

FDG-PET for predicting efficacy of EGFR-tyrosine kinase inhibitors in lung cancer

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Abstract

Non-small cell lung cancer (NSCLC) is the major cause of cancer-related deaths worldwide. Recent advances in molecular biology have resulted in the clinical use of several molecularly targeted drugs, which usually exhibit cytostatic antitumor activity, to improve the survival of NSCLC patients. The epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) gefitinib and erlotinib have been approved for the treatment of NSCLC, and several phase III trials have demonstrated that sensitizing *EGFR* mutations are biomarkers for predicting a favorable clinical outcome of NSCLC patients treated with the EGFR-TKIs. The Response Evaluation Criteria in Solid Tumors is generally used to assess the therapeutic response to antitumor drugs based on the morphological changes in tumor size as evaluated by computed tomography or magnetic resonance imaging. However, such assessment may not always reflect the treatment efficacy of cytostatic drugs, such as EGFR-TKIs. In this regard, functional imaging methods, including ¹⁸F-fluorodeoxyglucose measured by positron emission tomography (FDG-PET), are potentially beneficial. An increasing body of evidence indicates the usefulness of FDG-PET

to predict treatment efficacy for NSCLC patients treated with EGFR-TKIs. In this review, we summarize the current understanding of the potential role of FDG-PET in the clinical use of EGFR-TKIs for NSCLC.

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Key words: Non-small cell lung cancer; ¹⁸F-fluorodeoxyglucose measured by positron emission tomography; Epidermal growth factor receptor mutation; Gefitinib; Erlotinib; Survival; Biomarker

Core tip: Molecularly targeted drugs including epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs), which usually exhibit cytostatic antitumor activity, have emerged for the treatment of non-small cell lung cancer. The Response Evaluation Criteria in Solid Tumors is generally used to assess the therapeutic response based on the morphological changes in tumor size as evaluated by computed tomography or magnetic resonance imaging. However, such assessment may not always reflect the clinical outcome of cytostatic drugs, such as EGFR-TKIs. In this regard, ¹⁸F-fluorodeoxyglucose measured by positron emission tomography (FDG-PET) is potentially beneficial. Here we summarize the role of FDG-PET to predict the treatment efficacy in NSCLC treated with EGFR-TKIs.

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Lung cancer is the major cause of cancer-related deaths worldwide^[1]. Lung cancer comprises two major histological types: small cell lung cancer and non-small cell lung cancer (NSCLC), and the latter represents 80%-85% of

Table 1 Studies evaluating the predictive roles of early ¹⁸F-fluorodeoxyglucose measured by positron emission tomography assessment on clinical outcome in non-small cell lung cancer treated with epidermal growth factor receptor-tyrosine kinase inhibitors

Ref.	EGFR-TKIs	Patient no.	Evaluation timing	EGFR mutation status			Significant association	
				Mutant	Wild-type	Unknown	PFS or TTP ¹	OS
Takahashi <i>et al.</i> ^[25]	Gefitinib	20	2 d	12	3	5	Yes	NA
Soto Parra <i>et al.</i> ^[24]	Erlotinib	23	2 d	NA	NA	NA	Yes	No
Mileshkin <i>et al.</i> ^[23]	Erlotinib	51	2 wk	4	30	17	Yes	Yes
Zander <i>et al.</i> ^[26]	Erlotinib	34	1 wk	4	24	6	Yes	Yes
Benz <i>et al.</i> ^[22]	Erlotinib	22	2 wk	4	1	17	Yes ¹	Yes
Bengtsson <i>et al.</i> ^[21]	Erlotinib	125	2 wk	10	90	25	NA	Yes

¹Significant association with time to progression. NA: Data not available; EGFR-TKIs: Epidermal growth factor receptor-tyrosine kinase inhibitors; PFS: Progression-free survival; OS: Overall survival; TTP: Time to progression.

all lung cancers^[2]. The majority of patients with NSCLC have locally advanced or metastatic disease at the time of diagnosis, and chemotherapy with cytotoxic agents remains marginally effective^[3,4]. In recent years, molecularly targeted drugs, which usually exhibit cytostatic antitumor activity, have emerged for the treatment of NSCLC. The effective use of molecularly targeted drugs requires the identification of biomarkers to predict treatment response and clinical outcomes in NSCLC patients^[5]. Recent advances in basic and translational research have identified epidermal growth factor receptor (*EGFR*) mutation as the most promising biomarker for predicting the treatment efficacy of the EGFR-tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib for NSCLC patients^[6-11]. However, the clinical benefit of EGFR-TKI treatment is not confined to patients whose tumors harbor *EGFR* mutations, and some *EGFR*-mutated NSCLC patients do not respond to EGFR-TKIs^[12]. Furthermore, sufficient tumor samples to test *EGFR* mutation status are not always available, and alternative methods to predict the efficacy of EGFR-TKI therapy are therefore warranted.

The therapeutic response to antitumor drugs is generally evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST)^[13]. On the RECIST evaluation, target lesions are measured before and after chemotherapy by morphological imaging technologies, including computed tomography (CT) and magnetic resonance imaging (MRI). However, morphological changes in tumors usually take several weeks to occur after chemotherapy, and targeted tumor lesions contain noncancerous cell components such as necrotic, cystic and fibrotic lesions. Thus, RECIST evaluation based on size-measurements of total tumor volume may not always reflect the treatment efficacy, especially when patients are treated with cytostatic drugs^[14].

In a phase II trial of gefitinib monotherapy, NSCLC patients who had achieved stable disease (SD) had a favorable prognosis compared to those with progressive disease (PD)^[15]. Similarly, of the NSCLC patients treated with gefitinib, the overall survival (OS) of patients with SD was significantly longer compared to those with PD^[16]. In addition, erlotinib significantly prolonged OS despite a response rate of less than 10% in a large phase

III trial, possibly due to a high proportion of patients with SD^[17]. These findings highlight the limitations of the RECIST criteria regarding the assessment of treatment efficacy for cytostatic drugs such as EGFR-TKIs. In this regard, molecular imaging methods, such as ¹⁸F-fluorodeoxyglucose measured by positron emission tomography (FDG-PET), are advantageous because of their ability to detect changes in glucose metabolism, proliferative activities and the vascularization of tumors, which occur earlier than morphological changes^[18,19]. Currently, FDG-PET has been the most wide-spreading imaging technique used as a diagnostic tool in various cancers, including NSCLC^[20].

Several lines of evidence have indicated the value of FDG-PET to predict the therapeutic response and clinical outcome of EGFR-TKI therapy in NSCLC patients as shown in Table 1^[21-26]. In 2008, we reported a preliminary study that assessed the roles of FDG-PET in predicting the treatment efficacy of gefitinib in five NSCLC patients^[27]. The patients underwent FDG-PET 2 d (early phase) and 4 wk (late phase) after administration of gefitinib, and FDG uptake was evaluated as the maximum standardized uptake value (SUV_{max}) of the target lesions, which were evaluable by conventional CT. Of the four patients with sensitizing *EGFR* mutations, two patients exhibited a partial response (PR), and others had SD with decreased tumor size but did not achieve PR as evaluated by RECIST. In all of these patients, FDG uptake markedly decreased at the earlier phase from baseline as assessed by a mean \pm SD SUV_{max}% of 60% \pm 14% (60% \pm 18% and 59% \pm 12% for PR and SD groups, respectively). Notably, the two patients with SD had a long-term progression-free survival (PFS) of \geq 12.5 mo and an OS of \geq 16.9 mo. While these results were obtained from a small sample size, our findings suggest that FDG-PET can potentially assess the treatment efficacy of gefitinib for NSCLC patients more accurately than morphological evaluation.

Recently, Takahashi *et al.*^[25] reported a similar study of 20 lung adenocarcinoma patients receiving gefitinib monotherapy. In their study, changes in tumor FDG uptake 2 d after gefitinib initiation were positively correlated with changes in tumor size assessed by CT 1 mo after the treatment. In addition, metabolic responders defined as Δ

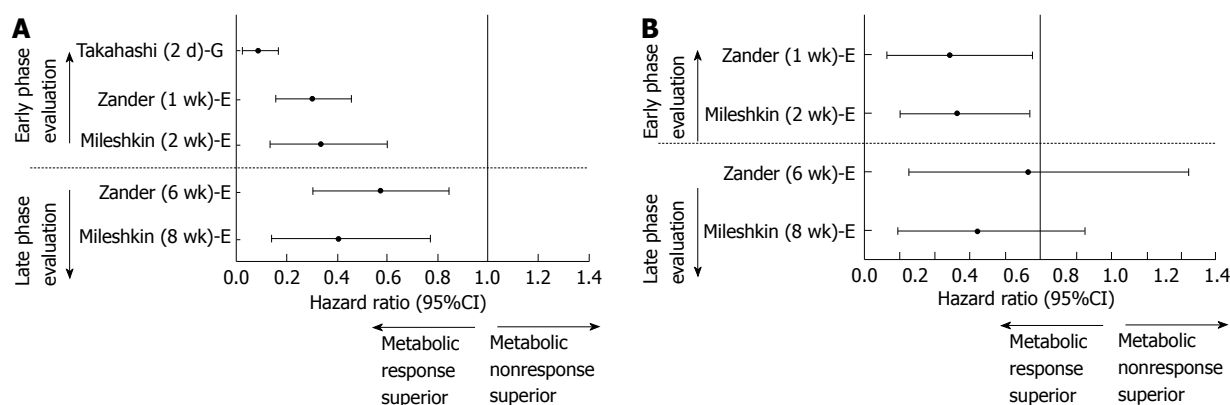


Figure 1 Progression-free survival (A) and overall survival (B) hazard ratios of 18F-fluorodeoxyglucose measured by positron emission tomography metabolic responders over the metabolic nonresponders with 95%CI based on the results from previous studies. The groups over the dotted line represent the data of early phase evaluation (2 d, 1 wk or 2 wk) and the groups under the dotted line represent the data of late phase evaluation (6 wk or 8 wk) after the initiation of epidermal growth factor receptor-tyrosine kinase inhibitor therapy. The data were available from references of [23,25,26].

$SUV_{max}\% < -20\%$ had significantly longer PFS than metabolic non-responders ($\Delta SUV_{max}\% \geq -20\%$) when SUV_{max} changes were evaluated after 2 d of treatment. This study demonstrates that the earlier metabolic response at 2 d could predict the prognosis of gefitinib-treated NSCLC patients. These findings indicate that early FDG-PET assessment is useful to predict the treatment efficacy of gefitinib monotherapy compared to the conventional morphological assessment by CT or MRI.

Several studies have assessed the role of FDG-PET to predict the treatment efficacy of the EGFR-TKI erlotinib^[21-24,26,28-30]. Aukema *et al.*^[28] assessed NSCLC patients who received neoadjuvant erlotinib by FDG-PET 1 wk after treatment. Of the resected tumors, 70% of metabolic responders defined as $\Delta SUV_{max}\% \leq -25\%$ [interquartile ranges (IQRs), 30%-91%] and 40% of non-responders (IQRs, 20%-50%) were necrotic. The metabolic and pathologic responses correlated significantly, suggesting that a change in FDG uptake is closely associated with the pathologic response to erlotinib. Other clinical studies have prospectively investigated whether an early FDG-PET assessment could predict the tumor response to erlotinib and survival in NSCLC patients. Soto Parra *et al.*^[24] reported that the metabolic response evaluated by FDG-PET 2 d after erlotinib initiation was significantly associated with a longer PFS in NSCLC patients. In a study by Mileskin *et al.*^[23], the metabolic response ($\Delta SUV_{max}\% \leq -15\%$) at 2 wk after erlotinib initiation was significantly associated with both improved PFS and OS in NSCLC patients receiving 2nd/3rd-line erlotinib monotherapy. Of note, in a subset of patients with wild-type *EGFR*, early metabolic responders tended to have a longer PFS compared to the metabolic non-responders^[23]. Similar findings were also observed in another study, in which the metabolic response ($\Delta SUV_{peak}\% \leq -30\%$) 1 wk after erlotinib initiation was significantly associated with both improved PFS and OS in NSCLC patients, irrespective of *EGFR* mutation status^[26]. The same group subsequently investigated the predictive values of changes in FDG uptake using different SUV

parameters (SUV_{max} , SUV_{2Dpeak} , SUV_{3Dpeak} , SUV_{50} , SUV_{A50} , SUV_{A41} , SUV_{70} , SUV_{A70} and SUV_{RTL}) and found that SUV_{max} best assesses the early metabolic response^[30]. They also found that a lower residual FDG uptake measured by SUV_{max} and SUV_{2Dpeak} (but not other SUV parameters) at the early phase of treatment was associated with a significantly longer PFS^[29]. Furthermore, another group reported that the patients with progressive metabolic disease ($\Delta SUV_{peak}\% \geq 30\%$) 2 wk after erlotinib initiation had a significantly shorter time to progression and OS compared to those with stable metabolic disease or a metabolic response of $\Delta SUV_{peak}\% \leq -30\%$ ^[22]. In a recent study that assessed FDG-PET in 2nd/3rd-line erlotinib monotherapy for NSCLC patients, the absence of new lesions by FDG-PET 2 wk after erlotinib initiation was the most predictive marker for OS as opposed to changes in FDG uptake ($\Delta SUV_{max}\% \leq -35\%$)^[21]. However, FDG changes were a predictor of OS only when *EGFR* mutation status was not accounted for^[21].

The predictive value of the late phase FDG-PET assessment on clinical outcome of EGFR-TKI-treated NSCLC patients has also been evaluated. In a recent study, of 38 NSCLC patients who underwent FDG-PET scan at 6 wk after erlotinib initiation, the metabolic responders with $\Delta SUV_{peak}\% \leq -25\%$ survived longer than the non-responders^[31]. Importantly, two studies evaluated the predictive value of both early and late FDG-PET assessments on survival of NSCLC patients treated with erlotinib^[23,26]. In both studies, FDG-PET response at the late phase (6 or 8 wk) was not significantly associated with improved overall survival. The hazard ratios for PFS and OS in these studies are summarized in Figure 1. Overall, these findings indicate that FDG-PET assessment at the early phases of EGFR-TKI therapy could predict the clinical outcome of NSCLC patients better than assessment at a later phase, irrespective of *EGFR* mutation status.

Previous studies have investigated the molecular mechanisms of FDG-PET to predict the tumor response to EGFR-TKIs at an early stage^[32,33]. Treatment with ge-

fitinib reduced FDG uptake in the H3255 and HCC4006 NSCLC cell lines harboring sensitizing *EGFR* mutations within 2 h and reduced FDG uptake in the xenografts of these tumor cells after 2 d of treatment^[33]. The gefitinib-mediated decrease in FDG uptake preceded the inhibition of cell proliferation and induction of apoptosis, and this phenomenon was accompanied with the translocation of glucose transporters from the cell membrane to the cytoplasm. This finding suggests that FDG-PET could detect the antitumor effects of EGFR-TKIs at a molecular level before phenotypic changes occur in tumors^[33]. In contrast, Ullrich *et al.*^[32] failed to demonstrate a significant decrease in FDG uptake after 2 and 4 d of erlotinib treatment in tumor xenografts of the *EGFR*-mutated NSCLC cell lines PC9 and HCC827. These inconsistent results may be due to the differences in cellular context, such as differences in the expression levels of glucose transporters and the sensitivity to EGFR-TKIs.

Clinical studies have also revealed the diverse effects of EGFR-TKIs on the early metabolic response of FDG-PET in *EGFR*-mutant NSCLC patients^[23,25,26]. For instance, in a study by Takahashi *et al.*^[25], 4 of 12 (33%) patients with *EGFR* mutations were metabolic non-responders. Three of these patients had stable metabolic disease and one patient had progressive metabolic disease 2 d after gefitinib initiation. Taken together, these findings suggest that FDG-PET assessment could identify the patients who benefit from EGFR-TKI therapies in a population of *EGFR*-mutated NSCLC patients. FDG metabolism is also likely closely linked to the sensitivity of NSCLC to EGFR-TKIs.

In summary, an increasing body of evidence indicates the potential of FDG-PET to predict the treatment efficacy and clinical outcome of NSCLC patients who are treated with EGFR-TKIs. The metabolic response has previously been assessed by different criteria, including EORTC^[34] and PERCIST^[14]. Thus, standardizing the PET response assessment is essential to establish the predictive values of FDG-PET. Moreover, further studies with larger patient numbers will be needed to evaluate the predictive values of FDG-PET to assess the clinical efficacy of EGFR-TKIs in NSCLC patients.

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