Diagnostic Accuracy of ^{18}F-FDG-PET and PET/CT in the Differential Diagnosis between Malignant and Benign Pleural Lesions:

A Systematic Review and Meta-Analysis

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Rationale and Objectives: To systematically review and meta-analyze published data about the diagnostic accuracy of fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and PET/computed tomography (CT) in the differential diagnosis between malignant and benign pleural lesions.

Methods and Materials: A comprehensive literature search of studies published through June 2013 regarding the diagnostic performance of ^{18}F-FDG-PET and PET/CT in the differential diagnosis of pleural lesions was carried out. All retrieved studies were reviewed and qualitatively analyzed. Pooled sensitivity, specificity, positive and negative likelihood ratio (LR+ and LR−) and diagnostic odds ratio (DOR) of ^{18}F-FDG-PET or PET/CT in the differential diagnosis of pleural lesions on a per-patient–based analysis were calculated. The area under the summary receiver operating characteristic curve (AUC) was calculated to measure the accuracy of these methods. Subanalyses considering device used (PET or PET/CT) were performed.

Results: Sixteen studies including 745 patients were included in the systematic review. The meta-analysis of 11 selected studies provided the following results: sensitivity 95% (95% confidence interval [95%CI]: 92–97%), specificity 82% (95%CI: 76–88%), LR+ 5.3 (95%CI: 2.4–11.8), LR− 0.09 (95%CI: 0.05–0.14), DOR 74 (95%CI: 34–161). The AUC was 0.95. No significant improvement of the diagnostic accuracy considering PET/CT studies only was found.

Conclusions: ^{18}F-FDG-PET and PET/CT demonstrated to be accurate diagnostic imaging methods in the differential diagnosis between malignant and benign pleural lesions; nevertheless, possible sources of false-negative and false-positive results should be kept in mind.

Key Words: Positron emission tomography; PET/CT; pleural lesions; pleura; differential diagnosis.

Malignant pleural lesions are not uncommon. In 90% of the cases, they are secondary and caused by metastatic disease or lymphoma. In only 10% of the cases, pleural malignancy is primary and caused by malignant pleural mesothelioma or, more rarely, by other primary pleural tumors (1). The correct differential diagnosis between malignant and benign pleural disease is crucial, because the management and the prognosis of these lesions are different (1).

Imaging methods may play an important role in the differential diagnosis between malignant and benign pleural lesions (2,3). Computed tomography (CT) is the first-line diagnostic method in pleural pathologies (2,3). However, this method is not always able to differentiate between malignant and benign pleural lesions because of the significant overlap between the radiological appearances of these conditions (2,3).

Invasive methods (such as thoracocentesis, needle biopsy, thoracoscopy, open pleural biopsy) are often required to establish the diagnosis but carry the risk of tumor seeding or other complications (4). Nevertheless, video-assisted thoracoscopic surgery is considered the gold standard for tissue diagnosis in pleural malignancies.

Acad Radiol 2014; 21:11–20

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http://dx.doi.org/10.1016/j.acra.2013.09.015

Fluorine-18-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) and PET/CT have been proposed as noninvasive imaging methods to assess the disease extent in cancer patients (5,6). Because ^{18}F-FDG is a glucose analogue, this radiopharmaceutical may be very useful in detecting malignant lesions, which usually present high-glucose metabolism (5,6). Hybrid PET/CT devices allow enhanced detection and characterization of neoplastic lesions by combining the functional data obtained by PET with morphological data obtained by CT (6).

Several studies in the literature have evaluated the diagnostic accuracy of ^{18}F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural lesions (presenting as pleural mass, nodularity, thickening, or effusion), reporting different values of sensitivity and specificity (7). The purpose of our study is to systematically review and meta-analyze published data on the diagnostic accuracy of ^{18}F-FDG-PET or PET/CT in this setting to provide more evidence-based data.

METHODS

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement that describes an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses (8).

Search Strategy

A comprehensive computer literature search of the PubMed/MEDLINE and Scopus databases was conducted to find relevant published articles on the diagnostic accuracy of ^{18}F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural lesions. We used a search algorithm that was based on a combination of the terms: (a) "PET" OR "positron emission tomography" AND (b) "pleural" or "pleura." No beginning date limit was used; the search was updated until June 30, 2013. To expand our search, references of the retrieved articles were also screened for additional studies.

Study Selection

Studies or subsets in studies investigating the usefulness of ^{18}F-FDG-PET or PET/CT in the differential diagnosis of pleural lesions were eligible for inclusion. The exclusion criteria were: articles not within the field of interest of this review; articles evaluating the diagnostic performance of ^{18}F-FDG-PET or PET/CT in assessing pleural lesions in patients with cancer history; review articles, editorials or letters, comments, or conference proceedings; case reports or small case series; and articles not in the English language.

Three researchers independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned previously. Articles were rejected if they were clearly ineligible. The same three researchers then independently reviewed the full-text version of the remaining articles to determine their eligibility for inclusion. Disagreements were resolved in a consensus meeting.

All selected studies with sufficient data to reassess sensitivity or specificity of ^{18}F-FDG-PET or PET/CT in the differential diagnosis of pleural lesions on a per-patient–based analysis were included in the meta-analysis.

Data Extraction

For each included study, information was collected concerning basic study (authors, journals and year of publication, country of origin, study design), patient characteristics (mean age, gender, number of patients evaluated), and technical aspects (device used, radiopharmaceutical injected dose, time between ^{18}F-FDG injection and image acquisition, image analysis, applied reference standard). For each study, the number of true-positive, false-positive, true-negative, and false-negative findings for ^{18}F-FDG-PET or PET/CT was recorded on a per-patient–based analysis considering the qualitative PET analysis (visual analysis) performed by the authors.

Quality Assessment

The 2011 Oxford Center for Evidence-Based Medicine checklist for diagnostic studies was used for quality assessment of the included studies (9). This checklist has five major parts as follows: representative spectrum of the patients, consecutive patient recruitment, ascertainment of the gold standard regardless of the index test results, independent blind comparison between the gold standard and index test results, and enough explanation of the test to permit replication.

Statistical Analysis

Sensitivity, specificity, accuracy, positive and negative predictive value, positive and negative likelihood ratio (LR+ and LR−), and diagnostic odds ratio of ^{18}F-FDG-PET or PET/CT in the differential diagnosis of pleural diseases were obtained from individual studies on a per-patient–based analysis. A random-effects model was used for statistical pooling of the data. Pooled data were presented with 95% confidence intervals (95%CI). An I-square index was used to test for heterogeneity between studies. The area under the summary receiver operating characteristic curve (AUC) was calculated to measure the accuracy of ^{18}F-FDG-PET or PET/CT. For publication bias evaluation, funnel plots, Egger's regression intercept (10), and Duval and Tweedie's method (11) were used.

Statistical analyses were performed using Meta-DiSc statistical software version 1.4 (Unit of Clinical Biostatistics, Ramón y Cajal Hospital, Madrid, Spain) (12) and Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA).

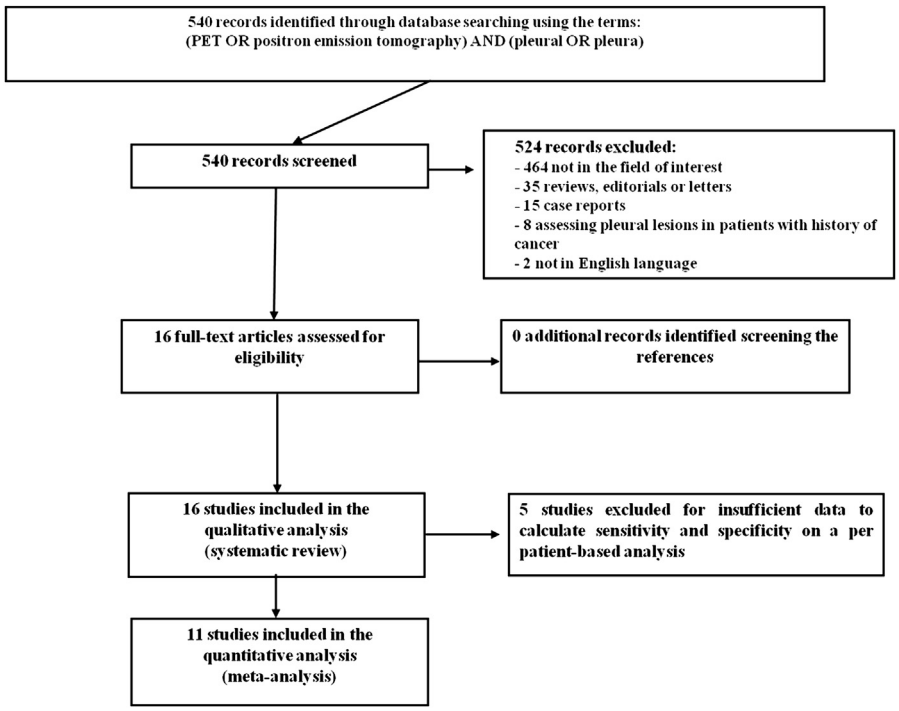

Figure 1. Flow chart of the search for eligible studies on the diagnostic accuracy of fluorine-18-fluorodeoxyglucose positron emission tomography (PET) or PET/computed tomography in the differential diagnosis between malignant and benign pleural lesions.

RESULTS

Literature Search

The comprehensive computer literature search from PubMed/MEDLINE and Scopus databases revealed 540 articles. Reviewing titles and abstracts, 524 articles were excluded: 464 because they were not in the field of interest of this review, 8 because they were evaluating the diagnostic performance of ^{18}F-FDG-PET or PET/CT in assessing pleural lesions in patients with history of cancer (13–20), 35 because they were reviews or editorials, 15 because they case reports, and 2 because they were not in English (21,22). Finally, 16 articles (including 745 patients) were selected and were eligible for the systematic review (23–38); no additional study was found screening the references of these articles (Fig 1). The characteristics of the studies included in the qualitative analysis (systematic review) are presented in Tables 1–4. Eleven articles including 212 patients had sufficient data to reassess sensitivity or specificity of ^{18}F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural lesions on a per-patient–based analysis and were included in the quantitative analysis (meta-analysis) (23–28,30,31,33,35,37).

Qualitative Analysis (Systematic Review)

Using the database search, 16 original articles written over the past 16 years were selected (23–38); of which six were prospective studies (27–30,34,37). The patient population included subjects with suspicious malignant pleural mesothelioma or who were undergoing evaluation for pleural lesions. There was a preponderance of the male gender (Table 1). Seven of 16 studies used hybrid PET/CT (30,31,34–38), whereas 9 studies used PET only (23–29,32,33). Heterogeneous technical aspects between the included studies were found (Table 2). PET image analysis was performed using qualitative criteria (visual analysis) in 13 studies (23–28,30,31,33–37) and semiquantitative criteria (based on the calculation of the standardized uptake value [SUV]) in 12 articles (24,25,27,29–36,38). Dual time-point PET was performed in four studies (32,33,35,36). The reference standard used to validate the ^{18}F-FDG-PET or PET/CT findings in the included studies were quite different (Table 4).

The results of the quality assessment of the studies included in this systematic review, according to the 2011 Oxford Center for Evidence-Based Medicine checklist for diagnostic studies, are shown in Table 4.

All the studies included in this systematic review support the usefulness of ^{18}F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural lesions, with a superior diagnostic accuracy compared to CT alone. ^{18}F-FDG-PET may provide complementary information compared to CT, which may be indeterminate in a relevant number of cases in the differential diagnosis between malignant and benign pleural lesions (including pleural thickening, nodularity, or effusions) (23–38).

A statistically significant difference in the SUV was found between malignant and benign pleural lesions at semiquantitative PET analysis (24,27,29–36,38). However, an overlap of the SUV between these two groups has been reported (29,30,33,35,38).

The role of dual time-point ^{18}F-FDG-PET or PET/CT in differential diagnosis between malignant and benign pleural

TABLE 1. Basic Study and Patient Characteristics of the Included Studies

Authors	Year	Country	Study Design	Patients Performing ^{18}F-FDG PET or PET/CT	Population	Mean Age (y)	Gender (%Male)
Terada et al (38)	2012	Japan	NR	76	Patients with suspicious MPM	67	79
Coolen et al (37)	2012	Belgium	Prospective	31	Patients undergoing evaluation for pleural disease	60	77
Abe et al (36)	2012	Japan	Retrospective	90	Patients with suspicious MPM	NR	NR
Elboga et al (35)	2012	Turkey	Retrospective	50	Patients undergoing evaluation for pleural disease	58	36
Kurata et al (34)	2010	Japan	Prospective	17	Patients with suspicious MPM	69	94
Yamamoto et al (33)	2009	Japan	Retrospective	33	Patients with suspicious MPM	64	91
Mavi et al (32)	2009	USA	NR	55	Patients with suspicious MPM	61	87
Yildirim et al (31)	2009	Turkey	NR	31	Patients with suspicious MPM	61	65
Orki et al (30)	2009	Turkey	Prospective	83	Patients undergoing evaluation for pleural disease	47	76
Duysinx et al (29)	2006	Belgium	Prospective	79	Patients undergoing evaluation for pleural effusions	63	59
Duysinx et al (28)	2004	Belgium	Prospective	98	Patients undergoing evaluation for pleural disease	61	68
Kramer et al (27)	2004	Netherlands	Prospective	32	Patients undergoing evaluation for pleural disease	NR	84
Gerbaudo et al (26)	2002	United States	Retrospective	15	Patients with suspicious MPM	60	73
Carretta et al (25)	2000	Italy	NR	14	Patients undergoing evaluation for pleural disease	58	79
Bénard et al (24)	1998	United States	NR	28	Patients with suspicious MPM	NR	NR
Bury et al (23)	1997	Belgium	NR	25	Patients undergoing evaluation for pleural disease	60	NR

CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; MPM, malignant pleural mesothelioma; NR, not reported; PET, positron emission tomography.

TABLE 2. Technical Aspects in the Included Studies

Authors	Device	Mean ^{18}F-FDG Injected Activity	Mean Time between ^{18}F-FDG Injection and Acquisition (min)	Image Analysis
Terada et al (38)	PET/CT	NR	60	Semiquantitative
Coolen et al (37)	PET/CT	370 MBq	50	Visual
Abe et al (36)	PET/CT	3.7 MBq/kg	60 and 120	Visual and semiquantitative at early and delayed phase
Elboga et al (35)	PET/CT	296–555 MBq	60 and 120	Visual and semiquantitative at early and delayed phase
Kurata et al (34)	PET/CT	5.2 MBq/kg	60	Visual and semiquantitative
Yamamoto et al (33)	PET	3.5 MBq/kg	60 and 120	Visual and semiquantitative at early and delayed phase
Mavi et al (32)	PET	5.2 MBq/kg	60 and 90	Semiquantitative at early and delayed phase
Yildirim et al (31)	PET/CT	350–400 MBq	NR	Visual and semiquantitative
Orki et al (30)	PET/CT	370–666 MBq	60–120	Visual and semiquantitative
Duysinx et al (29)	PET	2.1–3.7 MBq/kg	73	Semiquantitative
Duysinx et al (28)	PET	NR	NR	Visual
Kramer et al (27)	PET	400–600 MBq	90	Visual and semiquantitative
Gerbaudo et al (26)	PET	375 MBq	90	Visual
Carretta et al (25)	PET	3.7 MBq/kg	60	Visual and semiquantitative
Bénard et al (24)	PET	4.25 MBq/kg	60–90	Visual and semiquantitative
Bury et al (23)	PET	NR	NR	Visual

CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; NR, not reported; PET, positron emission tomography.

lesions is still controversial. In particular, in malignant pleural lesions a higher increase of SUV in delayed ^{18}F-FDG-PET imaging was reported compared to benign pleural abnormalities (32,33,35,36). Nevertheless, it is not clear whether the diagnostic accuracy of delayed PET imaging in differential diagnosis between malignant and benign pleural lesions significantly increases compared to early PET imaging.

Overall possible sources of false-negative (small malignant lesions or with low proliferative index) and false-positive results (mainly inflammatory lesions) of ^{18}F-FDG-PET or

TABLE 3. Diagnostic Accuracy Data of ^{18}F-FDG PET and PET/CT on a Per-patient–based Analysis Using Visual Analysis at about 1 Hour after ^{18}F-FDG Injection

Author	Number of Cases	Final Diagnosis: Malignant Lesions	Final Diagnosis: Benign Lesions	True Positive	False Positive	True Negative	False Negative	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value
Terada et al (38)	76	47	29	NR	NR	NR	NR	NC	NC	NC	NC	NC
Coolen et al (37)	31	14	17	14	11	6	0	100%	35%	65%	56%	100%
Abe et al (36)	78	31 MPM and 47 non-MPM lesions		NR	NR	NR	NR	NC	NC	NC	NC	NC
Elboga et al (35)	50	37	13	34	5	8	3	92%	62%	84%	87%	73%
Kurata et al (34)	17	6	11	NR	NR	NR	NR	NC	NC	NC	NC	NC
Yamamoto et al (33)	33	17	16	15	2	14	2	88%	88%	88%	88%	88%
Mavi et al (32)	55	44	11	NR	NR	NR	NR	NC	NC	NC	NC	NC
Yildirim et al (31)	31	17	14	15	1	13	2	88%	93%	90%	94%	87%
Orki et al (30)	83	44	39	44	2	37	0	100%	95%	98%	96%	100%
Duysinx et al (29)	79	51	28	NR	NR	NR	NR	NC	NC	NC	NC	NC
Duysinx et al (28)	98	63	35	61	4	31	2	97%	89%	94%	94%	94%
Kramer et al (27)	32	19	13	18	1	12	1	95%	92%	94%	95%	92%
Gerbaudo et al (26),*	15	11	4	11	0	4	0	100%	100%	100%	100%	100%
Carretta et al (25)	14	13	1	12	0	1	1	92%	100%	93%	100%	50%
Bénard et al (24)	28	24	4	22	1	3	2	92%	75%	89%	96%	60%
Bury et al (23)	25	16	9	16	2	7	0	100%	78%	92%	89%	100%

CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; MPM, malignant pleural mesothelioma; NC, not calculable; NR, not reported; PET, positron emission tomography.

*In the study by Gerbaudo et al, sensitivity, specificity, and accuracy on a per lesion-based analysis were 97%, 80%, and 94%, respectively.

PET/CT in assessing malignant pleural disease should be kept in mind (23–38).

Quantitative Analysis (Meta-analysis)

The diagnostic performance results of ^{18}F-FDG-PET or PET/CT in the 11 studies included in the meta-analysis are presented in Figures 2–4.

The sensitivity of ^{18}F-FDG-PET or PET/CT in diagnosing malignant pleural lesions calculated on a per-patient–based analysis ranged from 88% to 100%, with pooled estimate of 95% (95%CI: 92–97%) (Fig 2). The included studies were statistically quite homogeneous in their estimate of sensitivity (I-square: 22%).

The specificity of ^{18}F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural lesions calculated on a per-patient–based analysis ranged from 35% to 100%, with a pooled estimate of 82% (95%CI: 76–88%) (Fig 2). The included studies were statistically quite heterogeneous in their estimate of specificity (I-square: 69%).

The pooled accuracy and positive and negative predictive values of these methods were 90% (95%CI: 87–93%), 90% (95%CI: 86–93%), and 91% (95%CI: 86–95%), respectively.

The pooled LR+, LR−, and diagnostic odds ratio were 5.3 (95%CI: 2.4–11.8), 0.09 (95%CI: 0.05–0.14), and 74 (95%CI: 34–161), respectively. The AUC was 0.95 (Fig 3).

Funnel plots for assessing publication bias about sensitivity and specificity are shown in Figure 4. Egger's regression intercepts for sensitivity and specificity pooling were 1.3 ($P = .03$) and 2.0 ($P = .08$), respectively. Applying Duval and Tweedie's method, the funnel plot of sensitivity and specificity reached symmetry and the adjusted sensitivity and specificity decreased by 2.5% and 8.4%, respectively.

Because of the statistical heterogeneity found in our pooled analysis, we performed two subanalyses considering PET/CT studies or PET studies only. The results of these subanalyses

TABLE 4. Quality Assessment of the Included Studies

Author	Spectrum of Patients	Consecutive or Random Selection of Patients	Reference Standard	Application of Reference Standard Regardless of Indexed Test	Enough Explanation of the Index Test to Ensure Reproducibility	Independent Blind Comparison between Index Test and Reference Standard	Level of Evidence
Abe et al (36)	Patients referred because of a clinical diagnosis or suspicion of MPM	No	Tissue biopsy	Yes	Yes	N/A	3
Bénard et al (24)	Patients referred for the evaluation of pleural disease and suspected MPM	Yes	Tissue biopsy or pleural fluid cytology Clinical follow-up in one.	Yes	Yes	Yes	2
Bury et al (23)	Patients undergoing evaluation because of pleural diseases	N/A	Cytology or tissue biopsy	Yes	Yes	Yes	3
Carretta et al (25)	Patients with CT scan evidence of pleural thickening or fluid	N/A	Tissue biopsy	Yes	Yes	Yes	3
Coolen et al (37)	Patients with pleural abnormalities clinically suspicious for malignant pleural diseases	Yes	Tissue biopsy	Yes	Yes	Yes	2
Duysinx et al (28)	Patients presenting exudative pleural effusion and/or pleural thickening	Yes	Cytologic and histologic methods as well as radiological follow-up	Yes	Yes	Yes	2
Duysinx et al (29)	Patients presenting with an exudative pleural effusion after thoracocentesis	Yes	Pleural biopsy as well as follow-up	Yes	Yes	N/A	3
Elboga et al (35)	Patients with pleural pathologies such as pleural mass, pleural thickening, and pleural effusion	N/A	Surgical biopsy	Yes	Yes	N/A	3
Gerbaudo et al (26)	Patients with clinical and radiographic suspicion of malignant mesothelioma	Yes	Histopathology	Yes	Yes	N/A	3
Kramer et al (27)	Patients who had pleural abnormalities and presented at the pulmonary outpatient department (age >18 y)	Yes	Pleural fluid cytology or pleural biopsies as well as follow-up	Yes	Yes	Yes	2
Kurata et al (34)	Patients with asbestos-related pleural disease and suspected MPM	Yes	Pleural fluid cytology or pleural biopsies as well as follow-up	Yes	Yes	N/A	3

TABLE 4. (*continued*) Quality Assessment of the Included Studies

Author	Spectrum of Patients	Consecutive or Random Selection of Patients	Reference Standard	Application of Reference Standard Regardless of Indexed Test	Enough Explanation of the Index Test to Ensure Reproducibility	Independent Blind Comparison between Index Test and Reference Standard	Level of Evidence
Mavi et al (32)	Patients of suspected MPM and recurrence of MPM	Yes	Histopathology	Yes	Yes	N/A	3
Orki et al (30)	Patients with pleural lesions (63 with pleural effusion, 20 with pleural thickening) on CT scan	Yes	Histopathology	Yes	Yes	N/A	3
Terada et al (38)	Patients with confirmed MPM	N/A	Histopathology or cytology	Yes	Yes	N/A	3
Yamamoto et al (33)	Patients who were suspected of having MPM on CT	N/A	Histopathology or follow-up	No (patients with negative PET did not undergo invasive procedures)	Yes	Yes	4
Yildirim et al (31)	Patients with pleural effusions or pleural thickening	Yes	Histopathology or follow-up	Yes	Yes	No	3

CT, computed tomography; ^{18}F-FDG, fluorine-18-fluorodeoxyglucose; MPM, malignant pleural mesothelioma; N/A, not available; PET, positron emission tomography.

are reported in Figure 3. No significant improvement of the diagnostic accuracy was found analyzing PET/CT studies only; nevertheless, the statistically heterogeneity largely decreased (I-square was 0% for sensitivity and specificity in both subanalyses).

DISCUSSION

To the best of our knowledge, this systematic review and meta-analysis is the first to evaluate the diagnostic accuracy of ^{18}F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural lesions. Several studies have used ^{18}F-FDG-PET or PET/CT in this setting, reporting different values of sensitivity and specificity (Table 3). However, many of these studies have limited power, analyzing only relatively small numbers of patients. To derive more robust estimates of the diagnostic accuracy of ^{18}F-FDG-PET or PET/CT in this setting, we have pooled published studies (39). A systematic review process was adopted in ascertaining studies, thereby avoiding selection bias. Furthermore, the quality of the included studies was assessed by using the 2011 Oxford Center for Evidence-Based Medicine checklist for diagnostic studies (Table 4) (9).

Pooled results of our meta-analysis demonstrate that ^{18}F-FDG-PET and PET/CT have a high sensitivity (95%) and a good specificity (82%) in the differential diagnosis between malignant and benign pleural lesions. Furthermore, the value of the AUC (0.95) indicates that ^{18}F-FDG-PET and PET/CT are accurate diagnostic methods in this setting.

Subanalyses considering the devices used (PET/CT studies and PET studies only, respectively) were performed. However, a significant increase of the diagnostic accuracy in this setting considering PET/CT compared to PET alone was not demonstrated. Nevertheless, we cannot exclude that the low number of the included studies in these subanalyses may have influenced the results. However, performing such subanalyses has shown great merit because the different devices adopted basically represent a source of heterogeneity among the studies. In fact, no significant statistical heterogeneity between the studies was found pooling separate data from articles which performed PET or PET/CT only, respectively.

Possible sources of false-negative and false-positive results for pleural malignancies at ^{18}F-FDG-PET or PET/CT should be kept in mind. False-negative findings may be due to small malignant lesions (with size below the resolution of the method) or low-grade malignancies with low proliferative activity (and consequently low glycolytic activity and ^{18}F-FDG uptake). For example, some epithelioid subtypes of mesothelioma might not uptake ^{18}F-FDG (40). On the other hand, the most frequent sources of false-positive findings for pleural malignancies at ^{18}F-FDG-PET or PET/CT are inflammatory lesions. Furthermore, ^{18}F-FDG-PET or PET/CT cannot distinguish between different histologies in cases of pleural malignancies (23–38).

Overall, in cases in which conventional imaging cannot clearly establish whether a pleural lesion is malignant,

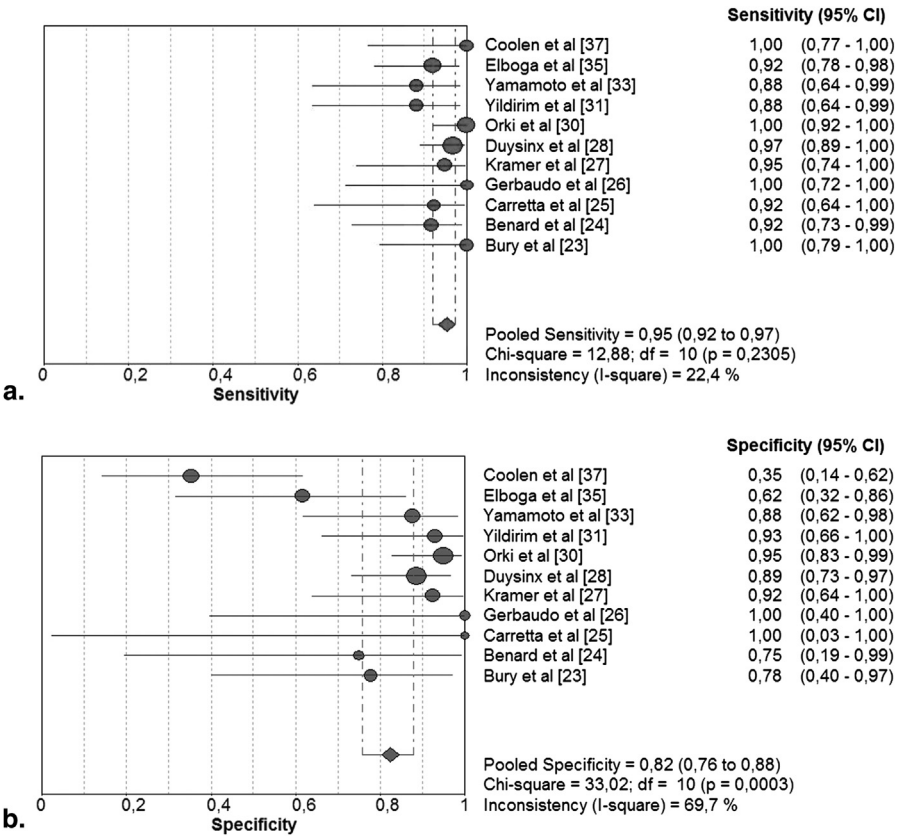

Figure 2. Plots of individual studies and pooled sensitivity **(a)** and specificity **(b)** of fluorine-18-fluorodeoxyglucose positron emission tomography (PET) or PET/computed tomography in the differential diagnosis between malignant and benign pleural lesions. The size of the circles indicates the weight of each study.

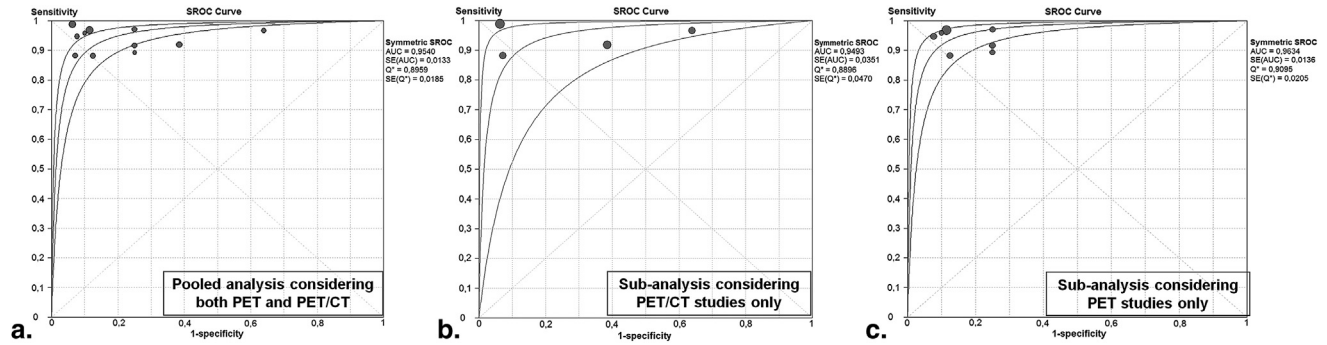

Figure 3. Summary receiver operating characteristic (ROC) curves and area under the curve of fluorine-18-fluorodeoxyglucose positron emission tomography (PET) or PET/computed tomography (CT) in the differential diagnosis between malignant and benign lesions in our pooled analysis **(a)** and in the subanalyses considering studies performing PET/CT **(b)** or PET only **(c)**. The curves represent the summary ROC curve (middle) and 95% confidence intervals.

^{18}F-FDG-PET or PET/CT are helpful in deciding whether to pursue the investigation with invasive methods (23–38). Specific tissue confirmation of a ^{18}F-FDG-PET–positive pleural lesion should be always obtained for a final diagnosis of malignant lesion (23–38). On the other hand ^{18}F-FDG-PET or PET/CT, because of their high sensitivity and negative predictive value, could reduce the number of invasive procedures performed for benign pleural disease. In particular, if a patient has a localized pleural thickening that does not exhibit ^{18}FDG uptake, an invasive procedure as a first step could be unnecessary and a follow-up by using CT could be preferred (23,24,27). Moreover, ^{18}F-FDG-PET or PET/CT can be used as reliable and noninvasive methods in patients with pleural effusion when thoracocentesis is not possible, or insufficient quantities of pleural fluid are present, identifying those patients in whom additional invasive procedures, such as thoracoscopic biopsy, are required (24,29). These functional imaging methods may even help to detect the areas of maximal metabolic activity of a pleural lesion to address the biopsy (23,24,30,32,33,36,38).

Some studies reported that semiquantitative PET analysis was useful in the differential diagnosis of pleural lesions (24,27,29–36,38). A statistically significant difference in

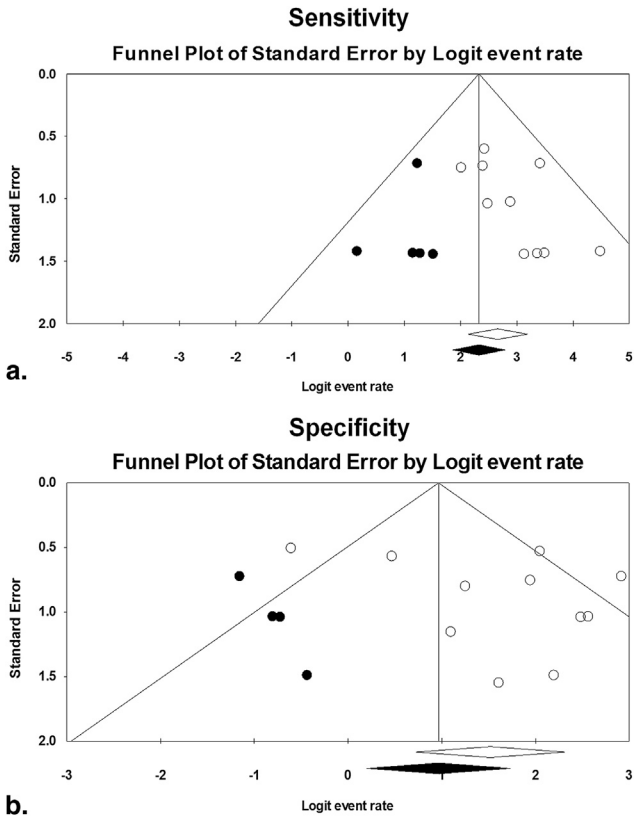

Figure 4. Funnel plots regarding the publication bias on the sensitivity **(a)** and specificity **(b)** of fluorine-18-fluorodeoxyglucose positron emission tomography (PET) and PET/computed tomography in the differential diagnosis between malignant and benign lesions. *Black circles* are the trimmed studies and the *black diamond* is the adjusted effect size for possible publication bias using Duval and Tweedie's trim and fill method.

SUV between benign and malignant pleural lesion has been reported; however, an overlap in SUV was also found between these two groups (29,30,33,35,38). When considering these factors, SUV alone should not be used to differentiate between malignant and benign pleural lesions.

We performed a meta-analysis considering visual PET analysis only. Data about the semiquantitative analysis were not meta-analyzed. In fact, because SUV is influenced by several factors, related to the patient as well as to technical aspects and procedures, any calculation of a pooled SUV obtained by different studies using different tomographs, scan protocols, ^{18}F-FDG injected activity, and patient characteristics is inappropriate in our opinion. Therefore, we did not perform a meta-analysis about SUV in differentiating benign and malignant pleural lesions.

Possible limitations of our meta-analysis could be the heterogeneity between the included studies and the publication bias; on the other hand, number and quality of the included studies (Table 4) and threshold effect do not represent a significant limitation of our analysis.

Heterogeneity between studies may represent a potential source of bias in a meta-analysis. In our pooled analysis, the included studies were statistically heterogeneous in their estimate of specificity. This heterogeneity is likely to arise through diversity in methodological aspects between different studies (Table 2). The baseline differences among the patients in the included studies (Table 1), the reference standard used, and the study quality (Table 4) may have contributed to the observed heterogeneity of the results, too. However, heterogeneity between studies was accounted for in a random-effects model and it was not found performing a subanalysis including PET or PET/CT studies only, respectively. Moreover, we excluded studies that evaluated pleural abnormalities in cancer patients from our meta-analysis to further limit the heterogeneity between the included studies.

Publication bias is a major concern in all meta-analyses because studies reporting significant findings are more likely to be published than those reporting nonsignificant results. Indeed, it is not unusual for small-sized early studies to report a positive relationship that subsequent larger studies fail to replicate. We assessed publication bias in our meta-analysis using qualitative and quantitative methods (Egger's regression and Duval and Tweedie's method). Funnel plots showed an asymmetry for both sensitivity and specificity pooling, but we corrected pooled sensitivity and specificity values using Duval and Tweedie's method (Fig 4).

Threshold effect may represent a source of heterogeneity for meta-analyses of diagnostic studies. Different thresholds of PET scan positivity can change the diagnostic performance. Strict threshold of positivity would decrease the sensitivity and increase the specificity. Liberal threshold of positivity would increase the sensitivity and decrease the specificity. We evaluated this effect by summary ROC analysis and AUC estimation. Summary ROC of our systematic review showed a curvilinear relationship between sensitivity and 1-specificity, which can be due to a threshold effect. However, the high AUC found (0.95) limits the clinical importance of threshold effect in our meta-analysis.

Overall, ^{18}F-FDG-PET and PET/CT demonstrated to be accurate noninvasive methods for the differential diagnosis between malignant and benign pleural lesions. Whether the information derived from PET imaging justifies the additional radiation exposure related to the radiopharmaceutical administration requires additional investigation. Furthermore, large clinical trials and cost-effectiveness analysis on the use of ^{18}F-FDG-PET or PET/CT in this setting are needed to strengthen the usefulness of these functional imaging methods.

CONCLUSIONS

^{18}F-FDG-PET and PET/CT demonstrated to be accurate diagnostic imaging methods in the differential diagnosis between malignant and benign pleural lesions; nevertheless, possible sources of false-negative and false-positive results should be kept in mind.

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