Diagnostic performance of Fluorine-18-Fluorodeoxyglucose positron emission tomography in the assessment of pleural abnormalities in cancer patients: A systematic review and a meta-analysis

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Abstract

Objective: To systematically review and meta-analyze published data about the diagnostic performance of Fluorine-18-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) and PET/computed tomography (PET/CT) in the assessment of pleural abnormalities in cancer patients.

Methods: A comprehensive literature search of studies published through June 2013 regarding the role of 18F-FDG-PET and PET/CT in evaluating pleural abnormalities in cancer patients was performed. All retrieved studies were reviewed and qualitatively analyzed. Pooled sensitivity, specificity, positive and negative likelihood ratio (LR+ and LR−) and diagnostic odd ratio (DOR) of 18F-FDG-PET or PET/CT on a per patient-based analysis were calculated. The area under the summary ROC curve (AUC) was calculated to measure the accuracy of these methods in the assessment of pleural abnormalities. Sub-analyses considering 18F-FDG-PET/CT and patients with lung cancer only were carried out.

Results: Eight studies comprising 360 cancer patients (323 with lung cancer) were included. The meta-analysis of these selected studies provided the following results: sensitivity 86% [95% confidence interval (95%CI): 80–91%], specificity 80% [95%CI: 73–85%], LR+ 3.7 [95%CI: 2.8–4.9], LR− 0.18 [95%CI: 0.09–0.34], DOR 27 [95%CI: 13–56]. The AUC was 0.907. No significant improvement considering PET/CT studies only and patients with lung cancer was found.

Conclusions: 18F-FDG-PET and PET/CT demonstrated to be useful diagnostic imaging methods in the assessment of pleural abnormalities in cancer patients, nevertheless possible sources of false-negative and false-positive results should be kept in mind. The literature focusing on the use of 18F-FDG-PET and PET/CT in this setting remains still limited and prospective studies are needed.

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1. Introduction

Pleural abnormalities are quite common in cancer patients, particularly in those with lung cancer [1]. Malignant pleural abnormalities in patients with known tumors may be caused by the local extension of a lung cancer or by metastatic disease, nevertheless some pleural abnormalities in these patients may be benign [2,3]. In cancer patients, differentiating between benign and malignant pleural abnormalities is crucial and may influence treatment strategy and prognosis. In fact, in cancer patients with malignant pleural lesions the prognosis is extremely worse when compared to benign pleural abnormalities and surgery is often contraindicated [2–5].

Several diagnostic tests have been used in this setting, including computed tomography (CT), magnetic resonance imaging (MRI), thoracocentesis, biochemical parameters, pleural biopsy, and thoracoscopy. However, these tests have some limitations being sometimes inaccurate or invasive [2–5].

Fluorine-18-Fluorodeoxyglucose (18F-FDG) positron emission tomography (PET) and PET/CT have been proposed as non-invasive imaging methods to assess the disease extent in cancer patients...
Since $^{18}$F-FDG is a glucose analog, this radiopharmaceutical may be very useful in detecting malignant lesions which usually present high glucose metabolism [6]. Hybrid PET/CT device allows enhanced detection and characterization of neoplastic lesions, by combining the functional data obtained by PET with morphological data obtained by CT [6].

Several studies have evaluated the diagnostic performance of $^{18}$F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural abnormalities, 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 performance of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients only, in order to provide more evidence based data and to address further studies in this setting.

2. Methods

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

2.1. Search strategy

A comprehensive computer literature search of the PubMed/MEDLINE and Scopus databases was conducted to find relevant published articles on the diagnostic performance of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients. 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 30th, 2013. No language restriction was used. To expand our search, references of the retrieved articles were also screened for additional studies.

2.2. Study selection

Studies or subsets in studies investigating the diagnostic performance of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients were eligible for inclusion. The exclusion criteria were: (a) articles not within the field of interest of this review, (b) articles evaluating the performance of $^{18}$F-FDG-PET or PET/CT in assessing pleural lesions in patients without cancer history, (c) review articles, editorials or letters, comments, conference proceedings, and (d) case reports or small case series.

Three researchers (GT, RS and SA) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria mentioned above. 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.

2.3. 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 type of primary tumor), 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.

2.4. 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 5 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, enough explanation of the test to permit replication.

2.5. Statistical analysis

Sensitivity, specificity, accuracy, positive and negative predictive value, positive and negative likelihood ratio (LR+ and LR−) and diagnostic odd ratio (DOR) of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients 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 ROC 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. Spearman correlation coefficient between false positive rate (1-specificity) and true positive rate (sensitivity) of the included studies was used for evaluation of the threshold effect and $p$-value < 0.05 was considered statistically significant.

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

3. Results

3.1. Literature search

The comprehensive computer literature search from PubMed/MEDLINE and Scopus databases revealed 540 articles. Reviewing titles and abstracts, 532 articles were excluded: 464 because not in the field of interest of this review, 18 because evaluating the performance of $^{18}$F-FDG-PET or PET/CT in assessing pleural lesions in patients without cancer history, 35 as reviews or editorials, 15 as case reports. Finally, eight articles (including 360 cancer patients) were selected and were eligible for the systematic review and meta-analysis [13–20]; no additional studies were found screening the references of these articles. The characteristics of the included studies are presented in Tables 1–4.

3.2. Qualitative analysis (systematic review)

Using the database search, 8 original articles written over the past 13 years were selected [13–20]; all except one [14] were retrospective studies. Most of the patients evaluated had lung cancer (323 out of 360), with a preponderance of the male gender (Table 1).

Five studies used hybrid PET/CT [16–20] whereas three studies used PET only [13–15]. Heterogeneous technical aspects between the included studies were found (Table 2).

The PET image analysis was performed by using qualitative criteria (visual analysis) in all the included studies [13–20] and semi-quantitative criteria (based on the calculation of the standardized uptake value [SUV]) in 5 out of 8 articles [16–20].
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 assessment of pleural abnormalities in cancer patients, with a superior diagnostic performance compared to CT alone. These methods may provide complementary information compared to CT alone, which may result indeterminate in a relevant number of cases in the differential diagnosis between malignant and benign pleural abnormalities (in fact, pleural thickening or nodularity on CT may appear both in malignant and in benign lesions) [13–20]. Furthermore, $^{18}$F-FDG-PET may detect early pleural malignant involvement which does not show significant pleural thickening or nodularity at CT [13–20], because functional abnormalities may precede morphological changes.

Abnormal $^{18}$F-FDG pleural uptake on PET images was demonstrated to be the most accurate parameter identifying malignant pleural abnormalities [16,17,19]. A statistically significant difference in the mean SUV was found between malignant and benign pleural abnormalities in the studies which performed semi-quantitative PET analysis. However a significant overlap of the SUV between these two groups has been reported [16–20].

One study demonstrated that dual-time-point $^{18}$F-FDG-PET/CT can improve the diagnostic accuracy in differentiating benign from malignant pleural disease, with high sensitivity and good specificity [18]. In particular in malignant pleural abnormalities a higher increase of SUV in delayed $^{18}$F-FDG-PET imaging was reported compared to benign pleural abnormalities [18].

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 PET/CT should be kept in mind [13–20].

### 3.2.1. Quantitative analysis (meta-analysis)

The diagnostic performance results of $^{18}$F-FDG-PET or PET/CT in the eight included studies in the meta-analysis are presented in Table 3 and Figs. 1 and 2.

The sensitivity of $^{18}$F-FDG-PET or PET/CT in diagnosing malignant pleural abnormalities in cancer patients calculated on a per patient-based analysis ranged from 83% to 100%, with pooled estimate of 86% (95%CI: 80–91%) (Table 3). The included studies were statistically heterogeneous in their estimate of sensitivity (I-square: 60%).

The specificity of $^{18}$F-FDG-PET or PET/CT in assessing pleural abnormalities in cancer patients calculated on a per patient-based analysis ranged from 67% to 94%, with pooled estimate of 80% (95%CI: 73–85%) (Table 3). The included studies were statistically quite homogeneous in their estimate of specificity (I-square: 30%).

The pooled accuracy, positive and negative predictive value of these methods were 83% (95%CI: 79–87%), 82% (95%CI: 76–87%) and 84% (95%CI: 78–89%), respectively (Table 3).
The pooled LR+, LR− and DOR were 3.7 (95%CI: 2.8–4.9), 0.18 (95%CI: 0.09–0.34) and 27 (95%CI: 13–56), respectively (Fig. 1). The AUC was 0.907 (Fig. 2). Spearman correlation coefficient between sensitivity and 1-specificity was 0.5 (p = 0.207).

Egger’s regression intercepts for sensitivity and specificity pooling were 3.7 (p = 0.02) and 1.4 (p = 0.03), respectively. Applying the Duval and Tweedie’s method, the funnel plot of sensitivity and specificity reached symmetry and the adjusted sensitivity and specificity decreased of 4.9% and 6%, respectively.

Due to the statistical heterogeneity found in the calculation of the sensitivity of $^{18}$F-FDG-PET or PET/CT in assessing pleural abnormalities in cancer patients, we performed two sub-analyses considering PET/CT studies only and patients with lung cancer only. The results of these sub-analyses are reported in Table 3 and Figs. 1 and 2.

No significant improvement of the diagnostic accuracy data was found performing these sub-analyses. Nevertheless, the statistically heterogeneity largely decreased (I-square was 0% for sensitivity and specificity in both sub-analyses) without significant publication bias demonstrated by Egger’s regression intercept.

### 4. Discussion

To the best of our knowledge, this systematic review and meta-analysis is the first to evaluate the diagnostic performance of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients. 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. In order to derive more robust estimates of the diagnostic performance of $^{18}$F-FDG-PET or PET/CT in this setting we have pooled published studies [21]. 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 indicate that $^{18}$F-FDG-PET and PET/CT have a good sensitivity (86%) and specificity (80%) in assessing pleural abnormalities in cancer patients. Furthermore, the value of the AUC (0.907) demonstrates that $^{18}$F-FDG-PET and PET/CT are accurate diagnostic methods in this setting.

Sub-analyses considering PET/CT studies only and lung cancer patients only, respectively, did not provide significant increase of the diagnostic accuracy data. Nevertheless we cannot exclude that the low number of the included studies in these sub-analyses may have influenced the results. However, performing such sub-analyses has substantially the great merit to show as the different device adopted and the different primary cancer of the patients included basically represent per se some sources of heterogeneity among the studies. In fact, considering patients evaluated with PET/CT only or patients with lung cancer only, no significant heterogeneity between the studies was found.

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 lesions (with size below the resolution of the method), or with low proliferative activity (and consequently low $^{18}$F-FDG uptake). On the other hand, the most frequent cause of false-positive findings for pleural malignancies at $^{18}$F-FDG-PET or PET/CT are inflammatory lesions. Talc pleurodesis is often used in cancer patients with pleural effusion, and it is a well-known source of false positive findings for pleural malignancies at $^{18}$F-FDG-PET. It should be performed after PET imaging and when cancer diagnosis have already been acquired [22]. None of the articles considered in this meta-analysis included

### Table 3

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of cases (Cases of malignancies)</th>
<th>Final diagnosis of pleural abnormalities</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
<th>Positive likelihood ratio</th>
<th>Negative likelihood ratio</th>
<th>Diagnostic accuracy data of $^{18}$F-FDG PET and PET/CT on a per patient-based analysis using visual analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liao et al. [20]</td>
<td>33 (33)</td>
<td>27</td>
<td>81%</td>
<td>83%</td>
<td>82%</td>
<td>50%</td>
<td>96%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Letovanec et al. [19]</td>
<td>50 (24)</td>
<td>17 (6)</td>
<td>83%</td>
<td>83%</td>
<td>83%</td>
<td>96%</td>
<td>50%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Alkhawaldeh et al. [18]</td>
<td>61 (61)</td>
<td>29</td>
<td>86%</td>
<td>72%</td>
<td>79%</td>
<td>57%</td>
<td>96%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Kim et al. [17]</td>
<td>33 (33)</td>
<td>24</td>
<td>88%</td>
<td>89%</td>
<td>88%</td>
<td>95%</td>
<td>73%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Schaffler et al. [15]</td>
<td>92 (92)</td>
<td>30</td>
<td>100%</td>
<td>71%</td>
<td>80%</td>
<td>63%</td>
<td>96%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gupta et al. [14]</td>
<td>35 (35)</td>
<td>18</td>
<td>89%</td>
<td>94%</td>
<td>91%</td>
<td>85%</td>
<td>89%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Erasmus et al. [13]</td>
<td>25 (25)</td>
<td>22</td>
<td>95%</td>
<td>67%</td>
<td>92%</td>
<td>85%</td>
<td>67%</td>
<td>2.8</td>
<td>0.9</td>
<td>----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Pooled analysis</strong></td>
<td>360 (188)</td>
<td>188</td>
<td>86%</td>
<td>80%</td>
<td>83%</td>
<td>95%</td>
<td>86%</td>
<td>2.8</td>
<td>0.9</td>
<td>(95%CI: 80–91)</td>
</tr>
<tr>
<td><strong>Sub-analysis on PET/CT studies only</strong></td>
<td>323 (170)</td>
<td>170</td>
<td>90%</td>
<td>78%</td>
<td>84%</td>
<td>95%</td>
<td>78%</td>
<td>2.8</td>
<td>0.9</td>
<td>(95%CI: 70–84)</td>
</tr>
<tr>
<td><strong>Sub-analysis on lung cancer patients only</strong></td>
<td>313 (153)</td>
<td>153</td>
<td>95%</td>
<td>84%</td>
<td>94%</td>
<td>95%</td>
<td>84%</td>
<td>2.8</td>
<td>0.9</td>
<td>(95%CI: 67–85)</td>
</tr>
</tbody>
</table>

Legend: number in parentheses are patients with lung cancer; and NR, not reported.
patients submitted to this procedure prior to PET imaging, thus limiting the number of false positive findings for pleural malignancy.

Because the pooled negative predictive value is not optimal, $^{18}$F-FDG-PET and PET/CT cannot replace invasive methods in the evaluation of suspected pleural malignant lesions in cancer patients. Nevertheless $^{18}$F-FDG-PET/CT can be used as a reliable and non-invasive method when thoracocentesis is not possible, or insufficient quantities of pleural fluid are present [17,19], as also supported by the satisfactory LR+ and LR− values provided by our meta-analysis (Fig. 2).

However the real clinical problem is the tendency to underdiagnose pleural malignant lesions when cytological findings on thoracocentesis are negative. $^{18}$F-FDG-PET and PET/CT may be useful in patients with negative results of pleural cytology on thoracocentesis but clinical or radiographic suspicion of pleural malignant lesions, identifying patients in whom additional staging examination, such as thoracoscopic biopsy, is required [13–15,19].

These functional imaging methods may even help to detect the areas of maximal metabolic activity of malignant pleural disease in order to address the biopsy [15].

Some studies reported that semi-quantitative PET analyses (using the SUV) [16–20] and dual-phase PET imaging [18] could increase the diagnostic accuracy of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients, compared to visual PET analysis. A statistically significant difference in mean SUV between benign and malignant pleural abnormalities has been reported [16–20]. However, a considerable overlap in SUV was also found between these two groups.

We performed a meta-analysis considering the results of the visual PET analysis only performed in all the included studies. As it is well known that 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 – acquired with 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 benign and malignant pleural abnormalities. These factors considering, SUV alone should not be used to differentiate between malignant and benign pleural abnormalities in cancer patients.

Volume parameters such as tumor lesion glycolysis (TLG) or total glycolitic volume (TGV) seem to offer a more reliable method of semi-quantitative analysis of PET results. This approach substantially improves the ability to calculate the disease burden by taking into consideration both volumetric and metabolic characteristics of the disease [23]. None of the articles included in this meta-

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**Fig. 1.** Plots of individual studies and pooled LR+ (A, D, G), LR− (B, E, H) and DOR (C, F, I) of $^{18}$F-FDG-PET or PET/CT in the differential diagnosis between malignant and benign pleural abnormalities in cancer patients. First row (A–C) shows the results of our pooled analysis including all patients. Second row (D–F) shows the results of the sub-analysis considering PET/CT studies only. Third row (G–I) shows the results of the sub-analysis considering lung cancer patients only.

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**Fig. 2.** Summary ROC curves of $^{18}$F-FDG-PET or PET/CT in the assessment of pleural abnormalities in cancer patients in our pooled analysis and in the sub-analyses considering PET/CT studies only and lung cancer patients only. The curves represent the summary ROC curve (middle) and 95% confidence intervals. The area under the summary ROC curve demonstrates that $^{18}$F-FDG-PET and PET/CT are accurate methods in this setting.
Table 4
Quality assessment of the included studies.

<table>
<thead>
<tr>
<th>First author/year</th>
<th>Spectrum of patients</th>
<th>Consecutive or random selection of patients</th>
<th>Reference standard</th>
<th>Application of reference standard regardless of indexed test</th>
<th>Enough explanation of the index test to ensure reproducibility</th>
<th>Independent blind comparison between index test and reference standard</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liao 2012</td>
<td>Patients with lung cancer and pleural effusion</td>
<td>No</td>
<td>Pleural cytology or biopsy as well as follow up</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Letovanec 2012</td>
<td>Patients with pleural effusion and known cancer</td>
<td>N/A</td>
<td>Pleural fluid cytology</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>4 (the reference standard is not the best)</td>
</tr>
<tr>
<td>Alkhawaldeh 2011</td>
<td>Patients with non-small-cell lung cancer and pleural effusion</td>
<td>N/A</td>
<td>Thoracentesis and pleural biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Kim 2011</td>
<td>Patients diagnosed with NSCLC who had a history of pleural effusion</td>
<td>Yes</td>
<td>Pleural fluid cytology or pleural biopsies</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>2</td>
</tr>
<tr>
<td>Toaff 2005</td>
<td>Patients with primary extrapleural malignancy and pleural effusion</td>
<td>N/A</td>
<td>Histopathology or cytology</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Schaffler 2004</td>
<td>Patients with pleural abnormalities detected at contrast material-enhanced thoracic CT, which was performed for newly diagnosed NSCLC (n = 41) or restaging (n = 51)</td>
<td>N/A</td>
<td>Chemical, cytologic, or histologic analyses</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Gupta 2002</td>
<td>Patients with proven lung cancer who underwent PET-FDG imaging for suspected malignant pleural effusion or pleural metastases</td>
<td>Yes</td>
<td>Thoracentesis or pleural biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>2</td>
</tr>
<tr>
<td>Erasmus 2000</td>
<td>Patients with primary non-small cell lung cancer and a pleural effusion on staging CT</td>
<td>N/A</td>
<td>Thoracentesis or pleural biopsy</td>
<td>Yes</td>
<td>Yes</td>
<td>N/A</td>
<td>3</td>
</tr>
</tbody>
</table>

Legend: NA, not available.
analysis performed the calculation of TLG and TGV, nevertheless studies using these volume parameters for the differential diagnosis between malignant and benign pleural abnormalities in cancer patients are expected.

Possible limitations of our meta-analysis could be the heterogeneity between the included studies, the publication bias and the low number and quality of the selected studies.

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 sensitivity. 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 not found performing sub-analyses including PET/CT studies only and lung cancer patients only, respectively. In order to avoid heterogeneity we decided to limit our meta-analysis to studies which evaluated pleural abnormalities in cancer patients, excluding studies which performed 18F-FDG-PET or PET/CT in patients without history of cancer.

Publication bias is a major concern in all meta-analyses as studies reporting significant findings are more likely to be published than those reporting non-significant 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 the Duval and Tweedie’s method.

Only eight studies are included in the quantitative analysis and this could limit the statistical power of our meta-analysis. Some of them presented a low sample size (Table 1). Overall the quality of the included studies was moderate (Table 4). Only two studies reported the consecutive recruitment of the patients and only four studies reported blind interpretation of the 18F-FDG-PET or PET/CT images, which can introduce interpretation bias (when observers of PET or PET/CT studies had prior knowledge influencing their interpretation of the results).

Overall, 18F-FDG-PET and PET/CT demonstrated to be useful non-invasive tools in the assessment of pleural abnormalities in cancer patients. Whether the information derived from PET imaging justifies the additional radiation exposure related to the radiopharmaceutical administration requires additional investigation. Furthermore, prospective studies, more studies in patients with tumors other than lung cancer, large clinical trials and cost-effectiveness analyses on the use of 18F-FDG-PET or PET/CT in this setting are needed to strengthen the usefulness of these functional imaging methods.

5. Conclusions

18F-FDG-PET and PET/CT demonstrated to be useful diagnostic imaging methods in the assessment of pleural abnormalities in cancer patients, nevertheless possible sources of false-negative and false-positive results should be kept in mind. The literature focusing on the use of 18F-FDG-PET and PET/CT in this setting remains still limited and prospective studies are needed.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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References