without documented progression. Overall, early response at 2 days was assessed in 20 patients, and late response assessment at 1 month and PFS analysis were performed in 19 patients.

Comparative analysis of metabolic and morphologic responses

Metabolic responses could be detected only at 2 days of treatment, when morphologic responses were still unrecognizable. Representative PET/CT images of responders and nonresponders during gefitinib treatment were shown in Fig. 1. Median percent change of the sum of SUVs (ΔSUV%) of target lesions was -23%. Sixteen patients experienced ΔSUV% reduction ranging from -2% to -52% (Fig. 2A). No patient achieved a CMR (SUVs of all lesions equivalent to background), and 10 (50%)
patients achieved a PMR ($\Delta$ SUV% < -25%). Four patients experienced an increase of $\Delta$ SUV% ranging from +6% to +36% and 2 of these were assessed with PMD ($+25\% \leq \Delta$ SUV%). These changes of target lesions in SUV at 2 days of treatment was compared with those in tumor size ($\Delta$ CTsize%) at 1 month of treatment, which was quantified on CT images, and there was a strong correlation ($R^2 = 0.496; P = 0.0008$) as shown in Fig. 2B. There was also a moderate agreement ($\kappa = 0.566$) between metabolic responses at 2 days based on the EORTC recommendations and morphologic overall responses at 1 month according to RECIST 1.0 (Fig. 2C). Of 10 metabolic responders at 2 days, 8 patients were morphologic responders and 2 were with stable disease by RECIST 1.0 at 1 month. Of 7 patients with SMD ($-25\% \leq \Delta$ SUV% < +25%) at 2 days, 5 patients were assessed with morphologically stable disease and 2 had progressive disease by RECIST 1.0 at 1 month. Median PFS of patients with PMR, SMD, and PMD was 290, 48, and 39 days, respectively. Median PFS of patients with morphologic partial response, stable disease, and progressive disease was 267, 100, and 29 days, respectively.

**EGFR mutation**

Biopsy samples from 5 patients were not suitable for molecular analysis. Mutation of EGFR gene was assessable in 15 patients, and 12 were EGFR mutation-positive: 6 patients had an exon 19 deletion, 5 patients had an exon 21 L858R mutation, and one had an exon 18 G719S mutation. Median $\Delta$ SUV% changes of target lesions in patients with mutated EGFR and wild-type EGFR were -29% and -2%, respectively (Fig. 2A). Of 12 patients with activating EGFR mutations, 8 (67%) were metabolic responders and 3 were with stable metabolic disease at 2 days, whereas 6 (50%) were morphologic responders and 5 were morphologically with stable disease at 1 month (Fig. 2C). Oppositely, of eight EGFR gene-assessable metabolic responders at 2 days, all had the activating mutations and 6 were assessed as morphologic responders at 1 month. Of 6 EGFR gene-assessable morphologic responders.
at 1 month, all had the mutations and were assessed as metabolic responders at 2 days. An 83-year-old female patient with an exon 19 deletion was assessed as having progressive metabolic disease while being with morphologically stable disease. During follow-up this patient suffered from a relapse at 48 days. Another 79-year-old female patient with an exon 19 deletion was with stable metabolic disease at 2 days but assessed as having progressive disease because a new lesion appeared on PET/CT images at 1 month. All of three patients with wild-type \textit{EGFR} were assessed with metabolically stable disease at 2 days. Two of these were assessed with morphologically stable disease and one had progressive disease at 1 month (Fig. 2C).

\section*{PFS according to metabolic and morphologic responses}

When a cutoff value of -25\% in $\Delta$ SUV\% was used between metabolic responders and nonresponders, PFS did not significantly correlate with metabolic response at 2 days. Median PFS of the responders and nonresponders was 290 days and 48 days, respectively (log-rank $P = 0.095$; Fig. 3A). This was attributable to a 58-year-old male nonresponder with an L858R mutation, who was assessed with 21\% decrease of $\Delta$ SUV\% and experienced the longest PFS of 680 days. When a cutoff value of -20\%, which was still within the extent recommended by EORTC (22), was used, this patient was included in responders, and 2-day metabolic responders had significantly prolonged PFS compared with metabolic nonresponders (median, 296 days versus 42 days; $P < 0.0001$; Fig. 3B). When metabolic response was evaluated at 1 month, PFS was also significantly longer in responders than in nonresponders even with the cutoff of -25\% (median, 302 days versus 42 days; $P < 0.0001$; Fig. 3C). Meanwhile, PFS did not correlate with morphologic response based on RECIST 1.0 even at 1 month of treatment (median, 296 days versus 48 days; $P = 0.100$; Fig. 3D), because the patient with the longest PFS of 680 days was assessed with stable disease. When this patient was excluded, 1-month morphologic response became significantly correlated with PFS ($P = 0.0003$).
In the clinical settings, SUV at baseline PET might be influenced by previous chemotherapy. Therefore, we also investigated whether an early metabolic assessment with a single post-gefitinib PET/CT scan would provide any useful prognostic information. We defined an SUV threshold of 7, which was the nearest integer to the average SUV of the hottest target lesions in PET at 2 days, to separate responders (i.e., SUV < 7) from poor responders (SUV ≥ 7). There was a significant association between post-gefitinib FDG uptake and PFS (median, 244 days with SUV < 7 versus 71 days with SUV ≥ 7; P = 0.045; Fig. 3E). Meanwhile, SUV in baseline PET studies was not predictive of PFS (median, 117 days with SUV < 10 versus 93 days with SUV ≥ 10; P = 0.611).

In univariate analysis using the Cox hazards model, metabolic response using a cutoff value of -20% of ΔSUV% at 2 days was the only predictive factor of PFS (hazard ratio = 0.04; P < 0.0001), other than EGFR mutation status (Table 2). In multivariate analysis including metabolic response at 2 days, morphologic response at 1 month, and smoking history, metabolic response at 2 days was the only statistically significant factor (P = 0.0007).

**OS according to metabolic and morphologic responses**

OS did not differ significantly between any metabolic responders and nonresponders and between the morphologic responders and nonresponders (Supplementary Fig. 1), although there was a trend for longer survival in metabolic responders who showed post-gefitinib SUV < 7 at 2 days (P = 0.066) (Supplementary Fig. 1E).

**Discussion**
It has been evident that EGFR TKIs, gefitinib and erlotinib, induce dramatic responses in a subpopulation of adenocarcinoma patients. Although the presence of somatic mutations in the EGFR gene is considered to be the best predictor of response to these TKIs (9, 10, 25, 26), its efficacy as biomarker is not satisfactory due to technical problems on biopsy, secondary mutation acquiring the resistance to the EGFR TKIs, and recent data showing response of patients with wild-type EGFR to erlotinib (27). Thus, an alternative approach optimizing clinical outcome of EGFR TKI therapy is necessary to accurately select patients who will benefit from the therapy and to avoid critical adverse effects such as interstitial lung disease (28).

Early response to therapy assessed by \[^{18}\text{F}]\text{FDG-PET} has been increasingly established as a prognostic biomarker in various malignancies (13). In NSCLC, two studies have just been published to show that early \[^{18}\text{F}]\text{FDG-PET} evaluation can predict PFS and OS in patients treated with erlotinib (29, 30). Another recent study reported that early \[^{18}\text{F}]\text{FDG-PET} predicted histopathologic response in NSCLC patients treated with erlotinib as neoadjuvant therapy (31). Metabolic tumor responses were assessed one to 8 weeks after the start of erlotinib treatment in these studies. Meanwhile, Su et al. showed that gefitinib treatment induced rapid decreases of FDG uptake within 48 hours in sensitive tumors using a mouse model, providing a rationale for earlier assessment in clinical settings (16). In these sensitive tumors, glucose transporters rapidly translocated from the plasma membrane to the cytosol and reduction of hexokinase activity was observed prior to changes in cell cycle distribution, thymidine uptake, and apoptosis. Such changes were not found in an early decline of FDG uptake in response to conventional cytotoxic chemotherapy (32). A more recent study preliminarily analyzed five advanced NSCLC patients and reported that, only 2 days after initiation of gefitinib therapy, SUV decreased by a mean of 61\% in patients who showed partial response by conventional CT evaluation 4 weeks later (17).
Consistent with these studies, SUV decreased by up to a maximum of 52% at 2 days in the present prospective study, and we observed a strong correlation between changes in SUV at 2 days and those in tumor size at 1 month. There was also a moderate agreement between metabolic responses at 2 days based on the EORTC recommendations and morphologic responses at 1 month according to RECIST 1.0. Moreover, metabolic response at 2 days could be a predictor of prolonged PFS when a cutoff value of -20% in SUV decline was used. The cutoff of -25%, which was used in several other studies (33-35) but did not reach statistical significance in the present study, might be too large for the evaluation only after 2 days and for the sample size as small as 20. A single PET study at 2 days might also provide prognostic information. Patients with favorable response with lower post-gefitinib SUVs (SUV < 7) revealed longer PFS than poorly responding patients with higher SUVs (SUV ≥ 7), although significance was weak. There was a trend for an association between morphologic response at 1 month and improved PFS but it did not reach statistical significance, due to the presence of an EGFR mutation-positive patient showing stable disease but with a long PFS. In terms of OS, there was not significant difference, probably due to the small sample size and because OS is influenced by the second-line or later treatment. Together, although our study was a single-centered with a small number of patients, we propose that assessment of FDG uptake at 2 days could be a superior predictor of post-gefitinib outcome to conventional CT evaluation in its accuracy and rapidity.

Of 12 patients with activating EGFR mutations, 10 (83%) showed partial response or were with stable disease both in FDG-PET at 2 days and CT evaluation at 1 month. Thus, mutated EGFR is a good biomarker for response to gefitinib, as previously reported (6). Exceptionally, an 83-year-old female patient with exon 19 deletion had progressive metabolic disease at 2 days while being with morphologically stable disease at 1 month. She had a PFS of 48 days and this was relatively short for morphologically stable disease, the median PFS of which was 100 days. Another 79-year-old female patient with exon 19 deletion was with stable metabolic disease at 2 days while having
morphologically progressive disease at 1 month. Her PFS was 30 days and relatively short for stable metabolic disease, the median PFS of which was 48 days. Thus, there was still inconsistency among \textit{EGFR} mutations, early FDG-PET evaluation, or conventional CT evaluation, and larger prospective studies will be needed to clarify which is the best predictor of survival. Meanwhile, although it appears reasonable that none of 3 patients with wild-type \textit{EGFR} showed metabolic or morphologic response, the number of patients is too small to discuss more about wild-type \textit{EGFR}.

Interstitial lung disease is the most severe adverse effect, which occurs in ~1% of EGFR TKI-treated patients worldwide. Onset of symptoms may begin only after 2 days of gefitinib therapy. Median onset was 24 days in Japan and 42 days in USA, and about 1 out of 3 of the cases were fatal (28). It has been suggested that [\textsuperscript{18}F]FDG-PET may help to evaluate interstitial lung disease. Positive FDG uptake was observed in 86% of patients with idiopathic pulmonary fibrosis and correlated with disease activity (36). In the present study, a 77-year-old male patient showed ground glass opacity suggestive of interstitial infiltrate on chest radiograph, and gefitinib was discontinued at 6 days of treatment. At 2 days of treatment his PET images did not show any positive uptake in lung parenchyma, and later on a CT scan this infiltrate was rather considered a secondary change associated with obstructive bronchus. No other patient presented with interstitial infiltrate on chest radiograph. Thus, we could not determine at the moment if [\textsuperscript{18}F]FDG-PET can early detect gefitinib-induced lung damage.

In summary, early response assessment by FDG-PET could help to identify lung adenocarcinoma patients who will benefit from gefitinib treatment. The present study showed promising data suggesting that clinical outcome can be predicted only after 2 days of the treatment. This early assessment may allow for rapid initiation of alternative strategies and minimize critical adverse effects such as interstitial lung disease when gefitinib is ineffective. The main limitation is the small sample size, and validation with prospective studies in a larger patient population is warranted.
Acknowledgements

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References


Table 1. Patient characteristics at baseline

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; PS, performance status; EGFR, epidermal growth factor receptor; ND, not determined; NT, not tested; SUV, standardized uptake value.
**Table 2.** Univariate analysis of predictive factors for progression-free survival

<table>
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<td>Morphologic response at 1 month (yes)</td>
<td>19</td>
<td>0.44</td>
<td>0.16 to 1.20</td>
<td>0.109</td>
</tr>
<tr>
<td>EGFR mutation (yes)</td>
<td>15</td>
<td>0.17</td>
<td>0.03 to 0.92</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Abbreviation: *EGFR*, epidermal growth factor receptor.

*A cutoff value of -20% in SUV decline was used.*
Figure Legends

Fig. 1. Pre- and post-treatment images of $^{[18}F]fluorodeoxyglucose$-positron emission tomography (PET)/computed tomography (CT) scans of a 67-year-old female (A, D, and G) and a 75-year-old female (B, E, and H), who achieved partial response at 1 month (G and H, respectively), and a 81-year-old male (C, F, and I), who had progressive disease (I) at 1 month as assessed by RECIST 1.0. The first two patients already showed partial metabolic response at 2 days (D and E), and the third patient was assessed with progressive metabolic disease at 2 days (F).

Fig. 2. A, Waterfall plot of maximal standardized uptake value (SUV) change of target lesions after 2-day treatment of gefitinib (n = 20). *This patient was excluded from later assessment because gefitinib was discontinued at 6 days. B, Correlation between SUV change ($\Delta$SUV%) at 2 days and CT size change ($\Delta$CTsize%) at 1 month of target lesions (n = 19). C, Agreement between metabolic response at 2 days on EORTC recommendations and morphologic overall response at 1 month on RECIST 1.0 (n = 19). $\kappa$ value = 0.566. EGFR mutation status was also shown. ND, not determined; NT, not tested; PR, partial response; SD, stable disease; PD, progressive disease; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease.

Fig. 3. A, Progression-free survival (PFS) of metabolic responders ($\Delta$SUV% < -25%) and nonresponders ($\Delta$SUV% $\geq$ -25%) at 2 days. B, PFS of metabolic responders ($\Delta$SUV% < -20%) and nonresponders ($\Delta$SUV% $\geq$ -20%) at 2 days. C, PFS of metabolic responders ($\Delta$SUV% < -25%) and nonresponders ($\Delta$SUV% $\geq$ -25%) at 1 month. One patient did not have an FDG-PET scan at 1 month,
without missing a CT scan. D, PFS of morphologic responders and nonresponders at 1 month. E, PFS according to a single PET activity at 2 days (SUV < 7, black; SUV ≥ 7, grey). P values were obtained using the log-rank test.
Fig. 1.

Baseline

2 days

1 month
Fig. 2.

- **Panel A**: Graph showing the relationship between ΔSUV% and ΔCTsize%.
- **Panel B**: Plot of ΔSUV% vs. ΔCTsize% with a linear trend line.
- **Panel C**: Table of PET and CT outcomes with EGFR mutation status.
- **Legend**:
  - ◇: Wild-type
  - ○: Exon 19 del
  - ●: Exon 21 L858R
  - ●: Exon 18 G719S
  - Δ: ND/NT

The graph and table illustrate the correlation between changes in SUV and CT size, with specific annotations for different EGFR mutation statuses.
Fig. 3.

A  Metabolic responders : 10  
    Metabolic nonresponders : 9  
    $P = 0.095$

B  Metabolic responders : 11  
    Metabolic nonresponders : 8  
    $P < 0.0001$

C  Metabolic responders : 10  
    Metabolic nonresponders : 8  
    $P < 0.0001$

D  Morphologic responders : 8  
    Morphologic nonresponders : 11  
    $P = 0.100$

E  SUV < 7 : 13  
    SUV ≥ 7 : 6  
    $P = 0.045$
Clinical Cancer Research

Early $[^{18}F]$Fluorodeoxyglucose Positron Emission Tomography at 2 days of Gefitinib Treatment Predicts Clinical Outcome in Patients with Adenocarcinoma of the Lung

Ryo Takahashi, Haruhiko Hirata, Isao Tachibana, et al.

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