Whole-Body ^{18}F-FDG PET and ^{18}F-FDG PET/CT in Patients with Suspected Paraneoplastic Syndrome: A Systematic Review and Meta-Analysis of Diagnostic Accuracy

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The purpose of this study was to assess the diagnostic performance of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT for detection of underlying malignancy in patients with clinically suspected neurologic and nonneurologic paraneoplastic syndromes. **Methods:** A systematic search was performed in PubMed (Medline), Embase, and Scopus (last updated November 2016) to identify relevant published studies reporting the performance of ^{18}F-FDG PET or ^{18}F-FDG PET/CT in patients with suspected paraneoplastic syndrome. Histopathologic confirmation or clinical follow-up was considered as the reference standard. Pooled estimates, with 95% confidence intervals (CIs), of sensitivity, specificity, and diagnostic odds ratio were calculated. A summary receiver-operating-characteristic curve was constructed, and the area under the curve (AUC) was determined along with the Q* index. **Results:** Twenty-one studies including a total of 1,293 individual patients suspected of having a paraneoplastic syndrome and who underwent ^{18}F-FDG PET or ^{18}F-FDG PET/CT examinations met our inclusion criteria. There was moderate to high heterogeneity among the included studies. The pooled sensitivity, specificity, and diagnostic odds ratio of ^{18}F-FDG PET or ^{18}F-FDG PET/CT for the detection of underlying malignancy were 0.81 (95% CI, 0.76–0.86), 0.88 (95% CI, 0.86–0.90), and 34.03 (95% CI, 18.76–61.72), respectively. The AUC and the Q* index were 0.916 (SE, 0.018) and 0.849, indicating excellent diagnostic accuracy. The diagnostic accuracy was slightly improved after studies with high applicability concerns were excluded (AUC, 0.931; SE, 0.020). In a subgroup analysis, ^{18}F-FDG PET/CT was found to have a significantly higher specificity (0.89 vs. 0.79) than ^{18}F-FDG PET alone, with no evidence of significant difference in the overall performance (AUC, 0.930 vs. 0.891; 2-tailed *P* value for difference, 0.31). **Conclusion:** This meta-analysis of available studies demonstrates that whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT has high diagnostic accuracy and moderate to high sensitivity and specificity for detection of underlying malignancy in patients suspected of having a paraneoplastic syndrome.

Key Words: paraneoplastic syndrome; ^{18}F-FDG-PET; sensitivity and specificity; meta-analysis

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Paraneoplastic syndromes are a rare systemic complication of malignancy that is not directly caused by local tumor extension or metastases (*1,2*). The pathogenesis of paraneoplastic syndromes is not completely understood, yet it is believed to be mediated by an altered immune response to the presence of cancer (*1*). Paraneoplastic syndromes comprise a heterogeneous group of disorders that can affect any organ system including the central and peripheral nervous systems as well as the musculoskeletal, dermatologic, hematologic, endocrine, or gastrointestinal systems (*2,3*). The nervous system involvements are the most commonly reported paraneoplastic syndrome (*2,4*). An immunologic response to an antigenic target that is shared between a component of the nervous system and tumor cells may be the underlying pathology (*1,4*).

Paraneoplastic symptoms can be the initial or the most prominent manifestation of malignancy (*2*). Timely recognition of these symptoms and detecting the underlying malignancy can play a critical role in the early treatment of tumors and can guide further management and improve patients' survival. Paraneoplastic signs and symptoms may regress by treating the underlying malignancy. Thus, accurate imaging examinations are essential in identifying the underlying malignancy whenever a paraneoplastic syndrome is suspected (*5*). Anatomic cross-sectional imaging including CT and MRI may fail to detect the underlying malignancy because most associated malignancies are small, often with only lymphatic metastases (*3,5*).

^{18}F-FDG PET and ^{18}F-FDG PET/CT have emerged as practical imaging modalities that allow for the detection of metabolically active tumors (*6*). Several studies have attempted to address the role of whole-body ^{18}F-FDG PET and ^{18}F-FDG PET/CT in the workup of patients with suspected paraneoplastic manifestations (*3,5,7–17*). Although some of these studies have shown promising results, they were mostly conducted in relatively small and preselected patient populations. Variations existed in their methodologic designs, patient populations, and conclusions. Currently, there is no consensus on the value of whole-body ^{18}F-FDG PET and ^{18}F-FDG PET/CT in patients with suspected paraneoplastic syndromes, warranting the need for a meta-analysis.

This study aimed to review the literature systematically and to extract the summary estimates of the diagnostic performances of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT for detection of underlying malignancy in patients with clinically suspected neurologic and nonneurologic paraneoplastic syndromes. The results of this study can provide further insight into the usefulness of whole-body ^{18}F-FDG PET and ^{18}F-FDG PET/CT in patients with suspected paraneoplastic syndromes.

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MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was followed (*18*).

Search Strategy

Systematic electronic searches of Medline (PubMed), Embase, Scopus, and abstract proceedings of major scientific meetings (Society of Nuclear Medicine and Molecular Imaging, Radiological Society of North America, European Association of Nuclear Medicine) were performed to identify relevant published studies evaluating the diagnostic performance of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT in detecting primary malignancies or metastasis in patients presenting with a paraneoplastic syndrome. The search strategy was based on the combination of the following key words: "paraneoplastic" OR "para neoplastic" OR "PNS"; AND "PET" OR "PET" OR "18 f FDG" OR "FDG"; AND "diagnostic" OR "sensitivity" OR "specificity."

A comprehensive search strategy was used without any restrictions on language or publication status. The search was last updated in November 2016, without beginning date limit.

Criteria for Study Consideration

Patients with clinically suspected neurologic and nonneurologic paraneoplastic syndromes were eligible for inclusion. Diagnostic whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT studies performed to detect occult malignancy were used as an index test. Histopathologic confirmation or imaging follow-up after whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT was considered as the reference standard.

Selection of Studies, Data Extraction, and Management

Two authors reviewed all records identified through the electronic search. Studies were initially evaluated on the basis of the title and abstract of the articles. Review articles, editorials, case reports, and irrelevant citations were excluded in the initial assessment. The full texts of the potentially relevant publications were retrieved for further consideration. All potentially eligible articles were independently checked by 2 authors for predefined inclusion criteria.

To avoid duplication of data, only the most recent articles with no overlapping study period were included when there was more than 1 published article from the same institution (*17,19*).

Two authors independently extracted the following data from each included study: bibliographic details, patient sampling and characteristics, number of patients or scans, index test, reference standard, prevalence of underlying malignancy, and the raw data to construct 2×2 contingency tables including the number of true-positive, false-positive, true-negative, and false-negative patients/scans. The diagnostic performance of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT for detection of malignancy was assessed by cross-relating index test results and the reference standards. All data extracted by 2 review authors were compared in each step and any discrepancies were resolved through consensus or by a third author.

Assessment of Methodologic Quality

The methodologic qualities of the included studies were assessed using a modified version of the Quality Assessment Tool for Diagnostic Accuracy (QUADAS-2) as recommended by Cochrane Collaborations (*20*).

The tool consists of 4 domains; each domain appraises the risk of bias and applicability/generalizability of the study through a series of questions (Supplemental Table 1; supplemental materials are available at http://jnm.snmjournals.org). Two authors independently assessed the quality of the studies. Disagreements were mediated by consensus.

Statistical Analysis and Data Synthesis

Studies with adequate data to reconstruct the 2×2 diagnostic table were included in the quantitative analysis. The sensitivity and specificity, along with 95% confidence intervals (CIs), were calculated for each study. The forest plots of sensitivity and specificity were used to display the variations in the results of the individual studies. Homogeneity among the studies was assessed using a χ^2 test, and a P value of less than 0.05 indicated statistically significant heterogeneity (*21,22*). The I^2 index was measured to quantify the degree of heterogeneity in studies. I^2 lies from 0 to 100, and the respective values around 0, 25, 50, and 75 indicate no, low, moderate, and high heterogeneity among studies (*23*). We calculated the pooled estimates of sensitivity, specificity, positive likelihood ratio (LR), negative LR, and diagnostic odds ratios (DOR) using random effect (DerSimonian–Laird) assumptions (*24*). The diagnostic tests with a DOR more than 25 and 100 are considered moderately and highly accurate, respectively (*25*). The summary receiver-operating-characteristic curve (SROC) space is defined by sensitivity (y-axis) and 1 − specificity (x-axis), and each data point represents 1 particular study. The area under the SROC curve (AUC) represented an overall summary of the diagnostic test performance and presents the tradeoff between sensitivity and specificity. An AUC value of 1.0 (100%) denotes a perfect discriminatory ability for a diagnostic test (*22*). To reduce the heterogeneity, subgroup analysis was performed to determine the effect of imaging modality (^{18}F-FDG PET alone vs. ^{18}F-FDG PET/CT) on the diagnostic performance. The statistical significance of the difference between 2 AUCs was estimated with the Hanley JA method (2-tailed P value) (*26*).

Publication bias was assessed using funnel plots of SE and Egger's regression intercept (*27*). To calculate the adjusted DOR, a trim and fill technique was used to account for the potentially missed studies (*27*). Analyses were performed using Meta-Disk (version 1.4; Hospital Universitario Ramon y Cajal), comprehensive meta-analysis (CMA version 2; Biostat), and MedCalc statistical software (version 16.8.3).

RESULTS

Search Results

Figure 1 illustrates the details of the study selection. A total of 887 relevant records were identified through a comprehensive literature search. After titles and abstracts were screened, we excluded 851 nonrelevant articles. To assess the eligibility of the remaining 36 records, we retrieved the corresponding full texts or

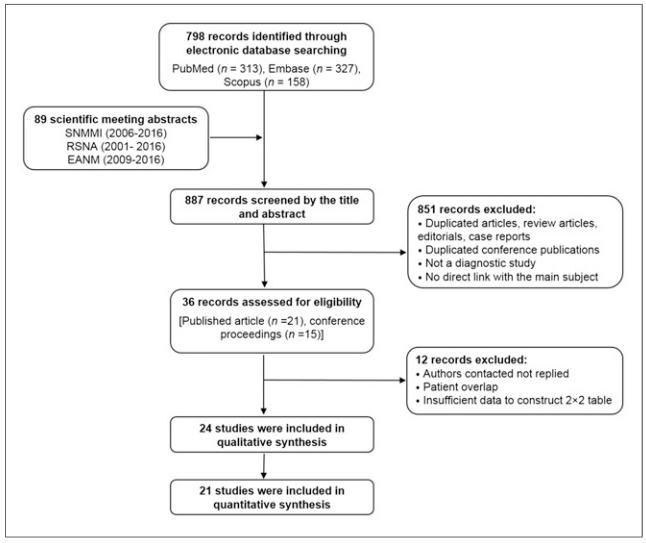

FIGURE 1. Flowchart of systematic literature review.

FIGURE 2. Risk of bias and applicability concerns: review of authors' judgments about each domain, presented as percentages across included studies.

contacted the study authors inquiring about more information. Ultimately, a total of 24 studies were included in the qualitative assessment, and 21 studies met our predefined criteria to be included in the quantitative analysis (*3,5,7–17,28–37*).

Study Characteristics and Methodologic Quality Assessment

The details of the study design, patient demographics and characteristics, paraneoplastic presentation, paraneoplastic antibody status, index test, proportion of patients diagnosed with underlying malignancy, and reference standards of each included study were summarized in Supplemental Tables 2 and 3 (*3,5,7–17,28–31*). Among the 24 studies included in the qualitative assessment, 4 studies were prospective and 20 studies were retrospective. All studies enrolled patients with a suspected paraneoplastic syndrome. The index test was whole-body ^{18}F-FDG PET (7 studies), ^{18}F-FDG PET combined with CT (1 study), ^{18}F-FDG PET or ^{18}F-FDG PET/CT (1 study), and hybrid ^{18}F-FDG PET/CT (15 studies).

Three studies did not clearly describe the reference standard used in patients with negative ^{18}F-FDG PET/CT results and were not included in the quantitative analysis (*29,30,36*).

Twenty-one studies including 1,293 individual patients suspected of having paraneoplastic syndrome assessed the diagnostic accuracy of ^{18}F-FDG PET or ^{18}F-FDG PET/CT in the detection of underlying malignancy and were included in the quantitative analysis. Detailed information on true-positive, false-negative, and false-positive sites is summarized in Supplemental Table 4. Figure 2 depicts the risk of bias and applicability concerns across the included studies according to QUADAS-2.

Findings

The proportion of patients diagnosed with underlying malignancy among the included studies ranged between 7.5% and 90%, with the pooled estimate of 16.9% (95% CI, 15.0%–19.1%).

The sensitivity of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT in the detection of underlying malignancy in patients with a suspected paraneoplastic syndrome ranged between 0.57 and 1.00, with a pooled sensitivity of 0.81 (95% CI, 0.76–0.86) (Fig. 3A). The specificity of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT ranged between 0.25 and 1.00, with a pooled specificity of 0.88 (95% CI, 0.86–0.90) (Fig. 3B). The random-effects model was used because of moderate to substantial heterogeneity among the included studies (I^2 = 57.7% for sensitivity and 81.5% for specificity). The pooled results for the positive LR, negative LR, and DOR of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT were 5.95 (95% CI, 4.01–8.84), 0.25 (95% CI, 0.18–0.35), and 34.03 (95% CI, 18.76–61.72), respectively.

The SROC curve summarizing the accuracy of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT examinations across all included studies is depicted in Figure 4. The AUC was 0.916 (SE, 0.018) and the Q* index was 0.849, indicating excellent diagnostic accuracy.

We performed a secondary analysis after excluding studies with high applicability concerns in all domains (*9,10,12,13,31*). The pooled estimates of sensitivity, specificity, and DOR were 0.88 (95% CI, 0.82–0.93; I^2, 24.9%), 0.87 (95% CI, 0.84–0.89; I^2, 81.2%), and 44.86 (95% CI, 19.72–102.07), respectively. The diagnostic performance was slightly improved, with the AUC of 0.931 (SE, 0.020) and Q* index of 0.866.

Patients with Neurologic Paraneoplastic Syndromes

In a subgroup analysis, we tried to include only patients with exclusively neurologic paraneoplastic symptoms, where possible. A total of 12 studies on 528 patients were included. The pooled estimates of sensitivity and specificity for ^{18}F-FDG PET or ^{18}F-FDG PET/CT were 0.89 (95% CI, 0.81–0.94; I^2, 38.4%) and 0.83 (95% CI, 0.79–0.87; I^2, 76.9%), respectively. The pooled result for the positive LR, negative LR, and DOR of ^{18}F-FDG PET or ^{18}F-FDG PET/CT were 4.47 (95% CI, 2.7–7.40), 0.25 (95% CI, 0.16–0.40), and 26.99 (95% CI, 11.17–65.23), respectively. The AUC

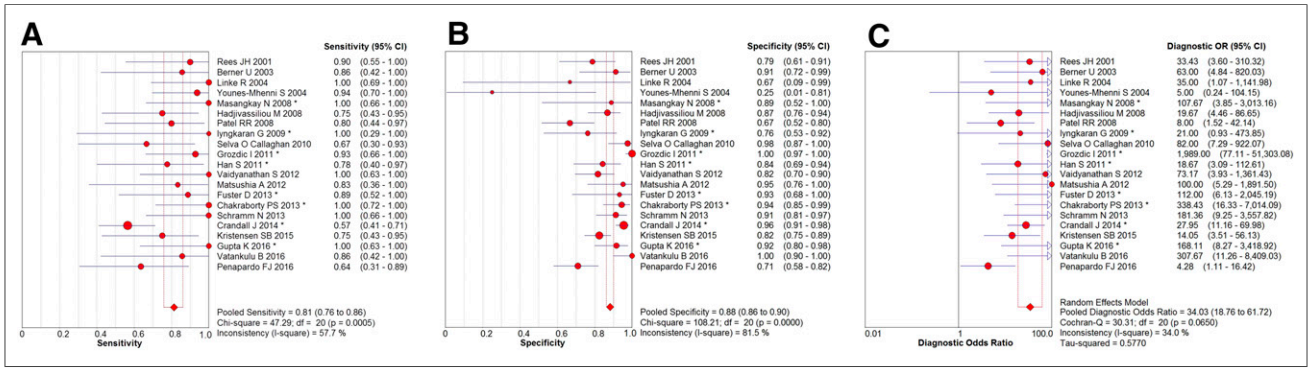

FIGURE 3. Forest plots of sensitivity, specificity, and DOR across included studies. *Conference abstracts.

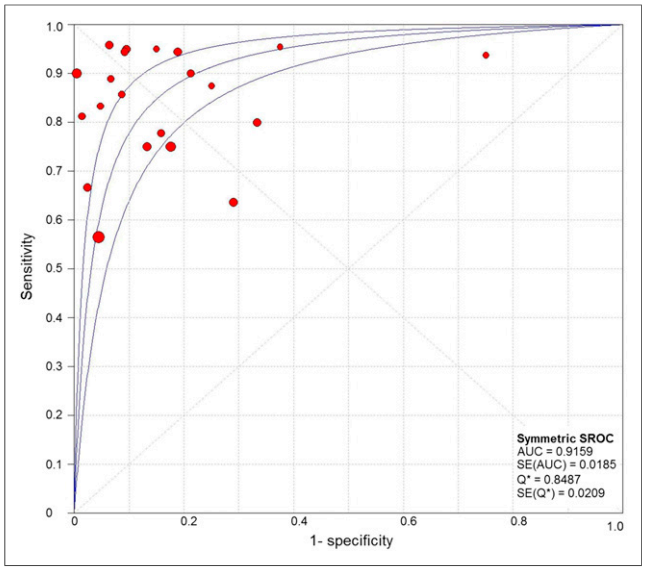

FIGURE 4. SROC curve and its 2-sided 95% CI for assessment of diagnostic accuracy of ^{18}F-FDG PET or ^{18}F-FDG PET/CT in detection of occult malignancy in patients suspected of having paraneoplastic syndrome.

was 0.915 (SE, 0.028), and the Q* index was 0.848, indicating excellent diagnostic accuracy.

Whole-Body ^{18}F-FDG PET/CT Versus ^{18}F-FDG PET Alone

In studies in which ^{18}F-FDG PET alone (7 studies, $n = 273$) was used, the pooled sensitivity and specificity were 0.88 (95% CI, 0.78–0.95; $I^2 = 0\%$) and 0.79 (95% CI, 0.73–0.84; $I^2 = 60.7\%$), respectively. In studies in which combined ^{18}F-FDG PET/CT (13 studies, $n = 895$) was performed, the pooled sensitivity and specificity were 0.77 (95% CI, 0.70–0.84; $I^2 = 66.9\%$) and 0.89 (95% CI, 0.87–0.91; $I^2 = 76.5\%$), respectively. ^{18}F-FDG PET/CT had a significantly higher specificity than ^{18}F-FDG PET alone (no overlap in 95% CIs), but there was no statistically significant difference in the pooled sensitivity. The pooled result for the positive LR, negative LR, and DOR were 3.5 (95% CI, 2.06–5.93), 0.22 (95% CI, 0.12–0.41), and 19.26 (95% CI, 8.45–43.92) for ^{18}F-FDG PET alone and 7.17 (95% CI, 4.59–11.21), 0.26 (95% CI, 0.17–0.42), and 37.34 (95% CI, 17.63–79.06) for ^{18}F-FDG PET/CT. There were no statistically significant differences between ^{18}F-FDG PET/CT and ^{18}F-FDG PET in the AUC with the respective values of 0.930 (SE, 0.023) versus 0.891 (SE, 0.031); the 2-tailed P value for difference was 0.31.

Risk of Publication Bias

Figure 5 demonstrates the funnel plot of the included studies. The log-DOR on the x-axis is plotted against the SE of the log-DOR on the y-axis. Egger's regression intercepts for DOR pooling were 1.76 (95% CI, = 0.62–2.89; 2-tailed P value = 0.004), suggesting the presence of publication bias. After adjustment for the potential effect of publication bias, looking for missing studies to the left of mean (trim and fill technique), the estimated adjusted DOR was decreased to 18.89 (95% CI, 10.01–35.65).

DISCUSSION

To our knowledge, this is the first meta-analysis to evaluate the diagnostic performance of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT in the detection of underlying malignancy in patients with paraneoplastic manifestations. This meta-analysis demonstrated a pooled sensitivity of 0.81, specificity of 0.88, and moderate DOR for ^{18}F-FDG PET or ^{18}F-FDG PET/CT in patients suspected of having a paraneoplastic syndrome. The SROC curve analysis yielded an excellent trade-off between sensitivity and specificity, with an AUC of 0.916.

There is considerable heterogeneity in the literature and yet no consensus on the value of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT in patients suspected of harboring a paraneoplastic syndrome. Our results showed substantial difference between the pre-pooled sensitivity and specificity of individual studies. This can be partly explained by different patient inclusion criteria, as well as different methods used for the reference standard. The selection bias appeared because some studies included a heterogeneous group of patients with different manifestations and with or without inconclusive/negative prior conventional imaging. Others only included highly selective patients with positive paraneoplastic antibodies. The pretest selection of patients suspected of having paraneoplastic syndrome can alter the diagnostic performance of whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT. We tried to reduce the effect of clinical diversity and heterogeneity by performing a secondary analysis after exclusion of studies with a high risk of bias. The performance of ^{18}F-FDG PET or ^{18}F-FDG PET/CT in the detection of underlying malignancy was slightly improved (AUC, 0.931; sensitivity, 0.88) in this setting. In addition, ^{18}F-FDG PET or ^{18}F-FDG PET/CT was found to have a fairly similar diagnostic performance when the analysis was limited to patients with neurologic paraneoplastic manifestations.

Our results showed a false-negative rate of 19% for whole-body ^{18}F-FDG PET or ^{18}F-FDG PET/CT. Therefore, a negative ^{18}F-FDG PET/CT cannot rule out the presence of malignancy. Patients with clinically suspected paraneoplastic syndrome can have relatively small tumors that may be missed by ^{18}F-FDG PET/CT or tumors may not be ^{18}F-FDG–avid. Therefore, careful follow-up and repeated screening by ^{18}F-FDG PET/CT or other imaging modalities is necessary in these patients. The European Federation of the Neurologic Societies has addressed this by recommending repeated screening in 3–6 mo after an initial negative evaluation, followed by screening every 6 mo up to 4 y, if testing remains unrevealing (*38*).

Sets of definitions are taken into consideration to establish diagnostic criteria and classify patients with paraneoplastic manifestations into definite or possible paraneoplastic syndrome categories,

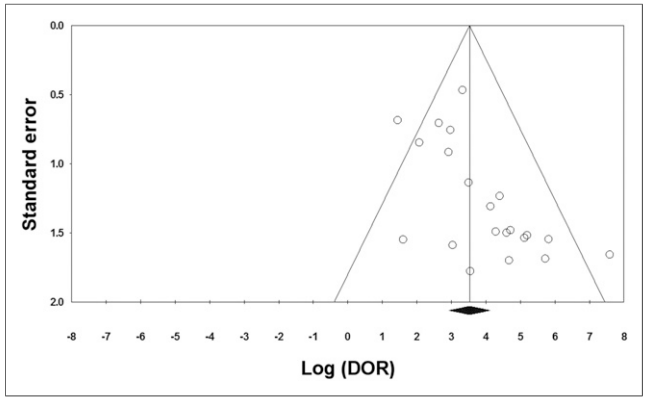

FIGURE 5. Funnel plot of included studies.

mainly based on the presenting clinical symptoms and presence or absence of paraneoplastic antibodies (*39*). The presence of the well-characterized paraneoplastic antibodies provides important additional diagnostic information to predict a specific underlying malignancy (*1,39*). Recent studies investigated the performance of whole-body ^{18}F-FDG PET/CT in relation to paraneoplastic antibody status (*16*). Several studies showed that whole-body ^{18}F-FDG PET and ^{18}F-FDG PET/CT are highly useful in the screening of patients with suspected paraneoplastic syndrome and positive paraneoplastic antibodies (*9,10*). However, a recent study by Vatankulu et al. suggested that paraneoplastic antibody presence should not be an indispensable factor for performing ^{18}F-FDG PET/CT in patients suspected of harboring a paraneoplastic syndrome (*16*).

Besides, Vaidyanathan et al. showed that ^{18}F-FDG PET/CT can help in risk classification of patients suspected of having a paraneoplastic syndrome. They showed that the ^{18}F-FDG PET/CT results could add confidence to clinical likelihood in 28% of patients and correctly downgrade (16%) or upgrade (12%) the clinical score (*5*). A recent study by Subramaniam et al. showed that ^{18}F-FDG PET has substantial impact in the management of patients with suspected paraneoplastic syndrome and those with cancer of unknown primary origin, resulting in change of the intended management in 25% and 43% of patients (*40*). Our meta-analysis showed that the diagnostic performance of ^{18}F-FDG PET/CT for the detection of underlying malignancy in patients with suspected paraneoplastic syndrome is comparable with its general performance in patients with cancer of unknown primary origin. A previous meta-analysis of 11 studies including 433 patients with cancer of unknown primary reported a sensitivity and specificity of 84% (95% CI, 78%–88%) and 84% (95% CI, 78%–89%) for ^{18}F-FDG PET/CT in the primary tumor detection (*41*). However, the translation of test performance characteristics into improved patient management has not been addressed in this meta-analysis and needs to be further investigated.

The development of the integrated ^{18}F-FDG PET and CT has helped to precisely localize lesions on ^{18}F-FDG PET scans (*6*). Over the last decade, more studies have investigated the application of combined ^{18}F-FDG PET/CT in the initial evaluation and diagnosis of paraneoplastic syndromes and occult malignancy (*3,5,14–17*). In our study, the subgroup analysis by imaging modality revealed that ^{18}F-FDG PET/CT showed a significantly higher specificity than ^{18}F-FDG PET alone. Because ^{18}F-FDG PET results are based only on the visual analysis of lesions with no anatomic correlate, any lesions with a higher metabolism than background could have been counted as positive (*6*). However, we found no evidence of significant difference in the sensitivity and overall performances (AUC) of whole-body ^{18}F-FDG PET versus ^{18}F-FDG PET/CT. A possible explanation can be the effect of publication year and the fact that older studies were performed on smaller sample sizes.

Because of the limited number of studies with direct comparison of ^{18}F-FDG PET or ^{18}F-FDG PET/CT and conventional imaging, we were not able to report the pooled diagnostic performance for conventional imaging. Five studies compared the diagnostic performance of ^{18}F-FDG PET or ^{18}F-FDG PET/CT with conventional screening methods (*9,11,13,15,28*). In these studies, the sensitivity and specificity of conventional screening modalities ranged between 30%–82% and 71%–100%, respectively. Further studies are needed to investigate the additional value of ^{18}F-FDG PET/CT and its cost effectiveness over conventional screening modalities in the workup of patients with suspected paraneoplastic syndrome.

Limitations of this analysis include the risk of selection bias and the lack of histopathologic confirmation of all lesions reported in the included studies. Although clinical follow-up data were recorded in some studies, patients who died shortly after the ^{18}F-FDG PET or ^{18}F-FDG PET/CT scan without proven malignancy were considered as false-positive, which could underestimate the performance of the modality. We cannot exclude the possibility of positive result publication bias because nonsignificant or unfavorable study results tend to be discarded. Besides, most results of the meta-analysis showed statistic heterogeneity. We analyzed the subgroups according to the index test and those patients presenting with neurologic symptoms, and this partly eliminated the effect of heterogeneity although further subgroup analyses were limited by the restricted original data. Surely, larger observational studies are warranted to further determine the utility of whole-body ^{18}F-FDG PET and ^{18}F-FDG PET/CT in relation to paraneoplastic antibody status and its effect on patient management and outcome.

CONCLUSION

This meta-analysis of available studies demonstrates that whole-body ^{18}F-FDG PET and ^{18}F-FDG PET/CT have excellent diagnostic accuracy and moderate to high sensitivity and specificity for the detection of underlying malignancy in patients suspected of having a paraneoplastic syndrome.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Storstein A, Vedeler CA. Paraneoplastic neurological syndromes and onconeural antibodies: clinical and immunological aspects. *Adv Clin Chem.* 2007;44:143–185.
2. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc.* 2010;85:838–854.
3. Kristensen SB, Hess S, Petersen H, Hoilund-Carlsen PF. Clinical value of FDG-PET/CT in suspected paraneoplastic syndromes: a retrospective analysis of 137 patients. *Eur J Nucl Med Mol Imaging.* 2015;42:2056–2063.
4. de Beukelaar JW, Sillevis Smitt PA. Managing paraneoplastic neurological disorders. *Oncologist.* 2006;11:292–305.
5. Vaidyanathan S, Pennington C, Ng CY, Poon FW, Han S. ^{18}F-FDG PET-CT in the evaluation of paraneoplastic syndromes: experience at a regional oncology centre. *Nucl Med Commun.* 2012;33:872–880.
6. von Schulthess GK, Steinert HC, Hany TF. Integrated PET/CT: current applications and future directions. *Radiology.* 2006;238:405–422.
7. Rees JH, Hain SF, Johnson MR, et al. The role of [^{18}F]fluoro-2-deoxyglucose-PET scanning in the diagnosis of paraneoplastic neurological disorders. *Brain.* 2001;124:2223–2231.
8. Berner U, Menzel C, Rinne D, et al. Paraneoplastic syndromes: detection of malignant tumors using [^{18}F]FDG-PET. *Q J Nucl Med.* 2003;47:85–89.
9. Linke R, Schroeder M, Helmberger T, Voltz R. Antibody-positive paraneoplastic neurologic syndromes: value of CT and PET for tumor diagnosis. *Neurology.* 2004;63:282–286.
10. Younes-Mhenni S, Janier MF, Cinotti L, et al. FDG-PET improves tumour detection in patients with paraneoplastic neurological syndromes. *Brain.* 2004;127:2331–2338.
11. Patel RR, Subramaniam RM, Mandrekar JN, Hammack JE, Lowe VJ, Jett JR. Occult malignancy in patients with suspected paraneoplastic neurologic syndromes: value of positron emission tomography in diagnosis. *Mayo Clin Proc.* 2008;83:917–922.
12. Hadjivassiliou M, Alder SJ, Van Beek EJ, et al. PET scan in clinically suspected paraneoplastic neurological syndromes: a 6-year prospective study in a regional neuroscience unit. *Acta Neurol Scand.* 2009;119:186–193.

13. Selva-O'Callaghan A, Grau JM, Gamez-Cenzano C, et al. Conventional cancer screening versus PET/CT in dermatomyositis/polymyositis. *Am J Med.* 2010; 123:558–562.
14. Matsuhisa A, Toriihara A, Kubota K, Makino T, Mizusawa H, Shibuya H. Utility of F-18 FDG PET/CT in screening for paraneoplastic neurological syndromes. *Clin Nucl Med.* 2012;37:39–43.
15. Schramm N, Rominger A, Schmidt C, et al. Detection of underlying malignancy in patients with paraneoplastic neurological syndromes: comparison of ^{18}F-FDG PET/CT and contrast-enhanced CT. *Eur J Nucl Med Mol Imaging.* 2013; 40:1014–1024.
16. Vatankulu B, Yilmaz Aksoy S, Asa S, et al. Accuracy of FDG-PET/CT and paraneoplastic antibodies in diagnosing cancer in paraneoplastic neurological syndromes. *Rev Esp Med Nucl Imagen Mol.* 2016;35:17–21.
17. Pena Pardo FJ, Garcia Vicente AM, Amo-Salas M, et al. Utility of ^{18}F-FDG-PET/CT in patients suspected of paraneoplastic neurological syndrome: importance of risk classification. *Clin Transl Oncol.* 2017;19:111–118.
18. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg.* 2010;8:336–341.
19. García Vicente AM, Vega Caicedo CH, Mondejar Solis R, et al. ^{18}F-FDG PET/CT in the evaluation of patients suspected of paraneoplastic neurological syndrome [in Spanish]. *Rev Esp Med Nucl Imagen Mol.* 2015;34:236–243.
20. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med.* 2011; 155:529–536.
21. Lijmer JG, Bossuyt PM, Heisterkamp SH. Exploring sources of heterogeneity in systematic reviews of diagnostic tests. *Stat Med.* 2002;21:1525–1537.
22. Lee YH, Choi SJ, Ji JD, Song GG. Diagnostic accuracy of ^{18}F-FDG PET or PET/CT for large vessel vasculitis: a meta-analysis. *Z Rheumatol.* 2016;75:924–931.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327:557–560.
24. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods.* 2010;1:97–111.
25. Deeks JJ. Systematic reviews in health care: systematic reviews of evaluations of diagnostic and screening tests. *BMJ.* 2001;323:157–162.
26. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology.* 1982;143:29–36.
27. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics.* 2000;56:455–463.
28. Masangkay NAA, Torigian D, Dalmau J. Comparison of FDG-PET and CT in detection of neoplasia in patients with paraneoplastic neurologic syndrome (PNS) [abstract]. *J Nucl Med.* 2008;49(suppl 1):369P.
29. Bannas P, Weber C, Derlin T, et al. ^{18}F-FDG-PET/CT in the diagnosis of paraneoplastic neurological syndromes: a retrospective analysis. *Eur Radiol.* 2010; 20:923–930.
30. McKeon A, Apiwattanakul M, Lachance DH, et al. Positron emission tomography-computed tomography in paraneoplastic neurologic disorders: systematic analysis and review. *Arch Neurol.* 2010;67:322–329.
31. Crandall JGP, Joshi K, Chaudhry M, Wahl R. Diagnostic performance of F18-FDG PET/CT in patients with suspected paraneoplastic syndrome [abstract]. *J Nucl Med.* 2014;55(suppl 1):1892.
32. Han S NC, Poon FW. The role of F-18 FDG PET/CT imaging in the investigation of suspected paraneoplastic syndrome [abstract]. *Eur J Nucl Med Mol Imaging.* 2011;38(suppl 2):S256.
33. Chakraborty PS SP, Soundararajan R, Karunanithi S., et al. Yield of 18F-FDG PET/CT in patients with paraneoplastic neurological syndrome for detection of primary malignancy [abstract]. *Eur J Nucl Med Mol Imaging.* 2013;40(suppl 2): S484.
34. Fuster D VM, Depetris M, Mayoral M, et al. Value of PET/CT with 18F-fluorodeoxyglucose in patients with paraneoplastic syndrome [abstract]. *Eur J Nucl Med Mol Imaging.* 2013;40(suppl 2):S378.
35. Iyngkaran G CB, Schultz C. The value of 18-FDG PET in the diagnosis of tumours associated with paraneoplastic neurological syndromes [abstract]. *Intern Med J.* 2009;39(suppl 4):A114.
36. Gupta N BR, Sasikumar A, Sood A, Bhattacharya A, Mittal BR. Role of F-18 FDG PET/CT in suspected cases of paraneoplastic neurological syndrome [abstract]. *Eur J Nucl Med Mol Imaging.* 2014;41(suppl 2):S313.
37. Grozdic I, Odalovic S, Al-Nahhas A. The value of PET and PET/CT imaging in paraneoplastic syndrome. *Nucl Med Commun.* 2011;32:453–454.
38. Titulaer MJ, Soffietti R, Dalmau J, et al. Screening for tumours in paraneoplastic syndromes: report of an EFNS task force. *Eur J Neurol.* 2011;18:19-e3.
39. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. *J Neurol Neurosurg Psychiatry.* 2004; 75:1135–1140.
40. Subramaniam RM, Shields AF, Sachedina A, et al. Impact on patient management of [^{18}F]-fluorodeoxyglucose-positron emission tomography (PET) used for cancer diagnosis: analysis of data from the National Oncologic PET Registry. *Oncologist.* 2016;21:1079–1084.
41. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. *Eur Radiol.* 2009; 19:731–744.