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META ANALYSIS AND SYSTEMATIC REVIEW

# The value of $^{18}$F-fluorodeoxyglucose positron emission tomography for prediction of treatment response in gastrointestinal stromal tumors: a systematic review and meta-analysis

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**Key words**
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## Abstract

**Background:** Early detection of response to treatment is critically important in gastrointestinal stromal tumors (GIST). Therefore, the present systematic review and meta-analysis assessed the value of $^{18}$f-fluorodeoxyglucose positron emission tomography ($^{18}$FDG–PET) on prediction of therapeutic response of GIST patients to systemic treatments.
**Methods:** The literature search was conducted using PubMed, SCOPUS, Cochrane, and Google Scholar databases, and review article references. Eligible articles were defined as studies included confirmed GIST patients who underwent $^{18}$FDG–PET as well as assessing the screening role of it.
**Results:** Finally, 21 relevant articles were included. The analysis showed the pooled sensitivity and specificity of 18FDG–PET in evaluation of response to treatment of GIST patient were 0.90 (95% CI: 0.85–0.94; $I^2 = 52.59$, $P = 0.001$) and 0.62 (95% CI: 0.49–0.75; $I^2 = 69.7$, $P = 0.001$), respectively. In addition, the pooled prognostic odds ratio of $^{18}$FDG–PET for was 14.99 (95% CI, 6.42–34.99; $I^2 = 100.0$, $P < 0.001$). The Meta regression showed that sensitivity of $^{18}$FDG-PET was higher if the sample size of study was equal or more than 30 cases (sensitivity = 0.93; 95% CI: 0.89–0.97), when using PET/CT (sensitivity = 0.92; 95% CI: 0.89–0.97), and self-design criteria (sensitivity = 0.93; 95% CI: 0.87–1.0).
**Conclusion:** The present meta-analysis showed $^{18}$FDG–PET has a significant value in predicting treatment response in GIST patients.

## Introduction

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors that originate from the gastrointestinal tract.[1] GISTs are often completely considered resistant to chemotherapy and are insensitive to irradiation.[2–4] The lack of therapeutic agents and its metastatic nature made a generally poor prognosis in patients with GISTs.[5–7] So, the accurate and early objective assessment of tumor response to treatment has a major important role in GIST patients.[8,9] After introducing of tyrosine kinase inhibitors such as Imatinib in 2001 for treatment of GISTs, monitoring of therapeutic response has posed a challenge in these tumors that often progress slowly.[10,11]

Current evidence showed the $^{18}$F-fluorodeoxyglucose positron emission tomography ($^{18}$FDG–PET) is a sensitive tool for evaluating tumor response in GISTs patients receiving systemic therapy.[12–14] $^{18}$FDG–PET may also be helpful in detecting resistance to tyrosine kinase inhibitors.[14–17] Although $^{18}$FDG–PET provides hopes for better tumor characterization, preoperative staging, and detection of treatment response, its usage is uncommon in many countries,[18] and its role in evaluation of response to treatment is under continuous investigations. Therefore, strong evidence is required on the routine use of this technique in clinical decision making. Meta–analyses provide practical evidence for researchers regarding advantages and side effects of an intervention to help them decide if to proceed with clinical trials or not. Although there are many studies in order to identify clinical benefits of $^{18}$F-FDG–PET in prediction of therapeutic response of GIST patients, but no meta-analyses have been conducted for this purpose. Therefore, the present systematic review and meta-analysis assessed the value of $^{18}$F-FDG–PET on prediction of therapeutic response of GIST patients to systemic treatments.

## Methods

***Search strategy.*** The present study was performed according to the meta-analysis of Observational Studies in Epidemiology (MOOSE) statement providing a detailed guideline of preferred reporting style for systematic reviews and meta-analyses.[19] Relevant articles were enrolled over a literature search of online databases including Medline (via PubMed), EMBASE (via OvidSP), SCOPUS, Cochrane Library, and Google Scholar databases from January 2000 to June 2015. There is no language limitation. The initial search was broad and included and based on following phrases: "Gastrointestinal Stromal Tumors" or "GIST", and "Positron-Emission Tomography" or "PET". In addition, a hand search was performed in the bibliography of eligible and reviews articles. In addition, it was attempted to contact with authors of all studies that met entrance criteria and requested them for unpublished data and abstracts to gather grey literature. A hand search was also conducted in Google search engine and Google scholar to include non-indexed reports. Moreover, hand-searching of journals was also carried out.

***Study Selection and Definitions.*** Two reviewers (M.Y, S.K) independently summarized all potentially relevant studies, and disagreement was resolved by discussion. We included all studies that investigated the role of $^{18}$F-FDG–PET and positron emission tomography – computed tomography (PET/CT) in predicting treatment response in eligible GIST patients from all age groups. Only prospective, blinded, and original research was enrolled. Eligible studies fulfilled all of the following criteria: (i) histological diagnosis of GIST; (ii) sample size of at least eight patients with GIST; (iii) $^{18}$F-FDG–PET and PET/CT performed in patients with GIST in order to predict treatment response to chemotherapy; and (iv) performing PET before and after treatment. Including patients with other cancers, lack of blinding of observer, and poor quality studies based on a modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2) tool[20] was exclusion crteria. In addition, for guaranteed of power of included study, studies with less than eight patients (in final follow-up) were excluded.

***Data extraction and management.*** Two reviewers (M. Y, S.K) independently summarized informations from studies with a standardized data abstraction form. Study design, patient characteristics, GIST diagnosis criteria, PET device, PET criteria for treatment response, CT criteria for treatment response, time interval of PET performance after intervention, and sampling method were included in the abstraction forms. In cases of missing or insufficient data, and if necessary, authors were contacted for clarification of study sample.

If a study included several types of cancers, only GIST patients' data were used.

***Quality assessment.*** Quality of the included studies was assessed based on 15-item modified Quality Assessment of Diagnostic Accuracy Studies (QUADAS2). Two reviewers (M.Y, S. K) independently assessed each potentially eligible study and assigned them as a quality rating of "good," "fair," or "poor". Quality assessment was conducted based on following criteria: study design and presence of bias including selection, performance, recording, and reporting bias. Studies with high risk of bias were defined as poor quality, presence of moderate risk (did not affect the results) as fair quality, and those with minimal risk as good quality. In this regards, inter-rater reliability was acceptably high (91%). Disagreements were settled with consensus decision.

***Data synthesis and statistical analysis.*** Statistical analysis was performed using STATA software version 12.0 (StataCorp, College Station, TX, USA). Data were presented as true positive (true prediction of response to treatment), true negative (true prediction of treatment failure), false positive (false prediction of response to treatment), and false negative (false prediction of treatment failure) values. In cases which findings of the study were reported as the number of lesions, authors were contacted to find the total sample size (number of patients). If they did not respond, estimation methods were used to calculate the true positive, true negative, false positive, and false negative values according to the web-based calculator. If the information was reported as graphs, data were extracted from them as recommended by Sistrom and Mergo.[21]

A mixed-effects binary regression model was used. This method is a type of random effect model when the heterogeneity source was not clear. Statistical heterogeneity was defined using the $I^2$ and $\chi^2$ tests ($P < 0.10$ was representative the significant statistical heterogeneity).[22] Sensitivity and subgroup analyses were performed to assess the expected or measured heterogeneity. For this purpose, a bivariate meta-regression model was fitted. All possible causes of heterogeneity including the sample size, PET device (PET or PET/CT), PET criteria, drug evaluated, and PET performance after intervention were included as covariates in the meta-regression model. Publication bias was assessed by funnel plot and associated regression test of asymmetry, introduced by Deeks *et al*.[23] Finally, the pooled sensitivity and specificity were calculated with 95% confidence intervals (CIs). Predictive odds ratio (POR) and receiver operative curves (ROCs) were also obtained.

## Result

- Literature search

In 1973, non-duplicate articles were identified by using search strategies from which 63 potentially relevant papers were screened. Finally, 32 study were eligible, and 21 full-text articles included in meta-analysis and studied in detail[13,15,24–42] (Table 1, Fig. 1). These studies contained 642 patients, with average age of 56.2 years and 402 (62.6%) male individuals. Twelve (57.1%) study used $^{18}$FDG–PET and 9 (42.9%) used PET/CT for assessment of treatment response. In average, first PET assessment was performed 27.2 days after chemotherapy (range: 0–180 days) (Table 1).

- Heterogeneity and publication bias

A bivariate mixed-effects binary regression model was used for performing analyses, because a significant statistical heterogeneity was found in calculation pooled sensitivity ($Q = 52.59$;

**Table 1** Studies of predictiv value of PET in response to treatment

| Authors | Year | Sample size | Age† | Male (%) | PET device | Timing of PET‡ | PET criteria | CT criteria | Drug |
|---|---|---|---|---|---|---|---|---|---|
| Van Oosterom *et al.*[24] | 2001 | 40 | 53 | 62 | PET | 30 | EORTC | RECIST | Imatinib |
| Stroobants *et al.*[25] | 2003 | 21 | 55 | 57 | PET | 8 | EORTC | RECIST | Imatinib |
| Gayed *et al.*[26] | 2004 | 54 | 56 | 57 | PET | 60 | EORTC | ≥5% decrease in tumor size | Imatinib |
| Jager *et al.*[27] | 2004 | 16 | 60 | 71 | PET | 7 | 20%-40% reduction of SUV | RECIST | Imatinib |
| Choi *et al.*[28] | 2004 | 29 | 55 | 50 | PET | 2 | EORTC | RECIST | Imatinib |
| Antoch *et al.*[15] | 2004 | 20 | 60 | 55 | PET/CT | 30 | EORTC | RECIST | Imatinib |
| Goldstein *et al.*[29] | 2005 | 18 | NR | NR | PET | 2 | EORTC | RECIST | Imatinib |
| Goerres *et al.*[30] | 2005 | 24 | 52 | 56 | PET/CT | 3 | EORTC | RECIST | Imatinib |
| Holdsworth *et al.*[31] | 2007 | 98 | 55 | 63 | PET | 0 | EORTC | SWOG | Imatinib |
| Choi *et al.*[32] | 2007 | 40 | NR | 47 | PET | 2 | 70% reduction of SUV | RECIST | Imatinib |
| Prior *et al.*[33] | 2009 | 22 | 53 | 69 | PET | 1 | EORTC | RECIST | Sunitinib |
| McAuliffe *et al.*[34] | 2009 | 16 | 59 | 58 | PET | 1 | 40% reduction of SUV | ≥10% decrease in tumor blood flow | Imatinib |
| Demetri *et al.*[35] | 2009 | 60 | 55 | 66 | PET | 7 | EORTC | RECIST | Sunitinib |
| Maurel *et al.*[36] | 2010 | 24 | 57 | 92 | PET/CT | 14 | EORTC | RECIST | Imatinib + doxorubicin |
| Fuster *et al.*[37] | 2010 | 21 | 57 | NR | PET/CT | 60 | EORTC | RECIST | Imatinib + doxorubicin |
| Bertagna *et al.*[38] | 2010 | 19 | 61 | 68 | PET/CT | 60 | SUV greater than 3 | RECIST | Imatinib |
| Van den Abbeele *et al.*[39] | 2012 | 40 | 55 | 50 | PET | 7 | EORTC | RECIST | Imatinib |
| Herrmann *et al.*[40] | 2012 | 38 | 53 | 49 | PET/CT | 30 | EORTC | RECIST | Ifosfamide + doxorubicin |
| Zukotynski *et al.*[41] | 2014 | 17 | 65 | 23 | PET/CT | 30 | EORTC | RECIST | Imatinib |
| Camacho *et al.*[13] | 2014 | 9 | 58 | 44 | PET/CT | 180 | PERCIST | RECIST | Yttrium |
| Chacón *et al.*[42] | 2015 | 15 | 49 | 50 | PET/CT | 37 | EORTC | RECIST | Imatinib |

†, Number is presented as mean (years)

‡, Time interval of PET performance after intervention (day)

CT: Computed tomography; EORTC: European organization for research and treatment of cancer; NR: Not reported; PET: Positron emission tomography; PERCIST: PET response criteria in solid tumors; RECIST: Response evaluation criteria in solid tumors; SUV: Standard uptake value; SWOG: Southwest oncology group.

$I^2 = 61.97\%$; $P = 0.001$), specificity ($Q = 65.93$; $I^2 = 69.66\%$; $P = 0.001$), POR ($Q = 26112$; $I^2 = 100.0\%$; $P < 0.001$). No publication bias was observed among included studies ($P = 0.19$).

- Meta-analysis

The analysis showed the pooled sensitivity and specificity of $^{18}$FDG–PET for prediction of response to treatment were 0.90 (95% CI: 0.85–0.94; $I^2 = 52.59$, $P = 0.001$) and 0.62 (95% CI: 0.49–0.75; $I^2 = 69.7$, $P = 0.001$), respectively (Fig. 2). The pooled POR for \$^{18}$FDG–PET was 14.99 (95% CI, 6.42–34.99; $I^2 = 100.0$, $P < 0.001$) (Fig. 3). The summary receiver operating characteristic (SROC) curves for PET is presented in Figure 4. The area under curve was 0.89 (95% CI: 0.86–0.92).

- Subgroup analysis

The subgroup analysis showed sample size, type of PET device for assessing response to treatment, and PET criteria were the main possible sources of heterogeneity. The meta-regression showed that the sensitivity (sensitivity = 0.93; 95% CI: 0.89–0.97) of $^{18}$FDG–PET was higher if the sample size of study was equal or more than 30 cases. In addition, using PET/CT was associated with higher pooled sensitivity (sensitivity = 0.92; 95% CI: 0.89–0.97). Interestingly, using European Organization for Research and Treatment of Cancer (EORTC) or PET Response Criteria In Solid Tumors (PERCIST) criteria is associated with lower sensitivity (sensitivity = 0.89; 95% CI: 0.84–0.94) compared with self-design criteria (sensitivity = 0.93; 95% CI: 0.87–1.0) (Table 2).

## Discussion

The present meta-analysis declared the value of $^{18}$FDG–PET for predicting treatment response in GIST patients. Overall, it seems that the value of $^{18}$FDG–PET is higher for detection of treatment failure (higher sensitivity) than prediction of good response (low specificity) even after adjusting for possible sources of heterogeneity (the lowest PET subgroup sensitivity was 0.85). Using

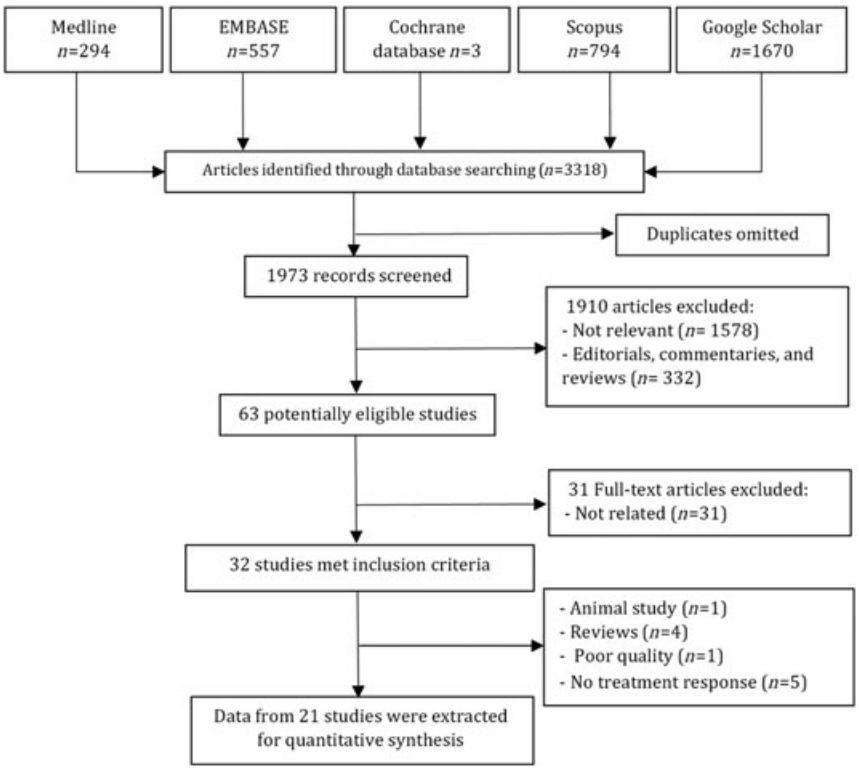


**Figure 1** Flow chart of the study. Diagram represents the review process and selection of included studies

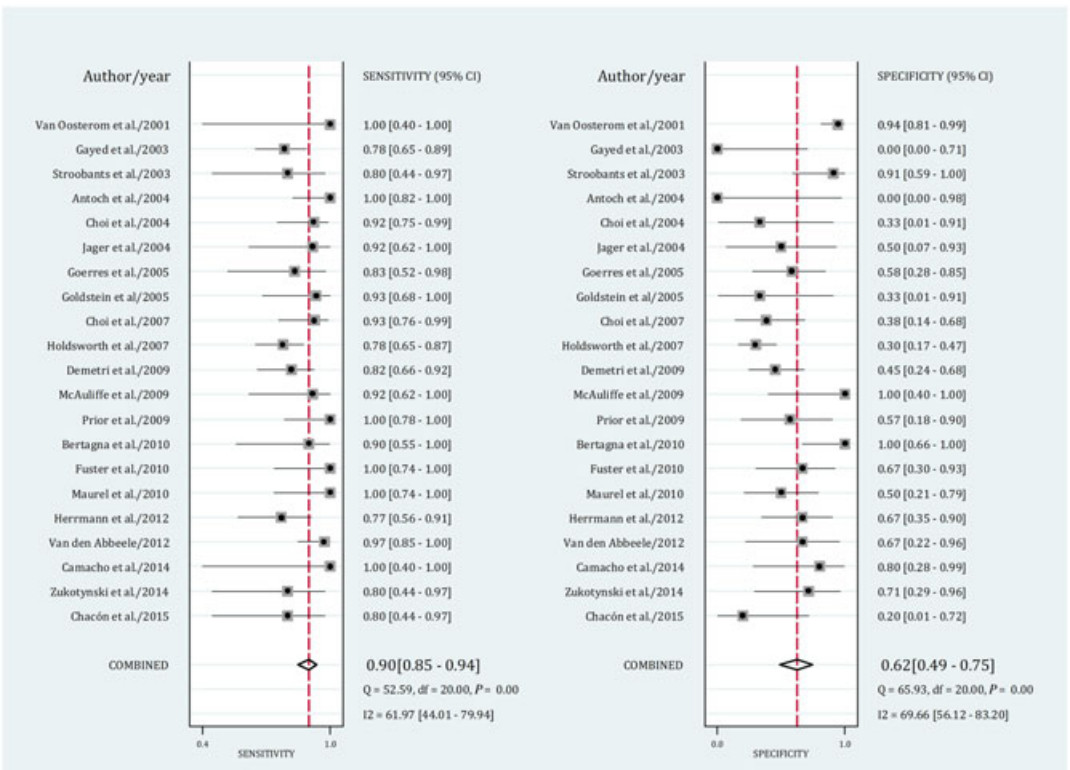


**Figure 2** Forest plot for sensitivity and specificity of PET for predicting treatment response.

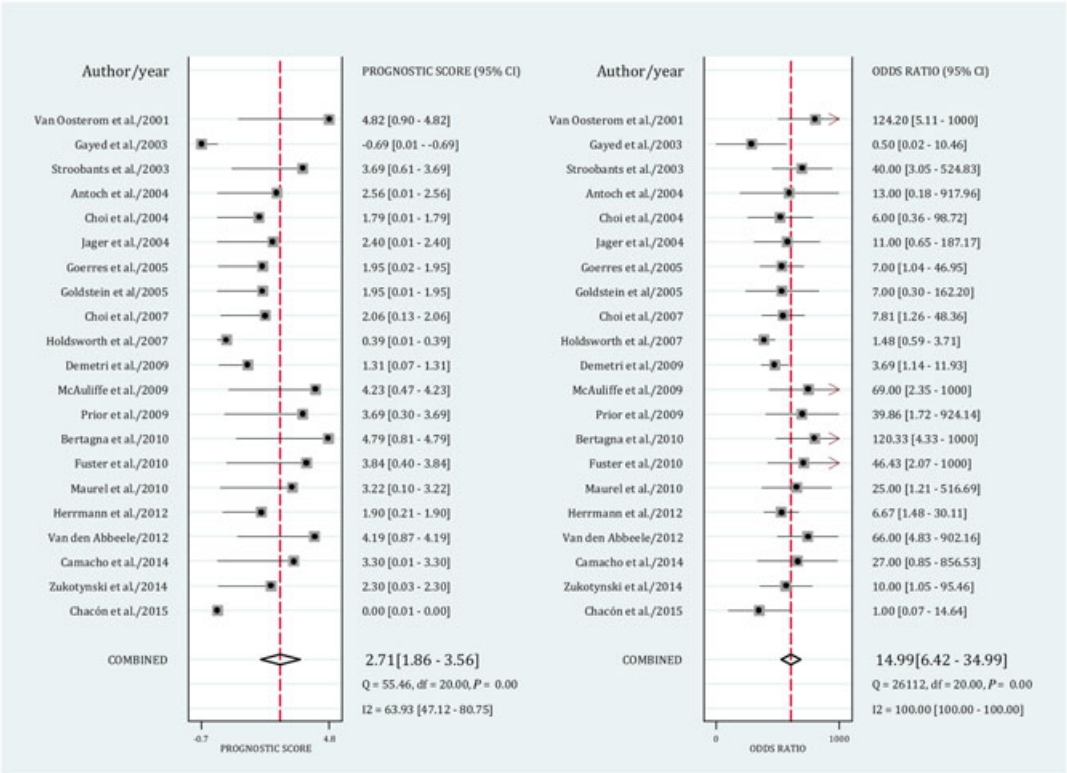


**Figure 3** Forest plot for predictive odds ratio of PET for predicting treatment response.

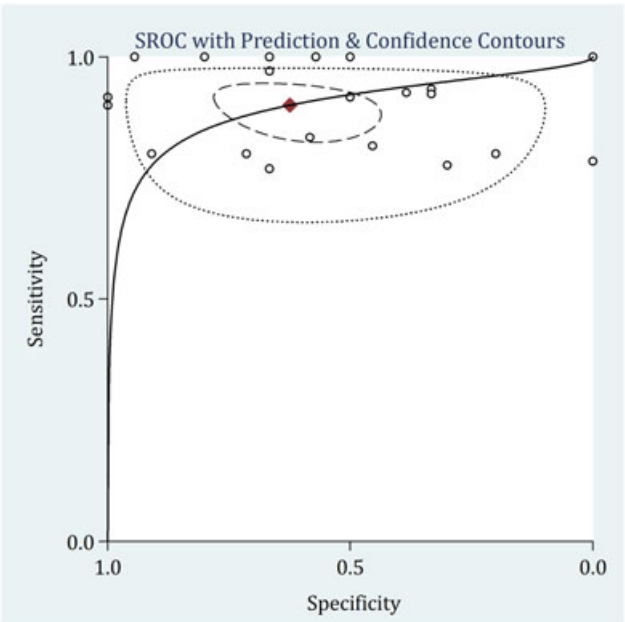


**Figure 4** Summary receiver operative curves (SROC) for PET. AUC, Area under the curve. (○) Observed Data, (◆) Summary Operating Point SENS = 0.90 [0.85−0.94]; SPEC = 0.62 [0.49−0.75], (—) SROC Curve; AUC = 0.89 [0.86−0.92], (—) 95% Confidence Contour, (•••) 95% Prediction Contour.

PET/CT was associated with higher sensitivity in prediction of treatment response. It might be due to fusion of transaxial, sagital, and coronal images obtained by PET and CT components of the study, which provide simultaneous functional and anatomical information, leading to more accurate diagnosis.

A systematic review performed by Treglia *et al.*, who reviewed 19 studies, demonstrated PET has a significant value in assessing treatment response to treatment in GIST. They stated this modality allows an early assessment of treatment response and is a strong predictor of clinical outcome.[43] In another review, Donswijk *et al.* showed PET (/CT) is a valuable tool to monitor response in patients with GIST treated by tyrosine kinase inhibitors.[44] Also, Sheikhbahaei *et al.* after reviewing 14 studies demonstrated that FDG–PET/CT provides advantages in the initial tumor staging, tumor grading, therapy assessment, and recurrence detection in these tumors.[45] These findings were in concordance with the present meta-analysis.

Based on our knowledge, the present study is the first quantitative, meta-analytic approach to review all available evidence regarding the predictive value of $^{18}$FDG–PET on treatment response in GIST tumor. We performed a wide search in several databases to include the extreme number of relevant studies. This search strategy led to find 21 relevant articles. However, the present meta-analysis had a number of potential limitations. First, the predictive value of $^{18}$FDG–PET in GIST patient was reported without adjusting for potential confounders such as grading and staging of patients. Moreover, the heterogeneity between studies was another issue. Therefore, it was decided to perform a bivariate mixed random effects model provided more conservative results.

**Table 2** Heterogeneity in the pooled sensitivity and specificity of PET for prediction of response to treatment

| Covariate | Sensitivity | Bivariate random-effect model | | | | |
|---|---|---|---|---|---|---|
| | | $I^2$ (%) | *P* | Specificity | $I^2$ (%) | *P* |
| Sample size | | | | | | |
| <30 patients | 0.85 (0.79–0.90) | — | — | 0.55 (0.35–0.75) | — | — |
| ≥30 patients | 0.93 (0.89–0.97) | 61 | <0.001 | 0.69 (0.54–0.84) | 13 | 0.22 |
| PET device | | | | | | |
| PET | 0.88 (0.85–0.92) | — | — | 0.6 (0.45–0.76) | — | — |
| PET/CT | 0.92 (0.89–0.97) | 0 | 0.02 | 0.71 (0.54–0.88) | 0 | 0.89 |
| PET criteria | | | | | | |
| EORTC | 0.89 (0.84–0.94) | | | 0.63 (0.49–0.76) | | |
| Other | 0.93 (0.87–1.0) | 0 | 0.02 | 0.73 (0.48–0.99) | 0 | 0.38 |
| Drug evaluated | | | | | | |
| Imatinib | 0.91 (0.87–0.96) | — | — | 0.65 (0.51–0.78) | — | — |
| Other | 0.87 (0.77–0.96) | 0 | 0.19 | 0.63 (0.37–0.89) | 0 | 0.84 |
| PET timing† | | | | | | |
| <30 days | 0.90 (0.86–0.95) | — | — | 0.56 (0.42–0.70) | — | — |
| ≥30 days | 0.90 (0.84–0.97) | 0 | 0.15 | 0.77 (0.63–0.91) | 0 | 0.47 |

†, Time interval of PET performance after intervention.
EORTC: European organization for research and treatment of cancer; PET: Positron emission tomography; PERCIST: PET response criteria in solid tumors.

## Conclusion

The present meta-analysis showed $^{18}$FDG–PET has a significant value in assessing treatment response in GIST patients. Accuracy of $^{18}$FDG–PET is higher in detection of treatment failure than prediction of good response to treatment even after adjusting for possible sources of heterogeneity. Using $^{18}$FDG–PET/CT was associated with higher sensitivity in prediction of treatment response.

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