

Clinical usefulness of ^{18}F -FDG PET/CT for the detection of distant metastases in patients with non-small cell lung cancer at initial staging: a meta-analysis

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Background: We undertook a meta-analysis to evaluate the clinical usefulness of ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) for the detection of distant metastases in patients with non-small cell lung cancer (NSCLC) at initial staging.

Materials and methods: All topic-related studies were comprehensively searched in the MEDLINE and Embase databases. We obtained the summary estimates and constructed the summary receiver operating characteristic curve for ^{18}F -FDG PET/CT using the bivariate regression model.

Results: Across 10 studies (1333 patients), the sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for ^{18}F -FDG PET/CT were 0.81 (95% confidence interval [CI] = 0.63–0.92), 0.96 (95% CI = 0.94–0.98), 22.9 (95% CI = 13.3–39.5), and 0.20 (95% CI = 0.09–0.42), respectively. Overall weighted area under the curve was 0.97 (95% CI = 0.96–0.98).

Conclusion: ^{18}F -FDG PET/CT has a good diagnostic performance for distant metastasis staging in patients with NSCLC at initial staging.

Keywords: ^{18}F -FDG PET/CT, distant metastasis, lung cancer, meta-analysis

Introduction

Lung cancer is the leading cause of cancer mortality worldwide.^{1,2} Non-small cell lung cancer (NSCLC) accounts for 80% of lung cancer.^{1,2} Distant metastasis is one of the most critical factors guiding treatment decisions in NSCLC patients. NSCLC patients with locoregional disease are generally treated with curative surgery or radiotherapy with/without chemotherapy.¹ In contrast, palliative chemotherapy or molecule-targeted treatment is the standard treatment for NSCLC patients with metastasis.¹

Conventional imaging procedure for distant metastasis staging of lung cancer is the combination of computed tomography, bone scan, and magnetic resonance imaging (MRI), and its accuracy is still unsatisfactory.³⁻⁸ ^{18}F -fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F -FDG PET/CT) can detect the increase in glucose metabolism in tumor cells and offer anatomical details at the same time, enabling whole-body examination in a single procedure.³ Although many previous studies about ^{18}F -FDG PET/CT have been reported for distant metastasis staging in NSCLC patients at initial staging,⁴⁻¹⁰ the results among studies are still controversial. Here, we undertook a meta-analysis to evaluate the diagnostic performance of ^{18}F -FDG PET/CT for detecting distant metastasis in NSCLC patients at initial staging.

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Materials and methods

Search strategy

We searched for studies evaluating ^{18}F -FDG PET/CT for the detection of distant metastasis in NSCLC patients at initial staging. Articles were identified with a search of the MEDLINE and Embase databases through October 29, 2017. We used a search algorithm that was based on a combination of text words: PET/CT, positron emission tomography/computed tomography, PET-CT, positron emission tomography-computed tomography, non-small cell lung cancer, NSCLC, staging, and distant metastasis. We had no language restrictions for searching and selecting relevant studies. References of pertinent articles (the retrieved articles, meta-analysis, reviews, and editorials) and guidelines were also screened manually to retrieve additional eligible studies. Authors of eligible studies were contacted and asked to supplement additional data when key information was missing.

Study selection

We included studies based on the following criteria: 1) ^{18}F -FDG PET/CT was used as a diagnostic tool for the detection of distant metastases in NSCLC patients at initial staging; 2) studies can provide sufficient data of the true-positive, false-negative, false-positive, and true-negative values to reconstruct a 2x2 table; 3) studies with a minimal sample size of 10 patients were included; 4) studies were based on a per-patient analysis; and 5) pathological analysis and/or imaging follow-up data served as the reference standard.

We excluded studies based on the following criteria: 1) studies enrolled patients with recurrent NSCLC; 2) studies enrolled patients with NSCLC and small cell lung cancer, if relevant data regarding the NSCLC patients could not be obtained; 3) studies came from the same study group; and 4) non-original articles (case reports, conference abstracts, and reviews).

Data extraction

Two reviewers extracted data from eligible studies independently and resolved discrepancies by discussion. For each report, we recorded the author names, publication time, country of origin, sample size, technical protocols of PET-CT (technical parameters, interpreters, criteria for defining positive PET/CT results), reference standards, and follow-up time. For each study, we also recorded the number of true-positive, false-positive, true-negative, and false-negative values for ^{18}F -FDG PET/CT.

Quality assessment

To evaluate the quality, two reviewers independently evaluated the methodological quality of all included studies using

the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) tool.¹¹ It consists of four key domains covering patient selection, index test, reference standard, and flow and timing.

Statistical analyses

All analyses were conducted with Stata version 12.0 (Stata-Corp LP, College Station, TX, USA). We used the bivariate regression model to obtain weighted overall estimates of the sensitivity and specificity as the main outcome measures and to construct summary receiver operating characteristic (SROC) curves for ^{18}F -FDG PET/CT.^{9,10} By using the pooled sensitivity and specificity, we also calculated diagnostic odds ratio (DOR), positive likelihood ratios (PLRs), and negative likelihood ratios (NLRs) for ^{18}F -FDG PET/CT.¹²⁻¹⁴

We used the summary estimates of sensitivity and specificity to calculate the negative predictive values of ^{18}F -FDG PET/CT when the prevalence of distant metastasis in NSCLC was assumed to be 10%, 20%, and 30%, respectively.

The Deeks' funnel plot was used to assess publication bias. An asymmetric Deeks' funnel plot ($p < 0.05$) would suggest that a publication bias is present.

Results

Eligible studies

The electronic search yielded 2460 articles; 2438 were excluded upfront by reading the abstract because they did not present any diagnostic information. We screened in full text 22 articles and rejected 12; 10 articles^{4-10,14-17} were eligible for meta-analysis. Reasons for exclusion are listed in Figure 1. Ten of the 10 (100%) studies stated that they were prospective (Prosp). A total of 10 studies (1333 patients) were analyzed for the accuracy of ^{18}F -FDG PET/CT to detect distant metastases (Table 1). In four studies, ^{18}F -FDG PET/CT was interpreted in a qualitative (QL) manner, whereas in six studies, it was interpreted in a quantitative and QL manner.

Quality assessment

The results of the quality assessment using the QUADAS-2 tool are shown in Table 2. The risk of bias and applicability concerns with regard to patient selection were unclear or low in three of all 10 studies.^{4,10,17} Risk of bias with regard to the index test was low in all 10 studies because the PET-CT results were consistently interpreted without knowledge of the reference standard results. However, the risk of bias for the reference standard was high in all 10 studies because the reference standard was not executed without knowledge of the PET-CT results.

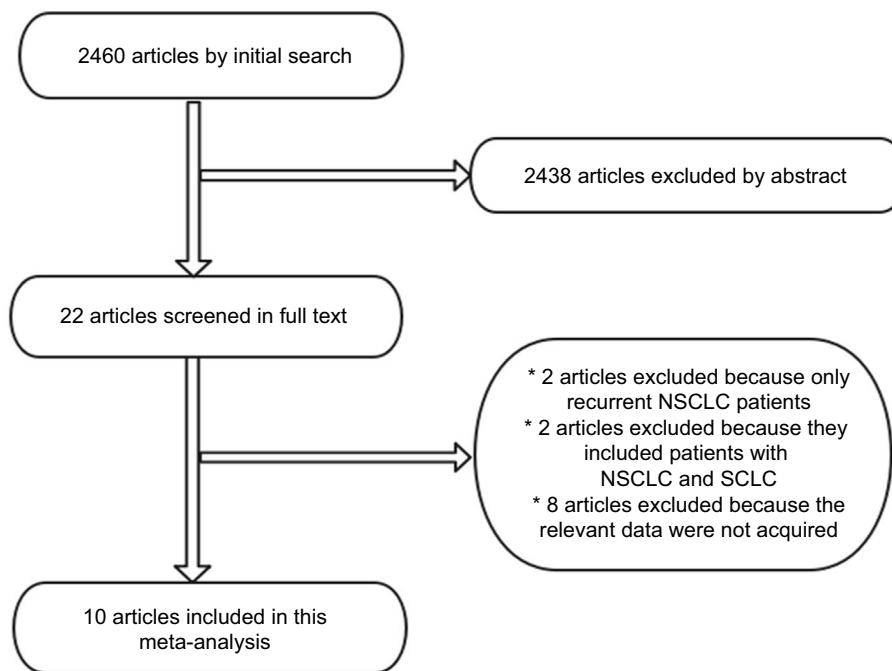


Figure 1 The flow chart of the search for eligible studies.

Abbreviations: NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

Table 1 Clinical characteristics and study quality of the included studies

Studies	Publication time	Origin	Study design	No. of patients	Male (%)	Age (years)	Imaging interpretation	Follow-up time (months)	Prevalence (%)
Antoch et al ⁴	2003	Germany	Prosp	20	80	39–70	QL + QN	4.7 (mean)	25 (5/20)
Cerfolio et al ⁵	2004	USA	Prosp	129	60	24–87	QL + QN	NR	15 (19/129)
Ohno et al ⁶	2008	Japan	Prosp	203	54	72 (mean)	QL	≥12	20 (40/203)
Yi et al ⁷	2008	Korea	Prosp	154	76	61 (mean)	QL	19.7 (mean)	20 (31/154)
Plathow et al ⁸	2008	Germany	Prosp	52	69	49–71	QL + QN	2.7 (mean)	8 (4/52)
Lee et al ⁹	2009	Korea	Prosp	442	54	23–88	QL	≥30	19.9 (88/442)
Opoka et al ¹⁰	2013	Poland	Prosp	99	71	41–88	QL + QN	NR	18.2 (18/99)
Ohno et al ¹⁵	2015	Japan	Prosp	140	53	40–83	QL	≥6	11 (16/140)
Huellner et al ¹⁶	2016	Switzerland	Prosp	42	69	35–89	QL	≥18.9	29 (12/42)
Lee et al ¹⁷	2016	Korea	Prosp	45	58	35–79	QL	≥13.1	13 (6/45)

Abbreviations: Prosp, prospective; QL, qualitative; QN, quantitative; NR, not reported.

Table 2 The results of the quality assessment using the QUADAS-2 tool

Studies	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Antoch et al ⁴	Unclear	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Cerfolio et al ⁵	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Ohno et al ⁶	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Yi et al ⁷	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Plathow et al ⁸	High risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Lee et al ⁹	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Opoka et al ¹⁰	Unclear	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Ohno et al ¹⁵	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Huellner et al ¹⁶	Low risk	Low risk	High risk	Low risk	High risk	Low risk	Low risk
Lee et al ¹⁷	Unclear	Low risk	High risk	Low risk	Low risk	Low risk	Low risk

Abbreviation: QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies version 2.

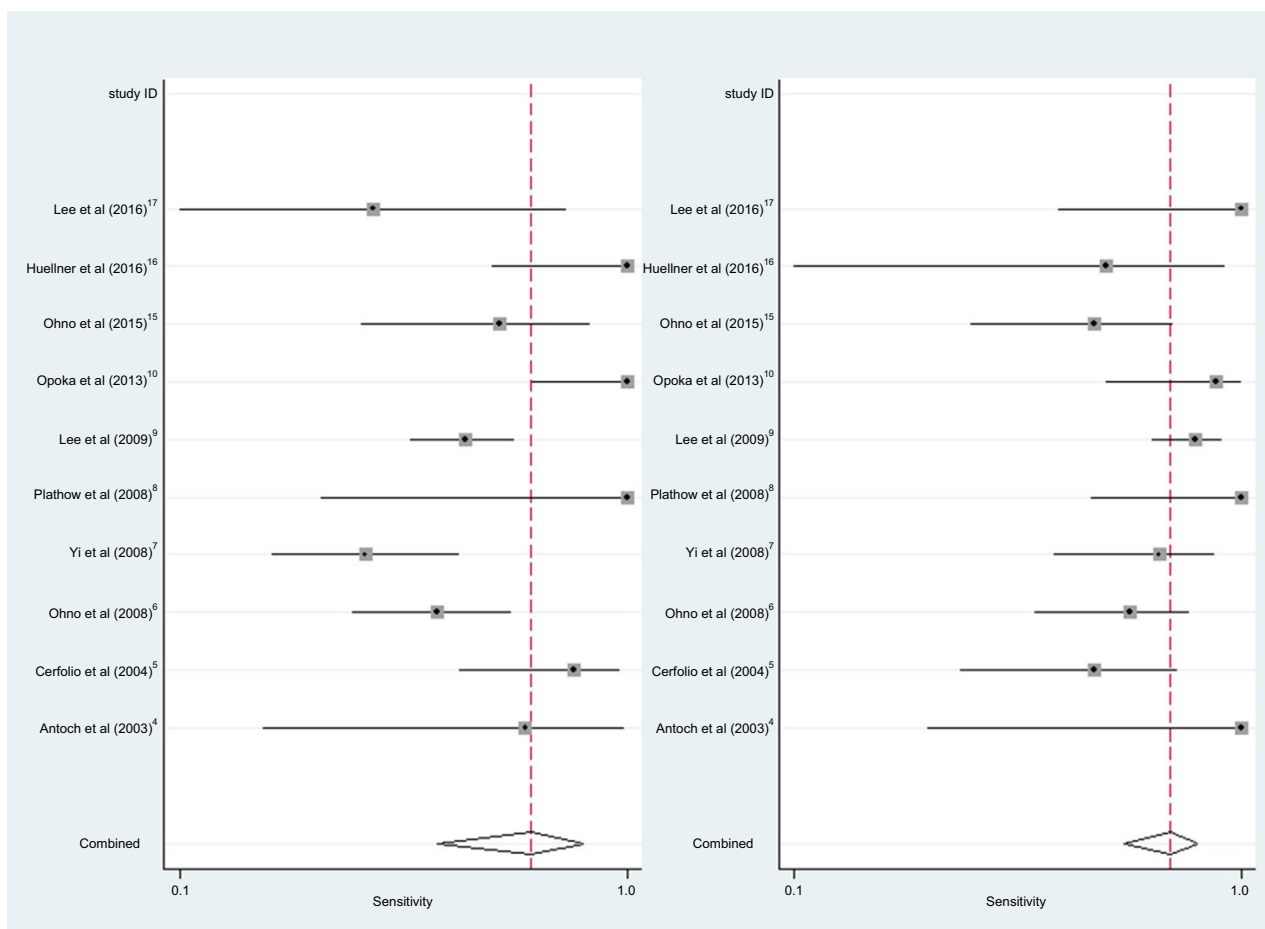


Figure 2 The forest plot of sensitivity and specificity for ¹⁸F-FDG PET/CT for the detection of NSCLC patients at initial M staging.
Abbreviations: ¹⁸F-FDG PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; NSCLC, non-small cell lung cancer.

Results of meta-analysis

Summary estimates of sensitivity, specificity, DOR, PLR, and NLR

Figure 2 shows the forest plot of sensitivity and specificity for ¹⁸F-FDG PET/CT in NSCLC patients at initial M staging. When considering 10 studies (1333 patients), the pooled sensitivity, specificity, DOR, PLR, and NLR for ¹⁸F-FDG PET/CT were 0.81 (95% confidence interval [CI] = 0.63–0.92), 0.96 (95% CI = 0.94–0.98), 117 (95% CI = 38–355), 22.9 (95% CI = 13.3–39.5), and 0.20 (95% CI = 0.09–0.42), respectively.

SROC curve

The SROC curve for ¹⁸F-FDG PET/CT in NSCLC patients at initial M staging is shown in Figure 3. The results showed that the overall weighted area under the SROC curve was 0.97 (95% CI = 0.96–0.98).

Negative predictive values

Assuming a prevalence of distant metastases of 10%, 20%, and 30% in NSCLC patients, the negative predictive values for ¹⁸F-FDG PET-CT were 0.98, 0.95, and 0.92, respectively.

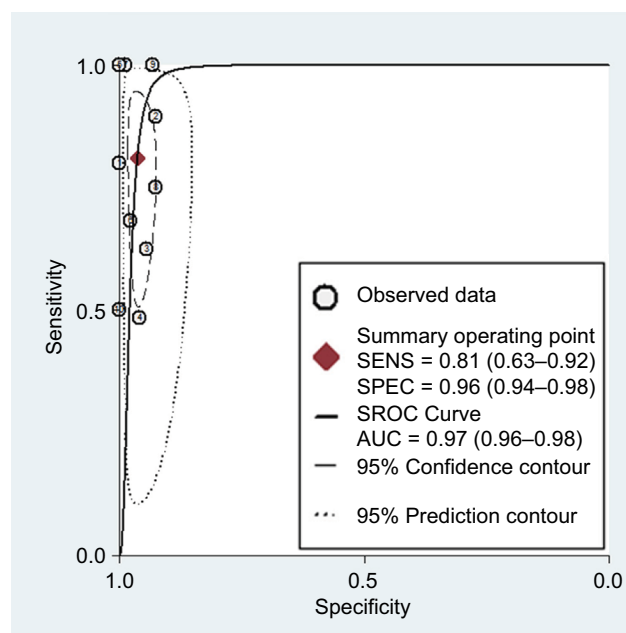


Figure 3 The SROC curve for ¹⁸F-FDG PET/CT for the detection of NSCLC patients at initial M staging.
Abbreviations: SROC, summary receiver operating characteristic; ¹⁸F-FDG PET/CT, ¹⁸F-fluorodeoxyglucose positron emission tomography/computed tomography; NSCLC, non-small cell lung cancer; AUC, area under the curve.

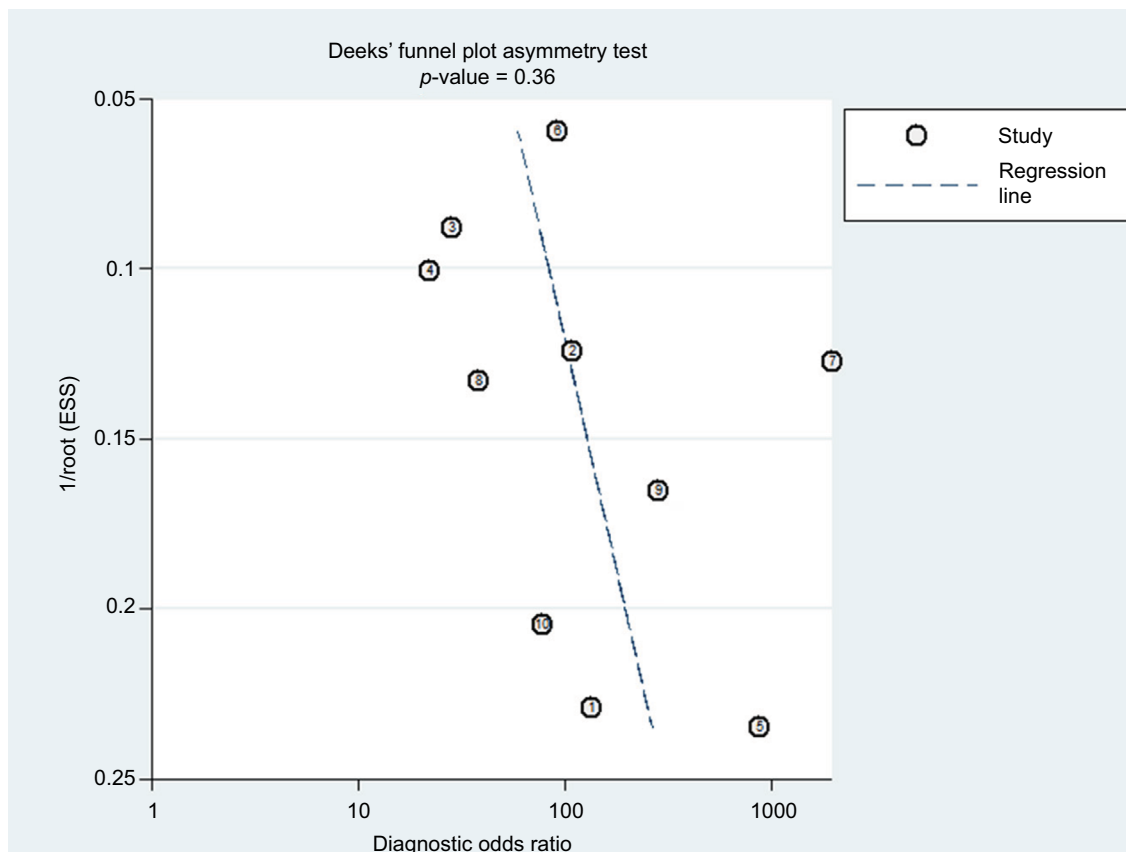


Figure 4 Funnel plot for publication bias.

Abbreviation: ESS, effect sizes.

Publication bias

The publication bias for ^{18}F -FDG PET/CT ($p = 0.38 > 0.05$) was insignificant. The funnel plot for ^{18}F -FDG PET/CT was symmetrical (Figure 4). These results indicated that the publication bias was not statistically significant.

Discussion

Distant metastasis staging is one of the major prognostic factors of survival in NSCLC patients. Accurate staging of distant metastasis is crucial, as the treatment strategy is directly dependent on tumor stage.¹ In this meta-analysis of 10 studies, distant metastasis involves 239 of 1333 (17.9%) eligible patients. ^{18}F -FDG PET/CT has a sensitivity and a specificity of 0.81 (95% CI = 0.63–0.92) and 0.96 (95% CI = 0.94–0.98), respectively. This meta-analysis documents that ^{18}F -FDG PET/CT has a good diagnostic performance for NSCLC patients at initial M staging. With the application of PET–CT in initial M staging of NSCLC, distant metastases may be detected earlier. This would have a considerable impact on patient staging of distant metastasis and the execution of more reliable treatment protocols.

As one of the best indicators of diagnostic meta-analysis, the likelihood ratio is widely considered to be more important

than sensitivity and specificity.^{12–14} In this meta-analysis, the PLR value of 22.9 suggested that the correct probability of testing the positivity of the PET–CT assay in NSCLC patients with distant metastasis would be ~23 times higher than that in patients without distant metastasis. The NLR value of 0.09 indicated that the incorrect probability of testing the negativity of the PET–CT assay in NSCLC patients with distant metastasis would be 0.20 times lower than that in patients without distant metastasis. In other words, the correct probability of testing the negativity of the PET–CT assay in NSCLC patients without distant metastasis would be approximately five (1/0.20) times higher than that in patients with distant metastasis.

The SROC curve has been recommended to represent the performance of a diagnostic meta-analysis, which indicates the balance between sensitivity and specificity to compare diagnostic values from different diagnostic tests.^{18,19} The SROC curve showed that the overall weighted area under the curve was 0.97 (95% CI = 0.96–0.98), suggesting that ^{18}F -FDG PET/CT has an excellent accuracy for the initial M staging of NSCLC patients.

Nevertheless, the present study has several limitations that should be considered. First, the exclusion of unpublished studies and meeting abstracts was probably a cause of publica-

tion bias. Second, the reference standard of the pathological analysis was not obtained from all distant metastatic lesions, which may affect the accuracy of ^{18}F -FDG PET/CT. Third, we did not perform subgroup analyses according to clinical stage and subtype of pathology because this would have required individual patient data. Clinical stage and subtype of pathology may influence the probability of distant metastases, which may also affect the diagnostic accuracy of ^{18}F -FDG PET/CT. Fourth, there is a unified protocol of PET/CT (technical parameters, interpreters, criteria for defining positive PET/CT results). The optimal accuracy of ^{18}F -FDG PET/CT for distant metastasis staging in NSCLC patients is still unclear.

Conclusion

^{18}F -FDG PET/CT has excellent diagnostic performance for the detection of distant metastases in NSCLC patients. Large and Prosp studies with a standardized protocol of ^{18}F -FDG PET/CT are needed to investigate the optimal value of ^{18}F -FDG PET/CT and could help establish ^{18}F -FDG PET/CT as an accurate tool for distant metastasis staging in NSCLC.

Acknowledgments

This meta-analysis has been financially supported by the National Natural Science Foundation of China (81760544 and 81360343), and the Key Laboratory of High-Incidence-Tumor Prevention and Treatment, Independent Research Project (Contract number: GKZ201605 and GJZ201605).

Disclosure

The authors report no conflicts of interest in this work.

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