Prognostic value of early response assessment using (18F)FDG-PET in patients with advanced non-small cell lung cancer treated with tyrosine-kinase inhibitors

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ABSTRACT

The purpose of this meta-analysis was to determine the prognostic value of early response assessment using (18F)fluorodeoxyglucose (FDG)-positron emission thermography (PET) in patients with advanced non-small cell lung cancer (NSCLC) treated with tyrosine-kinase inhibitors (TKIs). MEDLINE, PubMed, Cochrane, EMBASE, and Google Scholar databases were searched until August 1, 2016 using the keywords non-small cell lung carcinoma, positron-emission tomography, fluorodeoxyglucose, prognosis, disease progression, survival, erlotinib, gefitinib, and afatinib. Inclusion criteria were studies of patients with stage III or IV NSCLC treated with a TKI and had response assessed by FDG-PET. Outcome measures were overall survival (OS) and progression-free survival (PFS). Of the 167 articles identified, 10 studies including 302 patients were included in the analysis. In 8 studies, patients were treated with erlotinib, and in 2 they were treated with gefitinib. The overall analysis revealed that early metabolic response was statistically associated with improved OS (HR=0.54; 95% CI 0.46 to 0.63; p<0.001), and with longer PFS (HR=0.23; 95% CI 0.17 to 0.33; p<0.001). Early response of patients with NSCLC treated with TKIs identified on FDG-PET is associated with improved OS and PFS.

Significance of this study

What is already known about this subject?

- Tyrosine-kinase inhibitors (TKIs) have become a treatment option for patients with advanced non-small cell lung cancer (NSCLC).
- Response of NSCLC to therapy has traditionally been determined with CT.
- Fluorodeoxyglucose (FDG)-positron emission thermography (PET)/CT has become a tool in the staging and monitoring of patients with NSCLC.

What are the new findings?

- This is the first meta-analysis that evaluated the prognostic value of early response identified by FDG-PET/CT of patients with advanced NSCLC treated with TKIs.
- Early metabolic response identified by FDG-PET/CT was statistically associated with improved overall survival in patients with advanced NSCLC treated with TKIs.
- Early metabolic response identified by FDG-PET/CT was significantly associated with longer PFS in patients with advanced NSCLC treated with TKIs.

How might these results change the focus of research or clinical practice?

- These results are important as the life expectancy of patients with advanced NSCLS is short, and rapid determination of a treatment's effectiveness may allow more prompt usage of a different treatment that may be more effective, and thus prolong survival as well as improve quality of life.

INTRODUCTION

Lung cancer is the most common malignancy worldwide, and the leading cause of cancer-related deaths.[1] Despite advances in treatment, the prognosis remains poor, especially for patients with non-small cell lung cancer (NSCLC).[1 2] Most patients with NSCLC present with advanced disease (stage III or IV); the overall survival (OS) has not improved markedly over the past decades, with 5-year OS rates between 10% and 15%.[1 2] Chemotherapy is still currently the first-line treatment for patients with advanced NSCLC, but the response rates vary markedly and response typically cannot be determined until 6 or more weeks after therapy has been administered.[1–3]

Epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs), such as erlotinib and gefitinib, have become a treatment option for patients with advanced NSCLC. TKIs have been shown to improve survival in patients with EGFR mutations, as well as in some patients with the wild-type EGFR gene.[1–3] However, as with chemotherapy, it is difficult to predict which patients will respond to therapy, and which will not see a benefit.[3 4] A method of

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predicting response early in the course of treatment would be of great clinical value as it would allow alternative treatments to begin promptly for those patients who are not responding to the current treatment, and to provide reassurance to patients in whom the current treatment is providing a benefit.[4 5] In addition, a method of evaluating response early in the course of treatment would avoid the costs and side effects of ineffective treatments.[6]

Response of NSCLC to therapy, whether to cytotoxic chemotherapy or TKIs, has traditionally been determined with CT using the Response Evaluation Criteria In Solid Tumors (RECIST) guidelines and criteria.[7] However, tumor shrinkage generally cannot be identified until several cycles of chemotherapy have been given, and evaluation is subject to interobserver and intraobserver variation.[8] Furthermore, tumor shrinkage may not be seen with TKIs despite an adequate response to treatment.[9–12]

Over the past two decades, positron emission thermography (PET)/CT with (18F)fluorodeoxyglucose (FDG)-PET/CT has become an indispensable tool for the diagnosis, evaluation of treatment response, and post-treatment surveillance of patients with most malignancies.[13 14] It has also been proven to play a major role in the staging and monitoring of patients with NSCLC.[15] FDG-PET/CT measures tumor glucose metabolism, and thus can identify a treatment response (decreased glucose metabolism) much earlier than CT, and before volumetric changes or other signs of response to therapy occur.[15] Studies have shown that decreased glucose metabolism, and hence response to treatment, can be identified in lung tumors from as early as 2 days to 3 weeks after initiating treatment with a TKI.[16 17] Early changes identified on FDG-PET/CT have also been shown to be associated with important clinical outcomes such as OS and progression-free survival (PFS).[18–20]

We thus hypothesize that FDG-PET/CT performed early after the start of a TKI (erlotinib or gefitinib) in patients with advanced NSCLC can accurately identify patients who benefit from this targeted therapy. Therefore, the objective of the current study was to perform a meta-analysis of available data to determine the prognostic value of early response assessment using FDG-PET/CT in patients with advanced stage NSCLC treated with the TKIs erlotinib and gefitinib.

MATERIALS AND METHODS

Literature search strategy

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.[21] MEDLINE, PubMed, Cochrane, EMBASE, and Google Scholar databases were searched from inception until August 1, 2016. Combinations of the following keywords were used for the searches: non-small cell lung carcinoma, NSCLC, positron-emission tomography, PET, fluorodeoxyglucose, F18, 18FDG, prognosis, disease progression, survival, erlotinib, gefitinib, afatinib.

Study selection and data extraction

Inclusion criteria were: (1) randomized controlled trials, two-arm prospective studies, retrospective studies; (2) studies included patients with advanced NSCLC (stage III or stage IV) who received preoperative (neoadjuvant) treatment with TKIs (erlotinib or gefitinib); (3) (18F)FDG-PET was used to assess the response to TKI therapy; (4) drug response was assessed by the European Organisation for Research and Treatment of Cancer (EORTC), RECIST, or Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria; (5) survival data were presented.

Letters, comments, editorials, case reports, proceedings, and personal communication were excluded. Studies that examined patients with early-stage NSCLC, as well as those that did not stratify patients based on metabolic response determined by (18F)FDG uptake (standardized uptake value (SUV)max), were also excluded. Finally, studies that did not provide quantitative data regarding an outcome of interest (eg, response rate, progression rate) were also excluded.

Studies were identified by the search strategy by two independent reviewers. When there was uncertainty regarding eligibility, a third reviewer was consulted. Reference lists of relevant studies were also searched. The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants' age and gender, and outcome data.

Quality assessment

The Quality in Prognostic Studies (QUIPS) tool developed by Hayden *et al*[22] was used to assess the quality of the included studies. The tool is useful for evaluating observational studies with regard to six areas of potential bias: study participation, study attrition, measurement of prognostic factors, measurement of and controlling for confounding variables, measurement of outcomes, and analysis approaches. Quality assessment was also performed by two independent reviewers, and a third reviewer was consulted for any uncertainties.

Outcome measures and data analysis

The primary outcome was OS, and the secondary outcome was PFS. HRs and 95% CIs were extracted for the primary and secondary outcomes for individual studies, and calculated for studies combined. If an HR was not available, the methods of Parmar *et al*[23] and Williamson *et al*[24] were used to provide an estimate of the HR and its variance.

A χ^2-based test of homogeneity was performed, and heterogeneity among the studies was evaluated by the Cochrane's Q and I^2 statistics. A Q statistic with a value of $p<0.10$ was considered to indicate statistically significant heterogeneity. The I^2 statistic indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, and a value >50% was considered to indicate significant heterogeneity. A random-effects model (DerSimonian-Laird method) of analysis was used if heterogeneity was detected ($I^2>50\%$ or Q statistics $p<0.1$). Otherwise, a fixed-effects model (Mantel-Haenszel method) was used. Combined effects were calculated, and a two-sided p value <0.05 was considered to indicate statistical significance. Sensitivity analysis was carried out using the leave-one-out approach. Publication bias was only assessed if there were more than 10 studies, as more than 10 studies are required to detect funnel plot asymmetry.[25] All analyses were performed using Comprehensive Meta-Analysis statistical software, V.2.0 (Biostat, Englewood, New Jersey, USA).

RESULTS

Literature search and study characteristics

A flow diagram of study selection is shown in figure 1. A total of 216 articles were identified in the database searches and though other sources and after duplicates were removed, 167 remained. These articles were screened by title and abstract and 144 were excluded. The remaining 23 full-text articles were assessed for eligibility, and 13 were excluded, the reasons for which are shown in figure 1. Thus, 10 studies were included in the meta-analysis.[6 16–19 26–30]

The 10 studies enrolled a total of 302 patients with advanced NSCLC treated with a TKI. The basic characteristics of the studies are summarised in table 1. Seven of the studies were prospective and three were retrospective. The patient age ranged from 57 to 69 years, and the proportion of patients who were male ranged from 21% to 66%. In eight studies, patients were treated with erlotinib, while in two studies they were treated with gefitinib, and the majority of patients had adenocarcinoma. FDG-PET/CT was performed from 2 days to 3 weeks after beginning TKI treatment, and the early metabolic response ranged from 27% to 58%.

Meta-analysis

Seven studies provided complete OS data and were included in the meta-analysis of OS. No significant heterogeneity was observed among the seven studies; therefore, a fixed-effects model of analysis was used (I^2=39.93%, Q statistic=9.989, p=0.125). The overall analysis revealed that early metabolic response was statistically associated with improved OS (HR=0.54; 95% CI 0.46 to 0.63; p<0.001; figure 2A).

Eight studies provided complete PFS data and were included in the meta-analysis. No significant heterogeneity was observed among the eight studies; therefore, a fixed-effects model of analysis was used (I^2=27.46%, Q statistic=9.650, p=0.209). The overall analysis revealed that early metabolic response was significantly associated with longer PFS (HR=0.23; 95% CI 0.17 to 0.33; p<0.001; figure 2B).

Sensitivity analysis

Sensitivity analyses of the results of OS and PFS were performed using the leave-one-out approach. The direction and magnitude of combined estimates did not vary markedly with the removal of the studies, indicating that the

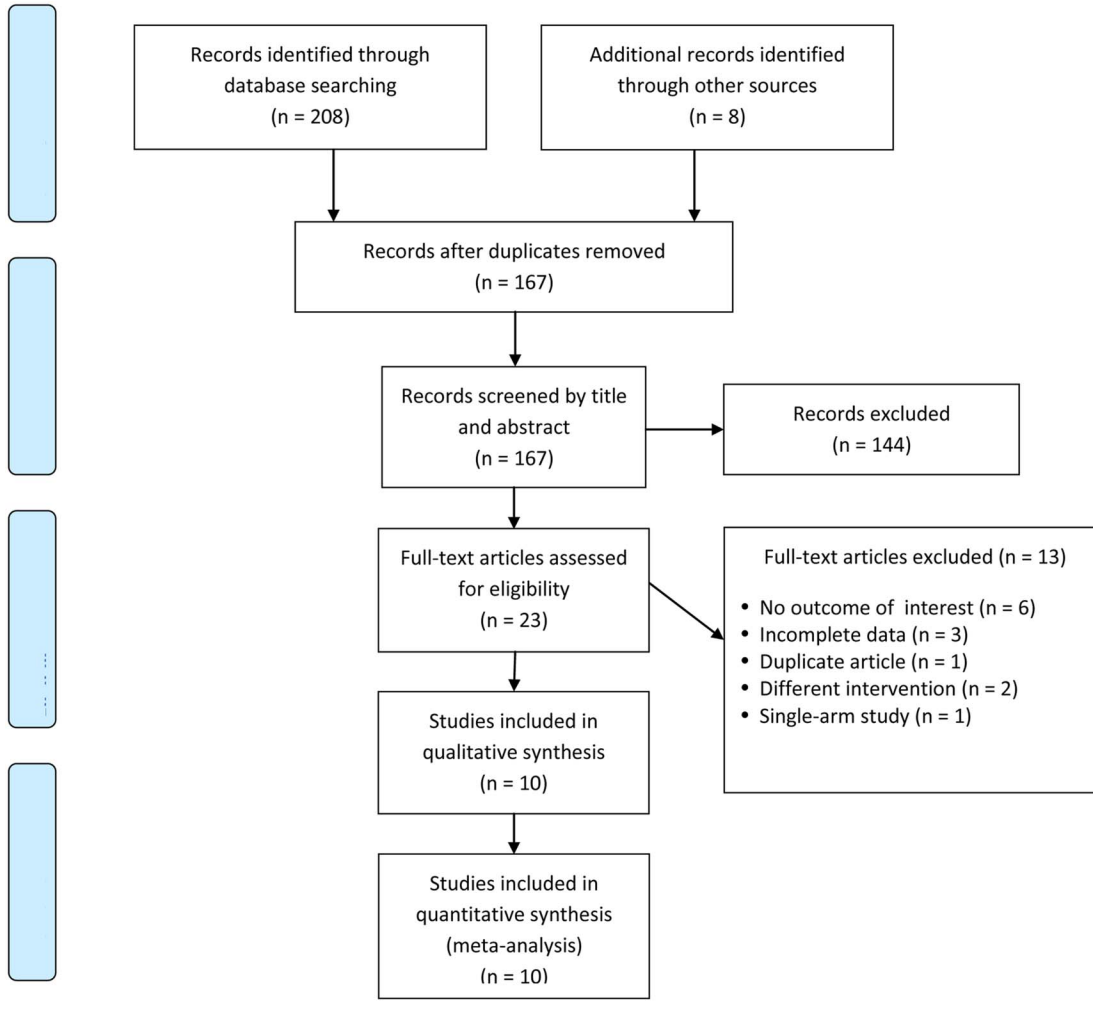

Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1 Basic characteristics of studies included in the meta-analysis

First author (publication year)	Study design	TKI	Number of patients	NSCLC stage III/IV	Adenocarcinoma (%)	Age (years)	Male (%)	Smoker (%)	EGFR mutation (%)	Response criteria	Definition/cut-off	Time PET performed	Metabolic response
Ho (2016)	Retrospective	150 mg/day erlotinib	26	4%/74%	100	57*	30	NA	NA	EORTC	ΔSUVmax<−25%	2 weeks	10 (38%)
Hachemi (2014)	Retrospective	150 mg/day erlotinib	12	17%/83%	58	60	50	58	17	RECIST	ΔSUVmax<−21.6%	2 weeks	7 (58%)
Kanazu (2014)	Prospective	Gefitinib	19	21%/79%	100	61*	21	11	63	EORTC	ΔSUVmax<−25%	3 days	7 (37%)
Tiseo (2014)	Prospective	150 mg/day erlotinib	53	0/100%	49	65*	66	49	NA	EORTC	ΔSUVmax	2 days	20 (37%)
Kahraman (2012)	Retrospective	Erlotinib	30	Advanced	77	64*	43	NA	17	TLG	ΔTLG≥20%	1 weeks	11 (58%)
Takahashi (2012)	Prospective	250 mg/day gefitinib	19	21%/79%	100	69*	25	25	63	EORTC	ΔSUVsum<−25%	2 days	9 (47%)
Benz (2011)	Prospective	Erlotinib	22	14%/86%	77	64	27	45	NA	Modified PERCIST	ΔSUVmax<−30%	2 weeks	6 (27%)
de Langen (2011)	Prospective	150 mg/day erlotinib	40	Advanced	NA	NA	NA	NA	NA	RECIST	ΔSUVmax<−25%	3 weeks	7 (18%)
Mileshkin (2011)	Prospective	150 mg/day erlotinib	51	Advanced	73	61*	59	90	11	EORTC	ΔSUVmax<−15%	2 weeks	13 (25%)
Zander (2011)	Prospective	150 mg/day erlotinib	30	0/100%	87	61*	57	NA	NA	PERCIST	ΔSUVpeak<−30%	1 weeks	8 (27%)

Time PET performed indicates time after beginning TKI treatment.
*Value presented as median.
EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; NA, not available; NSCLC, non-small cell lung cancer; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors; PET, positron emission thermography; RECIST, Response Evaluation Criteria In Solid Tumors; SUV, standardized uptake value; TKI, tyrosine kinase inhibitor; TLG, total lesion glycolysis.

meta-analysis had robustness, and the data were not overly influenced by each study (table 2).

Quality assessment

Quality assessment of the 10 studies is shown in figure 3. The assessment of individual showed that there were low risk bias and fair application concerns for most of the assessed criteria, except for higher risk of confounding measurement and account in seven studies (figure 3A). A summary of the risk of bias for all studies is shown in figure 3B.

DISCUSSION

To the best of our knowledge, this is the first meta-analysis that evaluated the prognostic value of early response identified by FDG-PET/CT of patients with advanced NSCLC treated with TKIs. The results indicated that an early response (from 2 days to 3 weeks after the start of therapy) was associated with prolonged OS and PFS. These results are important as the life expectancy of patients with advanced NSCLS is short, and rapid determination of a treatment's effectiveness may allow more prompt usage of a different treatment that may be more effective, and thus prolong survival as well as improve quality of life.

Since its introduction, PET has become an indispensable tool for the diagnosis and monitoring of treatment response of many malignancies. In brief, PET measures tumor glucose metabolism, and a response to treatment is indicated by a decrease in the metabolism of glucose in the tumor.[14] Since PET is measuring a different feature than CT, the RECIST criteria used for CT evaluation of tumor response (generally volume changes) are not entirely useful for evaluating the response examined by PET.[7 14] Qualitative and quantitative approaches to FDG-PET/CT response assessment have been developed, and require a consistent PET methodology to allow quantitative assessments. Statistically significant changes in tumor SUV have been found in careful test–retest studies of high-SUV tumors, with a change of 20% in SUV of a region 1 cm or larger in diameter; however, medically relevant beneficial changes are often associated with a 30% or greater decline.[7] The greater the decline in SUV, the more effective the treatment is considered.[7]

RECIST criteria have been modified for PET evaluation, and are referred to as PERCIST. Using PERCIST criteria, patients are generally classified as complete metabolic responders (CMR; complete resolution of tumor (18F) FDG uptake), partial metabolic responders (PMR; reduction of a minimum of 30% in target lesion uptake), progressive metabolic disease (PMD; increase of a minimum of 30% in target lesion uptake or presentation of a new lesion), and stable metabolic disease (not CMR, PMR, or PMD).[6 7] Total lesion glycolysis using a systematic approach is a relatively new method measuring response by PET, and some studies have suggested that it may be superior to PERCIST and EORTC methods.[29 31 32]

Although not meeting the criteria of the current meta-analysis, many other reports have indicated that early FDG-PET/CT can predict the response of patients with NSCLC to TKIs.[4 5 33–39] While it is beyond the scope of this report to discuss all of the relevant studies, some are particularly noteworthy. van Gool *et al*[35] studied 60

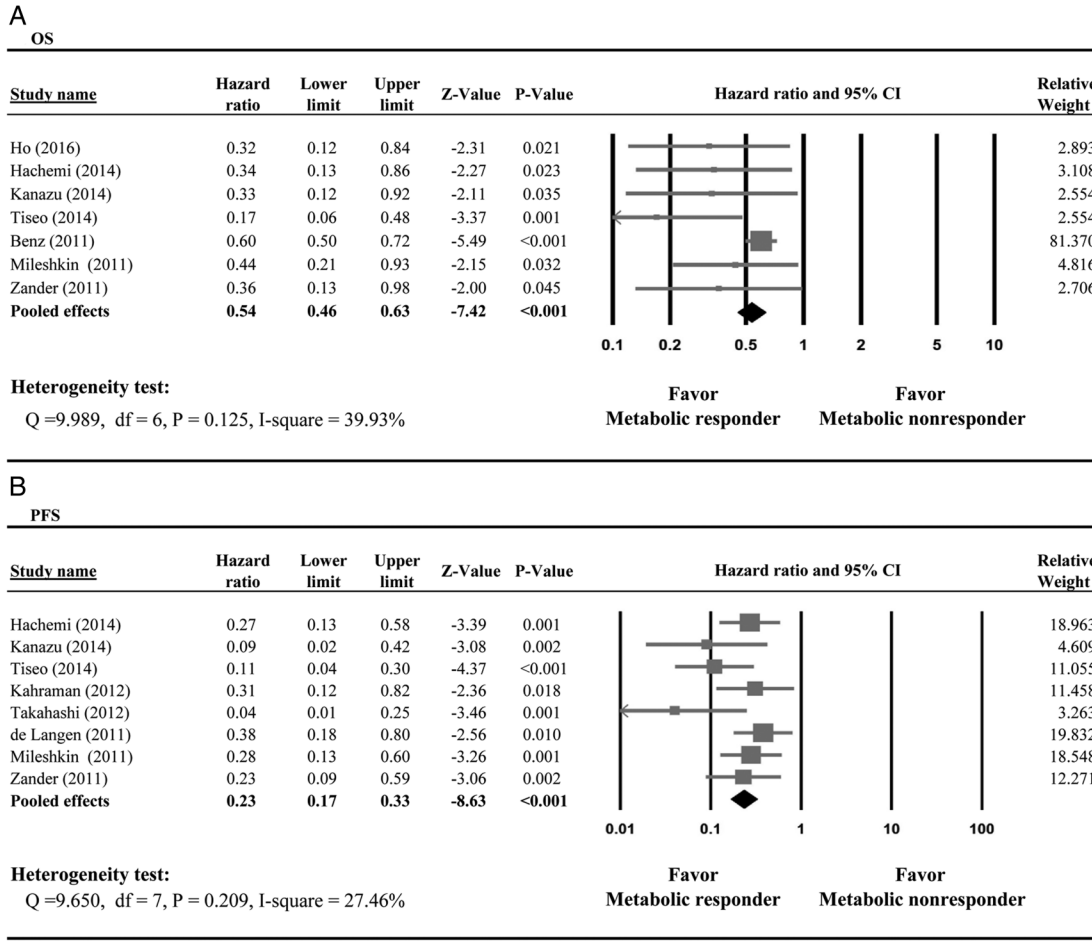

Figure 2 Meta-analysis for (A) OS and (B) PFS. OS, overall survival; PFS, progression-free survival.

Table 2 Sensitivity analysis

First author (publication year)	Statistics with study removed HR	Lower limit	Upper limit	Z-value	p Value
OS					
Ho (2016)	0.54	0.46	0.64	−7.13	<0.001
Hachemi (2014)	0.54	0.46	0.64	−7.14	<0.001
Kanazu (2014)	0.54	0.46	0.64	−7.18	<0.001
Tiseo (2014)	0.55	0.47	0.65	−6.97	<0.001
Benz (2011)	0.33	0.22	0.48	−5.72	<0.001
Mileshkin (2011)	0.54	0.46	0.64	−7.13	<0.001
Zander (2011)	0.54	0.46	0.64	−7.19	<0.001
PFS					
Hachemi (2014)	0.23	0.16	0.33	−7.95	<0.001
Kanazu (2014)	0.25	0.18	0.34	−8.16	<0.001
Tiseo (2014)	0.26	0.18	0.37	−7.62	<0.001
Kahraman (2012)	0.23	0.16	0.32	−8.33	<0.001
Takahashi (2012)	0.25	0.18	0.35	−8.14	<0.001
de Langen (2011)	0.21	0.14	0.30	−8.37	<0.001
Mileshkin (2011)	0.23	0.16	0.32	−8.01	<0.001
Zander (2011)	0.23	0.17	0.33	−8.07	<0.001

OS, overall survival; PFS, progression-free survival.

patients with NSCLC eligible for surgical resection and reported that FDG-PET/CT within 1 week after the start of erlotinib identified 64% of histological responders based on EORTC criteria. In a similar study, Aukema *et al*[37] studied 23 patients with NSCLC eligible for surgical resection. Patients received erlotinib (150 mg) daily for 3 weeks and FDG-PET/CT was performed before administration and 1 week after. The κ-agreement between metabolic and pathological responders was 0.55 (p=0.008).

In a study of 31 patients with stage IIIA/B NSCLC who received systemic therapy (5 gefitinib; 26 chemotherapy), Lee *et al*[36] reported that a single FDG-PET/CT scan taken after one cycle of therapy could predict disease progression earlier than radiographic evaluation. A study comparing FDG-PET/CT and CT alone for response to erlotinib in patients with resectable NSCLC found that FDG change in SUVmax could predict histological response after 3 weeks of treatment, whereas relative change in tumor size on CT was not different in responders and non-responders.[40]

While most studies have examined response to treatment, Scheffler *et al*[41] performed FDG-PET/CT on patients with metastatic NSCLC before first-line treatment with erlotinib and found that those with a pretreatment FDG SUVmax<6.6 had a significantly better OS (16.3 months) as compared with those with a pretreatment value of ≥6.6

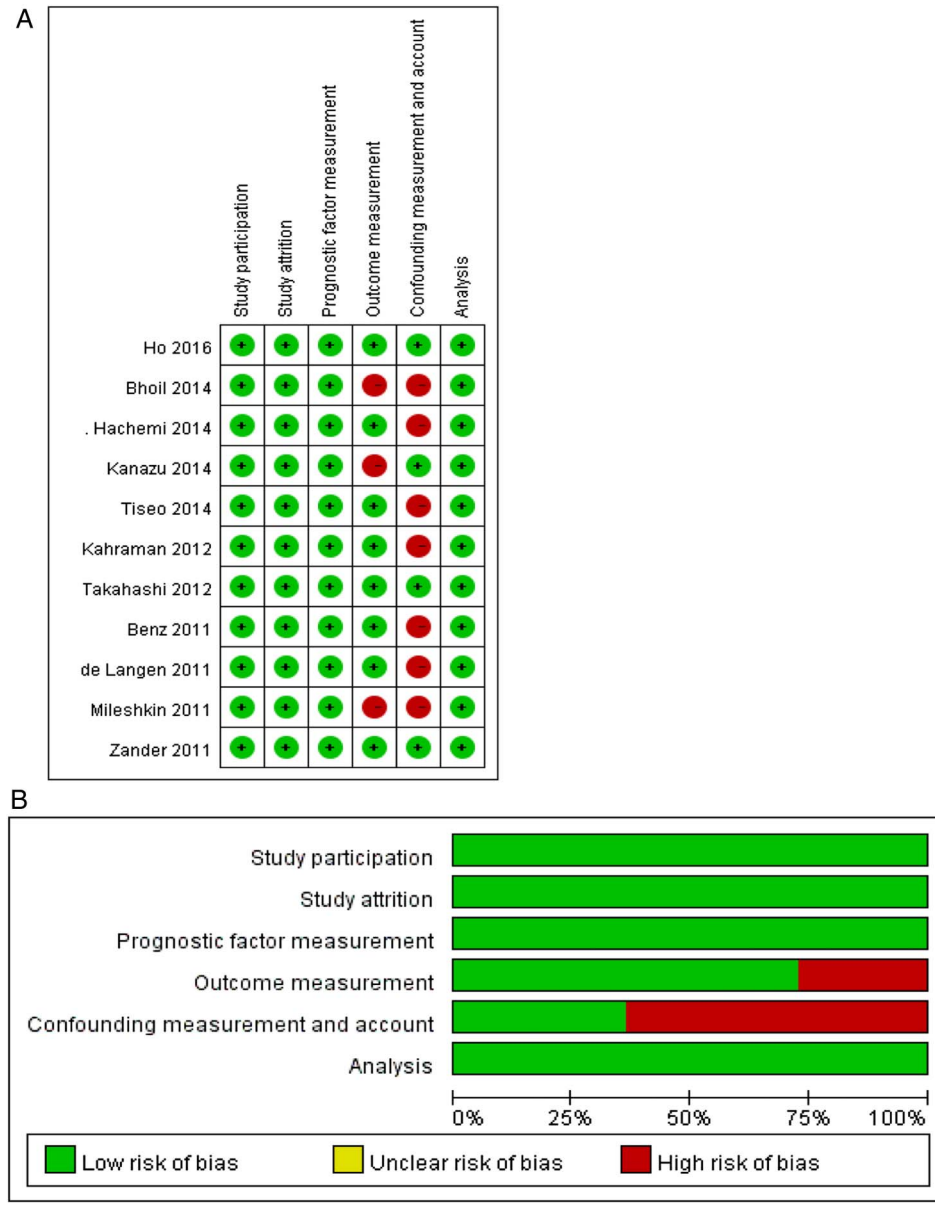

Figure 3 Quality assessment. (A) Risk of bias for individual studies. (B) Summary of risk of biases.

(OS 3.1 months). Similarly, Na *et al*[20] found that a low SUV at presentation was a favorable predictor of response and survival in patients with NSCLC treated with gefitinib. Interestingly, Bengtsson *et al*[38] reported that new lesions identified after 2 weeks of erlotinib were more predictive of survival than SUV.

There are a number of limitations to the current analysis that should be considered. Although 10 studies were included, of which 7 were prospective, there were only a total of 302 patients. This sample size is considered quite small to represent the general population of patients with NSCLC. The small number of patients may be due to the lack of adequate treatment for advanced stage disease, or the availability of FGD-PET/CT assessment. We also did not categorize patients into subgroups such as by age, ethnicity, or degree of response; the limited number of patients would have made subgroup analysis unreliable. Different cut-off values and criteria of metabolic response were used in the studies, and again the limited number of patients prevented subgroup analysis. In addition, the lack of raw data in the studies only allowed categorization of patients as responders or non-responders. No differentiation between complete and PMR was identified; hence, there may be a potential bias in presentation of results. We also did not categorize patients by EGFR mutation status, which is known to play a role in TKI response. Finally, quality of life was not consistently examined in the included studies and hence was not part of our analysis. However, we highly encourage future studies to evaluate quality of life. Patients with advanced NSCLC who are considering TKI treatment usually may also consider palliative treatment as a next step. It is important for physicians and patients to reach a consensus regarding how much time and effort they would devote toward a short extension of lifespan, and quality of life is an important factor in making this decision.

CONCLUSIONS

In summary, this meta-analysis provided a summary of prior clinical studies and indicated that early response to TKIs identified by FDG-PET/CT is predictive of increased OS and PFS in patients with NSCLC. The results support the clinical value of FDG-PET/CT response assessment in patients with NSCLC treated with TKIs.

Contributors JM was involved in manuscript editing and statistical analysis. XW was involved in literature research and data acquisition. JL was involved in study concepts and definition of intellectual content. ZW was involved in manuscript preparation. YW was involved in study design and manuscript review.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

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