

WJR 6th Anniversary Special Issues (6): CT**FDG-PET/CT response evaluation during EGFR-TKI treatment in patients with NSCLC**

Matthijs H van Gool, Tjeerd S Aukema, Koen J Hartemink, Renato A Valdés Olmos, Harm van Tinteren, Houke M Klomp

Matthijs H van Gool, Koen J Hartemink, Houke M Klomp, Department of Surgical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands

Tjeerd S Aukema, Renato A Valdés Olmos, Department of Nuclear Medicine, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands

Harm van Tinteren, Department of Biometrics, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, 1066 CX Amsterdam, The Netherlands

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Correspondence to: Houke M Klomp, MD, PhD, Department of Surgical Oncology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands. h.klomp@nki.nl

Telephone: +31-20-5122554 Fax: +31-20-5129111

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Abstract

Over recent years, [18F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography (FDG-PET/CT) has proven its role as a staging modality in patients with non-small cell lung cancer (NSCLC). The purpose of this review was to present the evidence to use FDG-PET/CT for response evaluation in patients with NSCLC, treated with epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI). All published articles from 1 November 2003 to 1 November 2013 reporting on 18F-FDG-PET response evaluation during EGFR-TKI treatment in patients with NSCLC were collected. In total 7 studies, including data of 210 patients were eligible for analyses. Our report shows that FDG-PET/CT response

during EGFR-TKI therapy has potential in targeted treatment for NSCLC. FDG-PET/CT response is associated with clinical and radiologic response and with survival. Furthermore FDG-PET/CT response monitoring can be performed as early as 1-2 wk after initiation of EGFR-TKI treatment. Patients with substantial decrease of metabolic activity during EGFR-TKI treatment will probably benefit from continued treatment. If metabolic response does not occur within the first weeks of EGFR-TKI treatment, patients may be spared (further) unnecessary toxicity of ineffective treatment. Refining FDG-PET response criteria may help the clinician to decide on continuation or discontinuation of targeted treatment.

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Key words: Non-small cell lung cancer; Epidermal growth factor receptor-tyrosine kinase inhibitors therapy; Positron emission tomography-computed tomography; Computed tomography; Response monitoring

Core tip: Our report shows that response monitoring using [18F]-fluorodeoxyglucose positron emission tomography (FDG-PET) acquired together with low dose computed tomography has potential in targeted treatment for non-small cell lung cancer and can be performed as early as 1-2 wk after initiation of treatment. Patients with substantial decrease of metabolic activity during epidermal growth factor receptor-tyrosine kinase inhibitors treatment will probably benefit from continued treatment. Refining FDG-PET response criteria may help the clinician to decide on continuation or discontinuation of targeted treatment.

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INTRODUCTION

Over recent years, [18F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography (FDG-PET/CT) has proven its role as a staging modality in patients with non-small cell lung cancer (NSCLC)^[1-3]. In addition, *FDG-PET/CT* has been evaluated as a method to monitor tumor response to chemotherapy. Several studies demonstrated that FDG-PET/CT is able to predict response to treatment in various malignancies, *i.e.*, breast cancer^[4,5], malignant lymphoma^[6,7] and colorectal cancer^[8]. Diagnostic CT has been the clinical standard for response evaluation in NSCLC. There is an ongoing discussion on the performance of FDG-PET/CT as compared to CT^[9-11].

With advances in molecular research, molecular-targeted agents such as epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKI) have emerged for the treatment of (advanced) NSCLC. EGFR-TKIs are able to induce swift responses in selected groups of NSCLC patients and TKI treatment is associated with survival benefit when given as second-line treatment in unselected patients^[12]. It blocks the tyrosine kinase domain of the EGFR, thereby inhibiting downstream signaling pathways involved in cell proliferation, angiogenesis, invasion and metastasis and prevention of apoptosis. They can be orally administered, have a relatively favorable toxicity profile, and are registered for the treatment of patients with advanced (chemotherapy-refractory) NSCLC^[13].

The probability of response to EGFR-TKIs is considerably higher in patients with EGFR-mutated tumors^[14-16]. However, prediction of response is suboptimal by mutation analysis only^[17,18]. It is known, that several patients without apparent sensitizing EGFR mutations do benefit from erlotinib therapy^[19]. This may be due to heterogeneity within the tumor or the limitations of biopsy analysis not always showing relevant mutations. On the other hand, patients who do not respond to EGFR-TKI's, despite the presence of activating mutations, could be spared unnecessary toxicity and costs. Therefore early decision making as to the effect of treatment is essential.

In this perspective, we present the evidence to use FDG-PET/CT for response evaluation in patients with NSCLC, treated with EGFR-TKI.

SEARCH

Study eligibility and identification

We performed a systematic computerized search of the of PubMed and Medline databases (last search: 01 November 2013) and the Cochrane library (Issue 10, 31 October 2013) to identify all published articles from 01

November 2003 to 01 November 2013 reporting on 18F-FDG-PET response evaluation during EGFR-TKI treatment in patients with NSCLC, using the algorithm: [(Non-Small Cell Lung Carcinoma OR NSCLC) AND (Epidermal Growth Factor Receptor OR EGFR) AND (Diagnostic Imaging) AND (18-FDG PET)]. We also hand-searched journals known to publish data relevant to our search, the reference lists of all articles we recovered and those of relevant review articles were also cross-referenced. Experts in the field were contacted to broaden our yield of potentially eligible articles. Whenever several reports pertained to overlapping groups of patients, we retained only the report with the largest number of events or largest patient population (where appropriate) to avoid duplication of information.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) histologically proven NSCLC; (2) use of 18F-FDG as a tracer; (3) use of an 18F-FDG-PET/CT scanning apparatus in humans; (4) use of EGFR-TKI; and (5) articles reported in English.

Studies examining EGFR-targeted agents in combination with other agents were considered eligible, as were single agent anti-EGFR studies, whether they were single arm non-randomised studies, phase II or III randomised studies, prospective studies, or retrospective studies. Abstracts, meeting proceedings and case reports, defined as studies reporting on fewer than five patients, were excluded. When datasets were incomplete for required data, corresponding authors were contacted; however, no additional data were obtained by this process. Our literature search was limited to published studies.

Data extraction

The following information was manually extracted from each recovered article: first author, journal and year of publication, number of patients screened, EGFR mutational rate, stage of disease correlations with clinicopathologic and demographic data (*i.e.*, smoking status, history, gender, histologic type), and also for data to treatment outcome [*i.e.*, CR, PR CR + PR, stable disease (SD), progressive disease (PD), and nonassessable patients] with the TKIs gefitinib and erlotinib when administered as single agent, *i.e.*, monotherapy TKI. No stratification has been made according to TKI with respect to response data. Information recorded about each recovered reference is listed in Table 1. Data extraction was done independently by two of the authors (MG and TA) and discrepancies were resolved by consensus including a third author (HK).

RESEARCH

During the search period, a total of 20 articles of potential interest have been screened for 18F-FDG-PET/CT response evaluation during EGFR-TKI treatment in patients with NSCLC. Of these, 13 were excluded because

Table 1 Patient characteristics n(%)

Ref.	Year of publication	n	Age, yr	M/F	Study type	Study protocol FDG response	Stage of disease	Histology	EGFR Selection
Riely <i>et al</i> ^[20]	2007	13	56	2/11	Prospective	21 d after stopping and 21 d after restarting	IV	Adenocarcinoma 11 (85) Other (including NOS) 2 (15)	Only EGFR mutated tumors
Aukema <i>et al</i> ^[21]	2010	23	63	8/15	Prospective	After 7 d	I - III	Adenocarcinoma 17 (73) Other 6 (26)	No selection
Mileshkin <i>et al</i> ^[11]	2011	51	61	30/21	Prospective	After 14 d and 56 d	III - IV	Adenocarcinoma 37 (72) Squamous cell carcinoma 8 (16) Large-cell carcinoma 1 (2) Other (including NOS) 5 (10)	No selection
Zander <i>et al</i> ^[22]	2011	34	61	17/17	Prospective	After 7 d and 42 d	IV	Adenocarcinoma 26 (76) Squamous cell carcinoma 4 (12) Large cell carcinoma 1 (3) Bronchioloalveolar carcinoma 3 (9)	No selection
Benz <i>et al</i> ^[23]	2011	22	64	6/16	Prospective	After 14 d and 78 d	III - IV	Adenocarcinoma 17 (78) Squamous cell carcinoma 3 (14) Other (including NOS) 1 (4) Large cell carcinoma 1 (4)	No selection
O'Brien <i>et al</i> ^[24]	2012	47	63	18/29	Prospective	After 42 d	III - IV	Adenocarcinoma 28 (60) Squamous cell carcinoma 6 (13) Bronchioalveolar carcinoma 7 (14) Other (including NOS) 6 (13)	No selection
Takahashi <i>et al</i> ^[25]	2012	20	69	5/15	Prospective	After 2 d and 28 d	III - IV	Adenocarcinoma 20 (100)	No selection

FDG: [18F]-fluorodeoxyglucose; EGFR: Epidermal growth factor receptor.

they did not meet the defined inclusion criteria. In total, data of 210 patients were eligible for analyses^[11,20-25]. The characteristics of eligible studies are summarised in Table 1.

FDG-PET/CT and response

The majority of studies used European Organization for Research and Treatment of Cancer (EORTC) criteria to determine response^[26] (Tables 2 and 3). Cut-off values to determine response varied from 15% to 30% change in SUVmax between baseline and response FDG-PET/CT scan. Median cut-off value was 15%. Time between initiation of EGFR-TKI therapy and response FDG-PET/CT scan varied from 2-78 d^[11,14,20-25].

FDG-PET/CT vs diagnostic CT

Four studies analysed FDG-PET and CT according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria for response (Tables 2 and 3). There was a large variety in days between initiation of EGFR-TKI therapy and response FDG-PET/CT scan (2-56 d) and response CT scan (28-84 d). However all studies showed that FDG-PET response correlated with CT response. The majority of patients with response on FDG-PET/CT scan also showed response on CT-scan. In addition, zero patients with progressive disease on FDG-PET/CT scan had a response on CT-scan^[11,14,22,24,25].

FDG-PET/CT and progression free survival

Four studies reported on progression free survival (PFS)^[11,22,23,25] (Tables 2 and 3). In general, patients with metabolic response showed a prolonged progression

free survival varying from 3.0 to 8.7 mo. Mileshkin *et al*^[11] showed that response at FDG-PET/CT on day 14 was associated with improved PFS using EORTC criteria and Wahl *et al*^[27] using Response Criteria in Solid Tumors (PERCIST). In addition Zander *et al*^[22] reported the same association on day 7. Takahashi *et al*^[25] found no significant relation at 2 d using a cut-off value of 30%, however when a cutoff value of 20% was used, metabolic responders had significantly longer PFS compared with metabolic non-responders.

FDG-PET/CT and overall survival

Five studies reported on metabolic response and overall survival (OS)^[11,22-25] (Tables 2 and 3). Metabolic response was associated with improved OS. Both Mileshkin *et al*^[11] and Zander *et al*^[22] reported early FDG-PET/CT response (resp. 14 d, 7 d) to be significantly associated with longer OS. Metabolic response as shown during later FDG-PET/CT evaluation (resp. 56 d, 42 d) was also associated with longer survival, although this trend was not statistically significant. Similarly O' Brien *et al*^[24] reported that responders on FDG-PET/CT scan at 42 d lived longer than patients with metabolic stable disease. Takahashi *et al* did not find significant survival differences between metabolic responders and non-responders.

FDG-PET/CT EGFR

Forty-eight patients (23%) had an EGFR mutant tumor (Table 4). In one study patients were selected based on EGFR mutation. As shown before, patients with an EGFR mutant tumor were more likely to respond to EGFR therapy and thus to have response on FDG-

Table 2 Early [¹⁸F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography response results < 21 d

Ref.	Year of publication	n	SUV	Response criteria	FDG response time	Cut-off value	FDG response n (%)	FDG response, FDG-PET/CT vs RECIST	PFS	OS
Riely <i>et al</i> ^[20]	2007	13	Max	EORTC	21 d	15%	PR 6 (46) SD 7 (54)			
Aukema <i>et al</i> ^[21]	2010	22	Max	EORTC	7 d	25%	PR 6 (26) SD 16 (70) PD 1 (4)			
Mileshkin <i>et al</i> ^[11]	2011	51	Max	EORTC	14 d	15%	PR 13 (26) SD 17 (33) PD 21 (41)	FDG PR: PR 4 SD 7 PD 2 FDG SD: PR 0 SD 12 PD 5 FDG PD: PR 0 SD 7 PD 14	R 5.5 mo NR 2.5 mo	R 11.6 mo NR 7.6 mo
Zander <i>et al</i> ^[22]	2011	34	Peak	EORTC	7 d	30%	PR 8 (24) SD/PD 26 (76)	FDG PR: PR/SD 6 PD 2 FDG SD/PD: PR/SD 5 PD 21	R 7.8 mo NR 1.5 mo	R 16.1mo NR 3.4mo
Benz <i>et al</i> ^[23]	2011	22	Max	PRECIST	14 d	30%	PR 6 (27) SD 7 (32) PD 9 (41)		R 11.1 mo NR 2.4 mo	R 16.4 mo NR 14.7 mo
Takahashi <i>et al</i> ^[25]	2012	20	Max	EORTC	2 d	25%	PR 10 (50) SD 8 (40) PD 2 (10)	FDG PR: PR 8 SD 2 PD 0 FDG SD: PR 2 SD 5 PD 1 FDG PD: PR 0 SD 1 PD 1	R 10.4 mo NR 1.7 mo	

FDG: [¹⁸F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography; RECIST: Response Evaluation Criteria in Solid Tumors; PFS: Progression free survival; EORTC: European Organization for Research and Treatment of Cancer.

Table 3 Late [¹⁸F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography response > 21 d

Ref.	Year of publication	n	SUV	Response criteria	Cut-off value	FDG response time	FDG Response n (%)	FDG-PET vs RECIST	PFS	OS
Mileshkin <i>et al</i> ^[11]	2011	51	Max	EORTC	15%	56 d	PR 8 (16) SD 12 (23) PD 31 (61)	FDG PR: PR 4 SD 4 PD 0 FDG SD: PR 0 SD 11 PD 1 FDG PD: PR 0 SD 11 PD 20	R 6.5 mo NR 2.7 mo	R 11.9 mo NR 7.6 mo
Zander <i>et al</i> ^[22]	2011	34	Peak	EORTC		42 d	n/a	n/a		
Benz <i>et al</i> ^[23]	2011	22	Max	PRECIST		78 d	n/a	n/a		
O'Brien <i>et al</i> ^[24]	2012	47	Max	EORTC	25%	42 d	PR 15 (32) SD 8 (17) PD 15 (32) NE 9 (19)	FDG PR: PR 11 SD 2 PD 2 FDG SD: PR 0 SD 4 PD 4 FDG PD: PR 0 SD 2 PD 7		
Takahashi <i>et al</i> ^[25]	2012	20	Max	EORTC		28 d	n/a	n/a		

FDG: [¹⁸F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography; RECIST: Response Evaluation Criteria in Solid Tumors; PFS: Progression free survival; EORTC: European Organization for Research and Treatment of Cancer; n/a: Not applicable.

PET^[11,23,25].

DISCUSSION

This review summarizes the available data regarding the potential of FDG-PET/CT to predict or monitor treatment efficacy and the relation of metabolic data to clinical outcome in NSCLC patients who are treated with EGFR-TKIs. Our report shows that FDG-PET/CT response during EGFR-TKI therapy is associated with clinical and radiologic response and with survival. FDG-PET shows informative results as early as 7-14 d after initiation of treatment.

This report includes a heterogeneous group of NSCLC subtypes. Over time, it has become clear that adenocarcinomas are more likely to respond to EGFR-TKI treatment^[28]. However, histological classification of squamous-cell and adenocarcinoma is challenging^[29]. This

difficulty increases in the preoperative setting where attempts at tumor classification in small diagnostic samples are hampered by the paucity of tumor cells and the absence of tissue architecture^[30]. Although the efficacy of EGFR-TKIs is higher in patients with EGFR-mutated tumors, prediction of response is not optimal by mutation analysis only. It is known, that several patients without sensitizing EGFR mutations do benefit from EGFR-TKI therapy. This may be due to heterogeneity within the tumor and biopsies will not always show relevant mutations^[31]. Tumor response monitoring is of value since unnecessary toxicity and additional cost of administering ineffective treatment can be avoided, especially if monitoring is feasible and informative early during treatment.

For categorization of metabolic response, varying response criteria were used (EORTC, PRECIST). Different cut-off values were used between studies, resulting in suboptimal comparison. However overall, results

Table 4 Epidermal growth factor receptor

Ref.	Year of publication	n	EGFR selection	EGFR mutation (n)	Cut-off value	FDG	PFS
Riely <i>et al</i> ^[20]	2007	13	Only EGFR mutated tumors	8	n/a		
Aukema <i>et al</i> ^[21]	2010	22	No selection	4	25%		
Milishkin <i>et al</i> ^[11]	2011	51	No selection	4	> 15%	EGFR + PR 3 PD 2 SD 0 EGFR - PR SD PD	
Zander <i>et al</i> ^[22]	2011	34	No selection	4			EGFR + 6.4 mo EGFR - 1.6 mo
Benz <i>et al</i> ^[23]	2011	22	No selection	5			
O'Brien <i>et al</i> ^[24]	2012	47	No selection	11			
Takahashi <i>et al</i> ^[25]	2012	20	No selection	12		EGFR+ PR 8 SD 3 PD 1 EGFR- PR SD PD	

EGFR: Epidermal growth factor receptor; FDG: [¹⁸F]-fluorodeoxyglucose positron emission tomography acquired together with low dose computed tomography; PFS: Progression free survival; n/a: Not applicable.

suggest that any significant metabolic response on FDG-PET/CT is associated with radiologic response later on and longer survival. For example, Mileskin *et al*^[11] and Benz *et al*^[23] show similar distributions of response relations using different cut-off values 15% vs 30% and different response criteria. As natural variability (repeatability) of FDG-PET is also relevant for implementation of response assessment, lower cut-off values (15%-20%) may increase false positive results for identification of response^[9].

Furthermore there is no consensus regarding the optimal timing in performing FDG-PET/CT after initiation of treatment. Several authors suggest that in advanced NSCLC metabolic response on FDG-PET/CT scan as early as 1-2 wk after chemotherapy can predict progression free survival and overall survival^[17,26-29]. In this review with studies on EGFR-TKIs, Mileskin *et al*^[11] and Zander *et al*^[22] found significant associations of early response (day 14, day 7) with survival data. Other authors report the same trend. However, changing FDG-uptake on PET (early) during treatment may reflect all kinds of tissue reactions, as tumor regression (or progression) but also senescence, fibrosis formation, and inflammatory reactions as macrophage infiltration.

Several authors in this report use RECIST criteria as golden standard for response evaluation. However early diagnostic CT for response evaluation in EGFR-TKI therapy has severe limitations. EGFR-TKI therapy is expected to induce response *via* cytostasis rather than objective morphologic response^[32]. RECIST is further confounded by structural abnormalities, before and after treatment, which may not actually contain tumor^[33]. In this report all early FDG-PET-CT responses were associated with CT responses (according to RECIST), when CT was performed after a period of 28-84 d presuming that morphologic response have took place^[11,22,24,25].

Presumably, in patients with NSCLC treated with EGFR-TKIs, the potential value of FDG-PET/CT response monitoring is best described by its possibilities of early response identification. If metabolic response does not occur within the first weeks of EGFR-TKI treatment, patients may be spared (further) unnecessary toxic-

ity of ineffective treatment. Furthermore, even disregarding EGFR mutation, metabolic response during EGFR-TKI treatment is associated with favorable (progression free) survival^[11,22-25].

Concluding, our report shows that response monitoring using FDG-PET/CT has potential in targeted treatment for NSCLC and can be performed as early as 1-2 wk after initiation of treatment. Patients with substantial decrease of metabolic activity during EGFR-TKI treatment will probably benefit from continued treatment. Refining FDG-PET response criteria may help the clinician to decide on continuation or discontinuation of targeted treatment.

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