Predictive value of positron emission tomography for the prognosis of molecularly targeted therapy in solid tumors

Xianhe Xie¹,*  
Hujuan Chen¹,*  
Haitao Yang¹  
Heng Lin³  
Sijing Zhou¹  
Ruiwen Shen¹  
Cuiping Lu³  
Liting Ling¹  
Wanzun Lin¹  
Ziyuan Liao¹

¹Department of Chemotherapy, The First Affiliated Hospital of Fujian Medical University, Fuzhou, Fujian, People’s Republic of China;  
²Department of Oncology, Fuzhou Pulmonary Hospital, Fuzhou, Fujian, People’s Republic of China;  
³Department of Medical Oncology, Longyan First Hospital Affiliated to Fujian Medical University, Longyan, Fujian, People’s Republic of China

*These authors contributed equally to this work

Objective: This study aimed at comprehensively exploring the value applying positron emission tomography (PET) to predict the effect of molecularly targeted therapy in solid tumors.

Materials and methods: A systematic search was performed for potentially relevant studies from the time of inception to February 2017. The primary endpoints were progression-free survival (PFS), overall survival (OS), and time to progression (TTP). The results were analyzed by Review Manager version 5.3 (RevMan 5.3) statistical software. Subgroup analyses were implemented based on the type of molecularly targeted agents (monoclonal antibodies arm and small molecular targeted agents arm), mechanism (erlotinib/gefitinib arm and bevacizumab arm), radioactive tracers, type of tumor, and reevaluated PET timing.

Results: Twenty-six studies incorporating 865 individuals were eligible. Compared with PET nonresponse group, PET response group displayed a decrease in maximal standard uptake value (SUVmax), which was associated with a significantly prolonged PFS (HR = 0.41, 95% CI [0.29, 0.59]; P < 0.00001), OS (HR = 0.52, 95% CI [0.40, 0.67]; P < 0.00001), and TTP (HR = 0.30, 95% CI [0.14, 0.66]; P = 0.003). Similar results were obtained in the subgroup analyses of PFS in erlotinib/gefitinib arm and small molecular targeted agents arm; and OS in lung cancer arm, erlotinib/gefitinib arm, bevacizumab arm, small molecular targeted agents arm, monoclonal antibodies arm, 18F-fluorodeoxythymidine (18F-FLT) arm, 18F-fluorodeoxyglucose (18F-FDG) arm, and early PET timing arm.

Conclusion: Our study demonstrated that PET was a favorable approach to predict the prognosis of molecularly targeted therapy for solid tumors. PET assessment within 2 weeks could be useful to predict clinical outcome.

Keywords: positron emission tomography, PET, molecularly targeted therapy, monoclonal antibody, malignancy, solid tumor

Introduction

It is well known that early prediction of the treatment response is critical for patients with malignancies to optimize effective therapeutic regimen, avoid adverse effects, and save cost.

Classical imaging tools, such as computed tomography (CT) and magnetic resonance imaging (MRI), are widely used for response assessment. Nevertheless, the limitations of these morphologic imaging techniques can hardly be neglected, for they barely distinguishes posttreatment fibrosis, scar, and necrosis from residual or recurrent disease¹ and only provides information on tumor anatomy by assessing volume change. Moreover, tumor shrinkage usually scarcely occurs until after several cycles of therapy,² which hinders an early estimating response.
Recently, molecularly targeted therapy, with its high specificity, efficacy, and fewer toxicities in managing malignant tumor, has been rapidly put into a routine clinical practice. They are designed to block pathological cellular pathways related to cancer cell survival, proliferation, and metastasis, and to decrease vascular permeability, microvascular density, and cell density. However, response monitoring in malignant tumor treated with molecularly targeted therapy is challenging. Individuals frequently benefit from targeted agents without volumetric change. Thus, with the evolution of treatment regimens and availability of molecularly targeted therapies, a novel imaging approach for supervising therapeutic efficacy focusing more on the biochemistry of the tumor is imperative.

Fortunately, positron emission tomography (PET) has been increasingly noted for its metabolic tumor response assessment, especially in targeted therapy. It was exerting a fascination on predicting long-term outcome via monitoring the metabolism of tissues even in the absence of tumor shrinkage, and was potentially providing an early assessment of the response of targeted therapy but was inconsistent in various tumors and evaluating time points. Therefore, the goal of this study was to investigate whether the early tumor uptake change in PET was associated with clinical outcomes, and to identify whether PET could be a candidate for measuring response in malignancies treated with molecularly targeted agents.

Materials and methods

Literature search

Researches were identified by a systematic electronic literature search for abstracts of relevant studies in the published literature. MEDLINE/PubMed, Google Scholar, EMBASE, and Cochrane Library were scrutinized and updated from July 1, 2016 to February 9, 2017. The following basic search terms were used: “positron emission tomography,” “PET,” “targeted therapies,” “bevacizumab,” “cetuximab,” “Erbitux,” “trastuzumab,” “Herceptin,” “sorafenib,” “Tarceva,” “gefitinib,” “Iressa,” “Nexavar,” “axitinib,” “laptatinib,” “tyrosine kinase inhibitor,” “antiangiogenic treatment,” “solid tumor,” “lung cancer,” “breast cancer,” “gliomas,” “gastrointestinal stromal tumor,” “colon cancer,” “renal cell carcinoma,” and “biliary tract cancer.” Full-text articles were reviewed if abstracts did not provide sufficient information. Moreover, the reference lists of relevant articles were traced for additional studies. Reviews, letters to the editor, case reports, conference abstracts, and editorials comments were excluded. The search was performed without any language restriction.

Selection of studies

Two investigators independently performed an initial screening of titles and abstracts, and then further examined the full-text articles to recruit relevant studies. Disagreement on whether an article should be included was resolved by a third reviewer.

Detailed inclusion criteria

Inclusion criteria were as follows: 1) prospective or retrospective studies exploring the correlation of maximal standard uptake value (SUVmax) with progression-free survival (PFS), overall survival (OS), and/or time to progression (TTP); 2) evaluating over 10 cases involving molecularly targeted agents; 3) individuals had been histologically or cytologically confirmed as having malignant solid tumors; 4) utilizing PET to monitor therapy response of pretherapy and posttreatment; 5) supervising response according to quantitative changes on SUVmax; and 6) HRs with 95% CIs of survival data were accessible.

Data extraction

Data extraction was conducted conforming to the PRISMA guidance (S1 PRISMA Checklist). Two authors independently extracted information from all the eligible studies. Disagreement between the two reviewers was resolved by a third reviewer. All of the eligible studies contained the following data: first author’s name, published year, median ages, number of patients, number of males, study design, type of tumor, molecularly targeted agents, reevaluated PET timing, and survival endpoints. PFS, OS, and/or TTP data were served as the endpoints to evaluate the prognostic significance of PET and expressed by HRs. HRs with 95% CIs were calculated from survival curves based on Tierney’s and Parmar’s methods if they were presented indirectly.

Quality assessment

Two reviewers independently evaluated the quality items and discrepancies were solved by conferring with a third reviewer. We deemed the description of PET to be qualified if the study elaborated the scanner type and the timing of scanning after injection.

Statistical methods

Statistical analyses were calculated by Review Manager version 5.3 (RevMan 5.3) statistical software. Survival data from each study were evaluated based on the Kaplan–Meier curves. The impact of SUVmax on PFS, OS, and TTP was measured using HRs with 95% CIs, which were extracted from papers.
or from the survival curves via the methods by Parmar et al.\textsuperscript{14} and Tierney et al.\textsuperscript{13} when HRs were not provided directly. Survival rates represented on the graphical survival curves were calculated by Engauge Digitizer version 2.5. An HR <1 denoted the survival benefit from a response PET scan, while an HR >1 implied worse survival outcomes. It was considered statistically significant when \(P\)-value was less than 0.05. Cutoff values of the change on SUVmax were determined by the definition in each individual study, and PET response and nonresponse groups were defined according to the alteration in cutoff value of SUVmax. Subgroup analyses were carried out based on the variety of molecularly targeted agents, mechanism, the reevaluated PET timing, types of malignancies, and radioactive tracers. Statistical heterogeneity was estimated via the chi-square and the \(I^2\)-square tests.\textsuperscript{15} The significant heterogeneity existed if \(P\geq0.1\) or \(I^2\geq50\%\), and no heterogeneity existed when \(P\leq0.1\) and \(I^2\leq50\%\). A fixed effect model was applied to calculate the pooled HRs when no heterogeneity was observed, otherwise, a random effect model was employed. Publication bias was exhibited via funnel plot.

Results

Study selection

Initially, 2,920 potentially relevant articles were thoroughly searched from all databases. Of them, 313 were filtered due to duplication. After screening the titles and abstracts, 2,527 were excluded for deviating from the subject. Then, the full text of remaining 80 papers was intensively scrutinized, and 55 were removed for the following reasons: SUVmax was unavailable (\(n=11\)), targeted therapy based on regimen was not administered in every individual (\(n=7\)), evaluating less than 10 patients (\(n=18\)), unable to calculate the log HR and its variance (\(n=13\)), and unfit design (\(n=6\)). Ultimately, a total of 25 articles (including 26 studies)\textsuperscript{2,3,16–38} were eligible for this analysis. The detailed study selection process is described in Figure 1.

Study characteristics

Totally, 865 participants in the 25 articles (including 26 studies) published from the time of inception to February 9, 2017 were eligible. The sample size varied from 12 to 86 subjects. Of these articles, 12 were on non-small cell lung cancer (NSCLC) (49.48% of patients),\textsuperscript{2,3,16,18,19,21,22,24,26,27,35,38} two on malignant glioma (5.90% of patients),\textsuperscript{23,34} two on metastatic colorectal cancer (CRC) (7.63% of patients),\textsuperscript{31,36} two on gastrointestinal stromal tumor (GIST) (7.28% of patients),\textsuperscript{29,30} two on metastatic renal cell carcinoma (RCC) (9.60% of patients),\textsuperscript{25,37} and five on other solid tumors (metastatic gastric adenocarcinoma, metastatic breast cancer, metastatic melanoma, biliary tract cancer, and mixed kinds of tumors; 20.12% of patients).\textsuperscript{17,20,28,32,33} Meanwhile, all of these articles coped with molecularly targeted therapy: six with erlotinib,\textsuperscript{3,16,21,22,24,27} six with bevacizumab,\textsuperscript{23,26,28,31,34,36} four with gefitinib,\textsuperscript{2,16,21,22,24,27} three with imatinib,\textsuperscript{17,29,32} two with sunitinib,\textsuperscript{25,30} one with cetuximab,\textsuperscript{33} and three with mixed kinds of molecularly targeted agents.\textsuperscript{18,20,37} PET-CT/PET was performed pretherapy and posttreatment. SUVmax was measured in all articles, which normalized values by body weight. PFS, OS, and TTP were defined as the endpoints to assess the prognostic significance of the changing SUVmax. Owing to the absence of consensus on metabolic response criteria, the participants were assigned to PET response or PET nonresponse group based on the change of SUVmax in each article. Of all the eligible studies, 17 provided an extractable HR value for PFS,\textsuperscript{3,16,18,20,21,22,24,26,27,30–32,35,36,38} 19 for OS,\textsuperscript{2,17,21,19,22,24,26,27,31,33–37} and five for TTP.\textsuperscript{2,17,27,29,33} The principal characteristics and further details are summarized in Table 1.

![Figure 1 Flowchart on selection including trials in the meta-analysis.](image-url)

Abbreviation: SUVmax, maximal standard uptake value.
| Study | Study design | Radioactive tracers | Tumor | Stage | Molecular targeted drug | Median age (range) | Time | Endpoint | Total cases | Male (%) | Evaluable cases | Responder | Non-responder |
|-------|-------------|---------------------|-------|-------|------------------------|-------------------|------|----------|-------------|----------|----------------|-----------|--------------|
| Benz et al | Prospectively, cohort study | FDG | NSCLC | IIb–IV | Erlotinib | 64 (42–86) | Baseline, 2 weeks | TTP, OS | 22 | 6 (27.2) | 22 | 6 | 16 |
| Chen et al | Prospectively, cohort study | FLT | Malignant gliomas | III – IV | Bevacizumab | 58 (26–78) | Baseline, 1–2 weeks | OS | 21 | 11 (52.4) | 19 | 9 | 10 |
| Choi et al | Prospectively, cohort study | FDG | GIST | / | Imatinib | / (28–86) | Baseline, 3 months | TTP | 40 | 19 (47.5) | 40 | 33 | 7 |
| de Jong et al | Prospectively, Phase II trial | FDG | NSCLC | IV | Bevacizumab | / | Baseline, 22–24 days | PFS, OS | 60 | 30 (50.0) | 60 | / | / |
| de Langen et al | Prospectively, Phase II trial | FDG | NSCLC | IIb–IV | Bevacizumab | / | Baseline, 20 days | PFS, OS | 33 | 13 (39.3) | 27 | 14 | 13 |
| Engelmann et al | Prospectively, cohort study | FDG | mCRC | / | Bevacizumab and erlotinib | 66 (42–81) | Baseline, 3 weeks | PFS | 47 | / | 40 | 7 | 33 |
| Di Fabio et al | Prospectively, Phase II trial | FDG | Metastatic gastric adenocarcinoma | / | Cetuximab | 64.5 (39–74) | Baseline, 6 weeks | TTP, OS | 22 | 16 (72.7) | 20 | 12 | 8 |
| Farnebo et al | Prospectively, cohort study | FDG | mRCC | / | Sunitinib (n=18), sorafenib (n=19), pazopanib (n=2) | / | Baseline, 14 days | PFS, OS | 39 | / | 32 | 8 | 24 |
| Hachemi et al | Prospectively, cohort study | FDG | NSCLC | IIb–IV | Erlotinib | 60 () | Baseline, 9±3 days | PFS, OS | 12 | 6 (50.0) | 12 | 4 | 8 |
| Ho et al | Retrospective, cohort study | FDG | Lung adenocarcinoma | IIb–IV | Erlotinib | 57 (38–81) | Baseline, 14 days | PFS | 23 | 7 (30.4) | 23 | 11 | 12 |
| Kanazu et al | Cohort study | FDG | NSCLC | IIb–IV | Gefitinib | 61 (34–84) | Baseline, 3 days | PFS, OS | 19 | 4 (21.0) | 19 | 7 | 12 |
| Kayani et al | Prospectively, Phase II trial | FDG | mRCC | / | Sunitinib | 61 (44–78) | Baseline, 4 weeks | PFS, OS | 44 | 33 (75.0) | 42 | 24 | 18 |
| Lastoria et al | Prospectively, Phase II trial | FDG | mCRC | / | Bevacizumab | 58 (30–71) | Baseline, 14 days | PFS, OS | 33 | 21 (63.4) | 33 | 12 | 21 |
| Lin et al (group 1) | Prospectively, Phase II trial | FDG | MBC | I–IV | Lapatinib and trastuzumab | 52 (32–83) | Baseline, 1 week | PFS, OS | 41 | 0 | 39 | 28 | 11 |
| Lin et al (group 2) | Prospectively, Phase II trial | FDG | MBC | I–IV | Lapatinib and trastuzumab | 52 (32–83) | Baseline, 1 week | PFS, OS | 45 | 0 | 43 | 21 | 22 |
| Mileshkin et al | Prospectively, cohort study | FDG | NSCLC | / | Erlotinib | 61 (47–78) | Baseline, 14 days | PFS, OS | 51 | 30 (58.8) | 51 | 13 | 38 |
| O’Brien et al | Prospectively, Phase II trial | FDG | NSCLC | IIb–IV | Erlotinib | 63 (42–82) | Baseline, 6 weeks | OS | 47 | 18 (38.3) | 38 | 15 | 23 |
| Prior et al | Prospectively, cohort study | FDG | GIST | / | Sunitinib | 53 (24–76) | Baseline, 4 weeks | PFS | 23 | 16 (69.6) | 23 | 12 | 11 |
| Rong et al | Cohort study | FDG | Lung adenocarcinoma | IIb–IV | Gefitinib | 62 (34–81) | Baseline, 6 months | OS | 46 | 17 (37.0) | 46 | 13 | 33 |
Data analysis

Predictive value of ΔSUVmax for PFS

A total of 16 articles including 17 studies focused on predictive value of ΔSUVmax for PFS. In pooled analysis, PFS was significantly prolonged in the responding group (HR =0.41, 95% CI [0.29–0.59]) by random model due to heterogeneity between the studies (F=54%, P=0.004) (Figure 2A). The funnel plot indicated that there was no significant publication bias for included studies on PFS (Figure 2D). Subgroup analyses based on the tumors, targeted agents, mechanism, radioactive tracers, and reevaluated PET timing were performed owing to the apparent heterogeneity. We implemented subgroup analyses based on the type of molecularly targeted agents (monoclonal antibodies arm and small molecular targeted agents arm), mechanism (erlotinib/gefitinib arm and bevacizumab arm), radioactive tracers (18F-fluorodeoxythymidine [18F-FLT] arm and 18F-fluorodeoxyglucose [18F-FDG] arm), type of tumor (NSCLC arm), and reevaluated PET timing (early assessment and late assessment arms). Repeating PET within 2 weeks was defined as early assessment arm; otherwise, it was defined as late assessment arm.

With respect to PFS, response group exhibited a significantly longer survival in both erlotinib/gefitinib arm (Figure 3A) (HR =0.24, 95% CI [0.15–0.39], P<0.00001),3,16,21,24,35,38 and small molecular targeted agents arm as compared to PET nonresponse group (Figure 3B) (HR =0.34, 95% CI [0.23–0.50], P<0.00001),3,16,21,24,25,30,32,35,38 without heterogeneity.

In regard to PFS of bevacizumab arm (Figure 3C),19,23,26,28,31,36 monoclonal antibodies arm (Figure 3D),18,23,26,28,31,36 NSCLC arm (Figure 3E),3,16,18,21,24,26,35,38 18F-FDG arm (Figure 3F),3,16,18,21,24,26,28,30,32,35,38 early assessment arm (Figure 3G),3,16,20,21,23,24,32,35,36,38 and late assessment arm (Figure 3H),18,25,26,28,30,31 the outcome demonstrated that response group predicted a significantly longer PFS compared to nonresponse group with obvious heterogeneity.

Predictive value of ΔSUVmax for OS

Nineteen eligible studies incorporating 600 individuals2,3,16,17,19,21–28,31,33–37 were compared to OS of PET response group with that of PET nonresponse group. A fixed effect model was utilized owing to no heterogeneity (P=0.42, F=3%). Compared to PET nonresponse group, PET response group displayed a prolonged pooled OS (HR =0.52; 95% CI [0.40–0.67]; P<0.00001) (Figure 2B). The shape of the funnel plots appeared to be generally symmetric, and indicated no publication bias (Figure 2E). Then further subgroup analyses showed that response group acquired a significant longer OS without heterogeneity in NSCLC arm (Figure 4A) (HR =0.52,
95% CI [0.38–0.72], P < 0.0001),

erlotinib/gefitinib arm (Figure 4B) (HR = 0.39, 95% CI [0.27–0.58],
P < 0.00001),

bevacizumab arm (Figure 4C) (HR = 0.65, 95% CI [0.43–0.99], P = 0.04),

monoclonal antibodies arm (Figure 4D) (HR = 0.65, 95% CI [0.43–0.98], P = 0.04),

small molecular targeted agents arm (Figure 4E) (HR = 0.46, 95% CI [0.34–0.63],
P < 0.00001),

18F-FDG arm (Figure 4H) (HR = 0.53, 95% CI [0.41–0.69], P < 0.00001),

18F-FLT arm (Figure 4I) (HR = 0.43, 95% CI [0.19–0.96], P = 0.04),

and in early assessment arm (Figure 4F) (HR = 0.38, 95% CI [0.27–0.53], P < 0.00001).

Figure 2 (Continued)
However, late assessment arm displayed a longer survival in response group despite no statistical significance (Figure 4G) (HR = 0.77, 95% CI [0.53–1.11], P = 0.16).

Predictive value of ΔSUVmax for TTP

Five studies comprising 127 individuals explored the correlation between the decrease of ΔSUVmax and TTP. A fixed effect model was employed because of no heterogeneity (P = 0.03). The result indicated that less decline of ΔSUVmax was associated with a significant shorter TTP (HR = 0.30, 95% CI [0.14–0.66]; P = 0.03) (Figure 2C). The funnel plot indicated that no remarkable publication bias existed, suggesting that the obtained results were reliable (Figure 2F).

Discussion

To our best knowledge, this is the first meta-analysis to systematically estimate the value of PET in solid tumor treated
with molecularly targeted therapy. Previous studies had proved PET to be competent to assess survival in diffuse large B-cell lymphoma after rituximab based regimen effectively. However, the prognostic value of PET in evaluating molecularly targeted therapy in solid tumor remained unclear.

Based on data from 25 articles, our study demonstrated that the decline of PET uptake administered with molecularly targeted therapy was related to a longer PFS, OS, and TTP, despite obvious heterogeneity in PFS. Further subgroup analyses displayed that in PET response group, a significantly longer PFS was observed in erlotinib/gefitinib arm and small molecular targeted agents arm; and a longer OS in NSCLC arm, erlotinib/gefitinib arm, bevacizumab arm, small molecular targeted agents arm, monoclonal antibodies arm, 18F-FDG arm, 18F-FLT arm, and early assessment arm with no heterogeneity. These evidences supported that PET was a favorable approach to determine response of solid tumor treated with molecularly targeted therapy, especially with small molecular targeted agents, and a promising tool for the early detection of response.

When measuring response to anticancer treatment, a reliable and standardized methodology is essential in determining whether the ongoing therapy is beneficial. Anatomic tumor response metrics comprising WHO criteria (1979), Response Evaluation Criteria in Solid Tumors (RECIST) (2000), and RECIST 1.1 (2009) were widely applied, but were incompetent to distinguish necrosis, inflammation, and cavitation from residual or recurrent tumor lesions. Meanwhile, necrosis and cavitation without an alteration in size are frequently observed in angiogenesis inhibitors and anti-vascular therapies. Therefore, these anatomic criteria are insufficient for the evaluation of response to molecularly targeted therapies. In 1999, the European Organization for Research and Treatment of Cancer proposed a set of criteria to judge PET response based on metabolism. However, a workshop of the National Cancer Institute stated that there was neither one best criterion for assessing 18F-FDG PET, nor one unified standard for determining the significance of 18F-FDG PET. Subsequently, Positron Emission tomography Response Criteria In Solid Tumors assessed by changes in peak standard uptake value-lbm (SULpeak) was formulated but not widely applied. Summarily, the role of PET in assessing response of molecularly targeted therapy in solid tumor remains to be explored. Thereby, we proceeded this analysis to elaborate this issue.

The reason for conducting the reevaluated PET timing subgroup analysis was that the optimal time point to judge PET response remains to be determined. For morphologic imaging techniques, such as CT, which was based on volume,
### C Study or subgroup  

| Log (hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|----|------------|---------------------------------|---------------------------------|
| **Bevacizumab**   |     |            |                                 |                                 |
| de Jong 2016      | 0.04688359 | 0.29220406 | 15.1                            | 1.05 (0.59, 1.86)               |
| Engelmann 2014    | -0.91629073 | 0.49149969 | 9.1                             | 0.40 (0.15, 1.05)               |
| Lastoria 2013     | -0.91629073 | 0.43894478 | 10.3                            | 0.40 (0.17, 0.99)               |
| Sahani 2015       | -1.66073121 | 0.67684744 | 5.8                             | 0.19 (0.05, 0.72)               |
| Schwarzenberg 2012 | -0.63487827 | 0.46308418 | 9.7                             | 0.53 (0.21, 1.31)               |
| **Subtotal (95% CI)** | 50 | 0.51 (0.29, 0.89) |                                 |                                 |

Heterogeneity: $\chi^2=0.20$, $p=8.13$, $df=4$ ($p=0.09$); $I^2=51$
Test for overall effect: $Z=2.37$ ($p=0.02$)

### D Monoclonal antibodies  

| Log (hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|----|------------|---------------------------------|---------------------------------|
| de Jong 2016      | 0.04688359 | 0.29220406 | 15.1                            | 1.05 (0.59, 1.86)               |
| Engelmann 2014    | -0.91629073 | 0.49149969 | 9.1                             | 0.40 (0.15, 1.05)               |
| Lastoria 2013     | -0.91629073 | 0.43894478 | 10.3                            | 0.40 (0.17, 0.99)               |
| Sahani 2015       | -1.66073121 | 0.67684744 | 5.8                             | 0.19 (0.05, 0.72)               |
| Schwarzenberg 2012 | -0.63487827 | 0.46308418 | 9.7                             | 0.53 (0.21, 1.31)               |
| **Subtotal (95% CI)** | 50 | 0.51 (0.29, 0.89) |                                 |                                 |

Heterogeneity: $\chi^2=0.20$, $p=8.13$, $df=4$ ($p=0.09$); $I^2=51$
Test for overall effect: $Z=2.37$ ($p=0.02$)

### E Study or subgroup  

| Log (hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|----|------------|---------------------------------|---------------------------------|
| **NSCLC**         |     |            |                                 |                                 |
| de Jong 2016      | 0.04688359 | 0.29220406 | 18.1                            | 1.05 (0.59, 1.86)               |
| de Langen 2011    | -0.96758403 | 0.37731533 | 16.3                            | 0.38 (0.18, 0.80)               |
| Hachemi 2014      | -1.30933332 | 0.6865416  | 10.4                            | 0.27 (0.07, 1.04)               |
| Ho 2016           | -1.07880966 | 0.61857212 | 11.5                            | 0.34 (0.10, 1.14)               |
| Kanazui 2014      | -2.40794561 | 0.78266656 | 9.0                             | 0.09 (0.02, 0.42)               |
| Mileshkin 2011    | -1.27296586 | 0.39015184 | 16.1                            | 0.28 (0.13, 0.60)               |
| Takahashi 2012    | -3.21887582 | 1.21044187 | 4.9                             | 0.04 (0.00, 0.43)               |
| Tiseo 2014        | -1.2039728  | 0.50294709 | 13.7                            | 0.30 (0.11, 0.80)               |
| **Subtotal (95% CI)** | 100 | 0.32 (0.17, 0.57) |                                 |                                 |

Heterogeneity: $\chi^2=0.43$, $p=19.56$, $df=7$ ($p=0.007$); $I^2=64$
Test for overall effect: $Z=3.77$ ($p=0.0002$)

### F Study or subgroup  

| Log (hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|-------------------|----|------------|---------------------------------|---------------------------------|
| **FDG-PET**       |     |            |                                 |                                 |
| de Jong 2016      | 0.04688359 | 0.29220406 | 9.5                             | 1.05 (0.59, 1.86)               |
| de Langen 2011    | -0.96758403 | 0.37731533 | 8.3                             | 0.38 (0.18, 0.80)               |
| Engelmann 2014    | -0.91629073 | 0.49149969 | 6.8                             | 0.40 (0.15, 1.05)               |
| Hachemi 2014      | -1.30933332 | 0.6865416  | 4.8                             | 0.27 (0.07, 1.04)               |
| Ho 2016           | -1.07880966 | 0.61857212 | 5.4                             | 0.34 (0.10, 1.14)               |
| Kanazui 2014      | -2.40794561 | 0.78266656 | 4.1                             | 0.09 (0.02, 0.42)               |
| Kayani 2011       | -0.13926207 | 0.40929219 | 7.9                             | 0.87 (0.39, 1.94)               |
| Lastoria 2013     | -0.91629073 | 0.43894478 | 7.5                             | 0.40 (0.17, 0.95)               |
| Lin 2015 group 1  | -1.23787436 | 0.41446566 | 7.8                             | 0.29 (0.13, 0.65)               |
| Lin 2015 group 2  | 0.42526774 | 0.3860444  | 8.2                             | 1.53 (0.72, 3.26)               |
| Mileshkin 2011    | -1.27296586 | 0.39015184 | 8.1                             | 0.28 (0.13, 0.60)               |
| Prior 2009        | -0.89159812 | 0.6688942  | 5.0                             | 0.41 (0.11, 1.52)               |
| Sahani 2015       | -1.66073121 | 0.67684744 | 4.9                             | 0.19 (0.05, 0.72)               |
| Stroobants 2003   | -0.96758403 | 1.02134954 | 2.8                             | 0.38 (0.05, 2.81)               |
| Takahashi 2012    | -3.21887582 | 1.21044187 | 2.1                             | 0.04 (0.00, 0.43)               |
| Tiseo 2014        | -1.2039728  | 0.50294709 | 6.7                             | 0.30 (0.11, 0.80)               |
| **Total (95% CI)** | 100 | 0.40 (0.28, 0.59) |                                 |                                 |

Heterogeneity: $\chi^2=0.32$, $p=35.01$, $df=9$ ($p=0.007$); $I^2=64$
Test for overall effect: $Z=3.77$ ($p=0.0002$)

Figure 3 (Continued)
the first evaluating response was generally performed not earlier than 4 weeks following the initial treatment since little change occurred at early stage. Accordingly, clinician was frequently in a dilemma to determine the early treatment response and modify treatment strategy opportually. However, in regard to PET, several investigations manifested that early PET assessment had been established as a prognostic biomarker for the response to targeted therapy in various tumors. Some studies advocated that early PET evaluation (on day 2–14) was competent to predict survival in NSCLC treated with erlotinib/gefitinib and 18F-FDG possessed comparable advantage in assessing therapeutic effect, minimize side effect, and save cost.

Furthermore, our results demonstrated that 18F-FLT and 18F-FDG possessed comparable advantage in assessing response in malignancies treated with molecularly targeted therapy. Currently, 18F-FDG PET has enjoyed widespread popularity for imaging extracranial tumors and 18F-FLT PET in gliomas, but it fails to distinguish proliferation ing tissues through the activity of thymidine kinase-1. Moreover, 18F-FDG uptake is influenced not only by tumor glucose metabolism but also by inflammation, for both of them possess active glycome metabolism. Furthermore, our results demonstrated that 18F-FLT revealed the potential of applying PET screening during the early change in tumor activity, thereby facilitating an early adjustment of therapeutic strategy and to maximize therapeutic effect, minimize side effect, and save cost.

![Table](image)

| Study or subgroup | Log (hazard ratio) | SE | Weight (%) | Hazard ratio IV, random, 95% CI | Hazard ratio IV, random, 95% CI |
|------------------|-------------------|----|------------|---------------------------------|---------------------------------|
| **2 weeks**      |                   |    |            |                                 |                                 |
| Hachemi 2014     | −1.30933332       | 0.6865416 | 4.4        | 0.27 (0.07, 1.04)               |                                 |
| Ho 2016          | −1.07890666       | 0.61857212 | 5.0        | 0.34 (0.10, 1.14)               |                                 |
| Kanazu 2014      | −2.04794561       | 0.76266566 | 3.7        | 0.09 (0.02, 0.42)               |                                 |
| Lastoria 2013    | −0.91629073       | 0.43894478 | 7.0        | 0.40 (0.17, 0.95)               |                                 |
| Lin 2015 group 1 | −1.2378436        | 0.41446566 | 7.3        | 0.29 (0.13, 0.65)               |                                 |
| Lin 2015 group 2 | 0.42526774        | 0.3860444 | 7.7        | 1.53 (0.72, 3.26)               |                                 |
| Mihashkin 2011   | −1.27296568       | 0.39015184 | 7.7        | 0.28 (0.13, 0.60)               |                                 |
| Schwarzenberg 2012 | −0.63487827      | 0.46308418 | 6.7        | 0.53 (0.21, 1.31)               |                                 |
| Stroobants 2003  | −0.96758403       | 1.0214954 | 2.5        | 0.38 (0.05, 2.81)               |                                 |
| Takahashi 2012   | −3.21887582       | 1.21044187 | 1.9        | 0.04 (0.00, 0.43)               |                                 |
| Tiseo 2014       | −1.2039728        | 0.50294709 | 6.2        | 0.30 (0.11, 0.80)               |                                 |
| **Subtotal (95% CI)** |                  |    |            | 60.2 | 0.35 (0.22, 0.57) |

**Heterogeneity:** $I^2=0.33; \chi^2=21.86, df=10 (P=0.02); I^2=54%$

Test for overall effect: $Z=4.27 (P<0.0001)$

| **>2 weeks**     |                   |    |            |                                 |                                 |
| de Jong 2016     | 0.04688359        | 0.29220406 | 9.1        | 1.05 (0.59, 1.86)               |                                 |
| de Langen 2011   | −0.96758403       | 0.37731533 | 7.1        | 0.38 (0.18, 0.80)               |                                 |
| Engelmann 2014   | −0.91629073       | 0.49149969 | 6.4        | 0.40 (0.15, 1.05)               |                                 |
| Kayani 2011      | −0.19326207       | 0.40929219 | 7.4        | 0.87 (0.39, 1.94)               |                                 |
| Prior 2009       | −0.89158812       | 0.6086942  | 4.6        | 0.41 (0.11, 1.52)               |                                 |
| Sahani 2015      | −1.66075212       | 0.6794744 | 4.5        | 0.19 (0.05, 0.72)               |                                 |
| **Subtotal (95% CI)** |                  |    |            | 39.8 | 0.54 (0.32, 0.89) |

**Heterogeneity:** $I^2=0.19; \chi^2=9.81, df=5 (P=0.08); I^2=49%$

Test for overall effect: $Z=2.40 (P=0.02)$

**Total (95% CI)**

| **Total (95% CI)** | 100 | 0.41 (0.23, 0.59) |

**Heterogeneity:** $I^2=0.28; \chi^2=35.05, df=16 (P=0.004); I^2=54%$

Test for overall effect: $Z=4.83 (P<0.00001)$

Test for subgroup difference: $\chi^2=1.45, df=1 (P=0.23); I^2=30.9%$

**Note:** Lin 2015 (group 1) and Lin 2015 (group 2) were two studies included in one article.

**Abbreviations:** FDG, fluorodeoxyglucose; NSCLC, non-small-cell lung cancer; PET, positron emission tomography; PFS, progression-free survival; SE, standard error.
activity, but 18F-FLT aggregates in proliferating cells, the latter exhibiting a proliferation specificity\textsuperscript{52,53} and being a potentially preferable candidate for evaluating response to targeted therapy.\textsuperscript{54} Further studies are recommended since only three eligible articles about 18F-FLT were recruited.

**Limitations**

The limitations of this study included: first, the sample size was relatively small and some recruited articles were retrospective, although the eligible studies contained 25 comprising 865 participants; second, the cutoff changing level of SUV\textsubscript{max} in eligible studies lacked uniform response criteria. This meta-analysis will be updated if further eligible studies are identified.

**Conclusion**

Our study demonstrated that PET was a favorable approach to predict the prognosis of molecularly targeted therapy for solid tumors. PET assessment within 2 weeks could be useful to predict clinical outcome.

### Table A

| Study or subgroup | Log (hazard ratio) | SE     | Weight (%) | Hazard ratio IV, fixed, 95% CI |
|-------------------|--------------------|--------|------------|-------------------------------|
| NSCLC             |                    |        |            |                               |
| Benz 2011         | 0.009995033        | 0.94816807 | 2.9        | 1.01 (0.16, 6.48)             |
| de Jong 2016      | 0.02469261         | 0.29764033 | 29.5       | 1.03 (0.57, 1.84)             |
| Hachemi 2014      | −1.07880966        | 0.67322891 | 5.8        | 0.34 (0.09, 1.27)             |
| Ho 2016           | −1.13943428        | 0.4933505  | 10.8       | 0.32 (0.12, 0.84)             |
| Kanazu 2014       | −1.02165125        | 0.53046978 | 9.3        | 0.36 (0.13, 1.02)             |
| Mileskin 2011     | −0.82098055        | 0.38233988 | 17.9       | 0.44 (0.21, 0.93)             |
| O’Brien 2012      | −0.41551544        | 0.58617648 | 7.6        | 0.66 (0.21, 2.08)             |
| Rong 2014         | −0.99425227        | 1.51026455 | 1.1        | 0.37 (0.02, 7.14)             |
| Sohn 2008         | −0.51082562        | 0.58739416 | 7.6        | 0.60 (0.19, 1.90)             |
| Tiseo 2014        | −1.96611286        | 0.59161082 | 7.5        | 0.14 (0.04, 0.45)             |
| **Subtotal (95% CI)** | 100               |        |            | 0.52 (0.38, 0.72)             |
| **Total (95% CI)** | 100               |        |            | 0.52 (0.38, 0.72)             |

### Table B

| Study or subgroup | Log (hazard ratio) | SE     | Weight (%) | Hazard ratio IV, fixed, 95% CI |
|-------------------|--------------------|--------|------------|-------------------------------|
| Erlotinib/gefitinib |                    |        |            |                               |
| Benz 2011         | 0.00995033         | 0.94816807 | 2.3        | 1.01 (0.16, 6.48)             |
| Hachemi 2014      | −1.07880966        | 0.67322891 | 4.5        | 0.34 (0.09, 1.27)             |
| Ho 2016           | −1.13943428        | 0.4933505  | 8.4        | 0.32 (0.12, 0.84)             |
| Kanazu 2014       | −1.02165125        | 0.53046978 | 7.3        | 0.36 (0.13, 1.02)             |
| Mileskin 2011     | −0.82098055        | 0.38233988 | 14.0       | 0.44 (0.21, 0.93)             |
| O’Brien 2012      | −0.41551544        | 0.58617648 | 6.0        | 0.66 (0.21, 2.08)             |
| Rong 2014         | −0.99425227        | 1.51026455 | 0.9        | 0.37 (0.02, 7.14)             |
| Sohn 2008         | −0.51082562        | 0.58739416 | 6.0        | 0.60 (0.19, 1.90)             |
| Tiseo 2014        | −1.96611286        | 0.59161082 | 5.9        | 0.14 (0.04, 0.45)             |
| **Subtotal (95% CI)** | 55.3               |        |            | 0.39 (0.27, 0.58)             |

### Table C

| Study or subgroup | Log (hazard ratio) | SE     | Weight (%) | Hazard ratio IV, fixed, 95% CI |
|-------------------|--------------------|--------|------------|-------------------------------|
| Bevacizumab       |                    |        |            |                               |
| Chen 2007         | −0.65392647        | 1.01692222 | 2.0        | 0.52 (0.07, 3.82)             |
| de Jong 2016      | 0.02469261         | 0.29764033 | 23.2       | 1.03 (0.57, 1.84)             |
| Engellmann 2014   | −0.77652879        | 0.59809931 | 5.7        | 0.46 (0.14, 1.49)             |
| Lastoria 2013     | −2.52572864        | 1.0528404  | 1.9        | 0.08 (0.01, 0.63)             |
| Sahani 2015       | −0.46203546        | 0.51177789 | 7.8        | 0.63 (0.23, 1.72)             |
| Schwarzenberg 2012| −1.42711636        | 0.70729304 | 4.1        | 0.24 (0.06, 0.96)             |
| **Subtotal (95% CI)** | 44.7               |        |            | 0.65 (0.43, 0.93)             |

**Figure 4 (Continued)**
### Study or subgroup  | Log (hazard ratio)  | SE  | Weight (%)  | Hazard ratio IV, fixed, 95% CI  | Hazard ratio IV, fixed, 95% CI  
--- | --- | --- | --- | --- | ---  
**Monoclonal antibodies**  
Chen 2007 | -0.65392647 | 1.0169222 | 1.6 | 0.52 (0.07, 3.82) |  
de Jong 2016 | 0.02469261 | 0.29764033 | 18.4 | 1.03 (0.57, 1.84) |  
Engelmann 2014 | -0.77652879 | 0.59800931 | 4.6 | 0.46 (0.14, 1.49) |  
Fabio 2007 | -0.61618614 | 1.44758689 | 0.8 | 0.54 (0.03, 9.22) |  
Lastoria 2013 | -2.52572864 | 1.0526404 | 1.5 | 0.08 (0.01, 0.63) |  
Sahani 2015 | -0.46203546 | 0.5177789 | 6.2 | 0.63 (0.23, 1.72) |  
Schwarzenberg 2012 | -1.42711636 | 0.70729304 | 3.3 | 0.24 (0.06, 0.96) |  
**Subtotal (95% CI)** | | | | | **36.3** | **0.65 (0.43, 0.98)**  
**Total (95% CI)** | | | | | **100** | **0.52 (0.41, 0.67)**  
**Small molecular targeted agents**  
Benz 2011 | 0.00995033 | 0.94816807 | 1.8 | 1.01 (0.16, 6.48) |  
Farnebo 2014 | -0.54472718 | 0.40661575 | 9.9 | 0.58 (0.26, 1.29) |  
Hachemi 2014 | -1.07880966 | 0.67322891 | 3.6 | 0.34 (0.09, 1.27) |  
Ho 2016 | -1.13943428 | 0.4933505 | 6.7 | 0.32 (0.12, 0.84) |  
Kanazu 2014 | -1.02165125 | 0.53046978 | 5.8 | 0.36 (0.13, 1.02) |  
Kayani 2011 | -0.22314355 | 0.45214166 | 8.7 | 0.80 (0.34, 1.87) |  
Mileshkin 2011 | -0.82098055 | 0.38233988 | 11.2 | 0.44 (0.21, 0.93) |  
O’Brien 2012 | -0.41551544 | 0.58617648 | 4.7 | 0.66 (0.21, 2.08) |  
Rong 2014 | -0.99425227 | 1.51026455 | 0.7 | 0.37 (0.02, 7.14) |  
Sohn 2008 | -0.51082562 | 0.58739416 | 4.7 | 0.60 (0.19, 1.90) |  
Tiseo 2014 | -1.96611286 | 0.59161082 | 4.7 | 0.14 (0.04, 0.45) |  
Zukotynski 2014 | -0.89198812 | 1.18294725 | 1.2 | 0.41 (0.04, 4.17) |  
**Subtotal (95% CI)** | | | | | **63.7** | **0.46 (0.34, 0.63)**  
**S2 weeks**  
Benz 2011 | 0.00995033 | 0.94816807 | 1.8 | 1.01 (0.16, 6.48) |  
Chen 2007 | -0.65392647 | 1.0169222 | 1.6 | 0.52 (0.07, 3.82) |  
Farnebo 2014 | -0.54472718 | 0.40661575 | 9.9 | 0.58 (0.26, 1.29) |  
Hachemi 2014 | -1.07880966 | 0.67322891 | 3.6 | 0.34 (0.09, 1.27) |  
Ho 2016 | -1.13943428 | 0.4933505 | 6.7 | 0.32 (0.12, 0.84) |  
Kanazu 2014 | -1.02165125 | 0.53046978 | 5.8 | 0.36 (0.13, 1.02) |  
Lastoria 2013 | -2.52572864 | 1.0528404 | 1.5 | 0.08 (0.01, 0.63) |  
Mileshkin 2011 | -0.82098055 | 0.38233988 | 11.2 | 0.44 (0.21, 0.93) |  
Schwarzenberg 2012 | -1.42711636 | 0.70729304 | 3.3 | 0.24 (0.06, 0.96) |  
Sohn 2008 | -0.51082562 | 0.58739416 | 4.7 | 0.60 (0.19, 1.90) |  
Tiseo 2014 | -1.96611286 | 0.59161082 | 4.7 | 0.14 (0.04, 0.45) |  
**Subtotal (95% CI)** | | | | | **54.6** | **0.38 (0.27, 0.53)**  
**G >2 weeks**  
de Jong 2016 | 0.02469261 | 0.29764033 | 18.4 | 1.03 (0.57, 1.84) |  
Engelmann 2014 | -0.77652879 | 0.59800931 | 4.6 | 0.46 (0.14, 1.49) |  
Fabio 2007 | -0.61618614 | 1.44758689 | 0.8 | 0.54 (0.03, 9.22) |  
Kayani 2011 | -0.22314355 | 0.43214166 | 8.7 | 0.80 (0.34, 1.87) |  
O’Brien 2012 | -0.41551544 | 0.58617648 | 4.7 | 0.66 (0.21, 2.08) |  
Rong 2014 | -0.99425227 | 1.51026455 | 0.7 | 0.37 (0.02, 7.14) |  
Sahani 2015 | -0.46203546 | 0.5177789 | 6.2 | 0.63 (0.23, 1.72) |  
Zukotynski 2014 | -0.89198812 | 1.18294725 | 1.2 | 0.41 (0.04, 4.17) |  
**Subtotal (95% CI)** | | | | | **45.4** | **0.77 (0.53, 1.11)**  
**Total (95% CI)** | | | | | **100** | **0.52 (0.41, 0.67)**  
---

Figure 4 (Continued)
| Study or subgroup | Log (hazard ratio) | SE  | Weight (%) | Hazard ratio IV, fixed, 95% CI | Hazard ratio IV, fixed, 95% CI |
|------------------|------------------|-----|------------|-----------------------------|-----------------------------|
| FDG              |                  |     |            |                             |                             |
| Benz 2011        | 0.00995033       | 0.94816807 | 1.8 | 1.01 (0.16, 6.48) |                             |
| de Jong 2016     | 0.02469261       | 0.29764033 | 18.4 | 1.03 (0.57, 1.84) |                             |
| Engelmann 2014   | -0.77652879      | 0.59809931 | 4.6  | 0.46 (0.14, 1.49) |                             |
| Fabio 2007       | -0.61618614      | 1.44758389 | 0.8  | 0.54 (0.03, 9.22) |                             |
| Farnebo 2014     | -0.54472718      | 0.40661575 | 9.9  | 0.58 (0.26, 1.29) |                             |
| Hachemi 2016     | -1.07880966      | 0.67322891 | 3.6  | 0.34 (0.09, 1.27) |                             |
| Ho 2016          | -1.13943428      | 0.4933505  | 6.7  | 0.32 (0.12, 0.84) |                             |
| Kanazu 2014      | -1.02165125      | 0.53046978 | 5.8  | 0.36 (0.13, 1.02) |                             |
| Kayani 2011      | -0.22314355      | 0.43214166 | 8.7  | 0.80 (0.34, 1.87) |                             |
| Lastoria 2013    | -2.52572864      | 1.0528404  | 1.5  | 0.08 (0.01, 0.63) |                             |
| Mileschkin 2011  | -0.82098055      | 0.38233988 | 11.2 | 0.44 (0.21, 0.93) |                             |
| O’Brien 2012     | -0.41551544      | 0.58617648 | 4.7  | 0.66 (0.21, 2.08) |                             |
| Rong 2014        | -0.99425227      | 1.51026455 | 0.7  | 0.37 (0.07, 2.14) |                             |
| Sahani 2015      | -0.46203546      | 0.51177789 | 6.2  | 0.63 (0.23, 1.72) |                             |
| Tiseo 2014       | -1.96611286      | 0.59161082 | 4.7  | 0.14 (0.04, 0.45) |                             |
| Zukutynski 2014  | -0.89159812      | 1.18294725 | 1.2  | 0.41 (0.04, 4.17) |                             |
| **Subtotal (95% CI)** |              |     | 90.4 | 0.53 (0.41, 0.69) |                             |
| **Heterogeneity:** $\chi^2=17.28$, df=15 ($P=0.30$); $I^2=13\%$ | | |
| **Test for overall effect:** $Z=4.69$ ($P<0.00001$) | | |

| FLT              |                  |     |            |                             |                             |
|------------------|------------------|-----|------------|-----------------------------|-----------------------------|
| Chen 2007        | -0.65392647      | 0.1069222  | 1.6  | 0.52 (0.07, 3.82) |                             |
| Schwarzenberg 2012 | -1.42711636     | 0.70729304 | 3.3  | 0.24 (0.06, 0.96) |                             |
| Sohn 2008        | -0.51082562      | 0.58739416 | 4.7  | 0.60 (0.19, 1.90) |                             |
| **Subtotal (95% CI)** |              |     | 9.6  | 0.43 (0.19, 0.96) |                             |
| **Heterogeneity:** $\chi^2=1.04$, df=2 ($P=0.60$); $I^2=0\%$ | | |
| **Test for overall effect:** $Z=2.05$ ($P=0.04$) | | |
| **Total (95% CI)** |              |     | 100 | 0.52 (0.41, 0.67) |                             |
| **Heterogeneity:** $\chi^2=18.57$, df=18 ($P=0.42$); $I^2=3\%$ | | |
| **Test for subgroup differences:** $z=2.85$, df=1 ($P=0.062$); $I^2=0\%$ | | |

Figure 4 Subgroup analyses on the incidence of OS in patients treated with: (A) NSCLC; (B) erlotinib/gefitinib; (C) bevacizumab; (D) monoclonal antibodies; (E) small molecular targeted agents; (F) ≤2 weeks; (G) >2 weeks; (H) FDG-PET; and (I) FLT-PET. Abbreviations: FLT, fluorodeoxythymidine; FDG, fluorodeoxyglucose; NSCLC, non-small-cell lung cancer; OS, overall survival; PET, positron emission tomography; SE, standard error.

Disclosure
The authors report no conflicts of interest in this work.

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