Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography in the evaluation of solitary pulmonary nodule: a scoping review

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Background: The role of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) in the surgical approach of solitary pulmonary nodule (SPN) is still debated, as the increased metabolic avidity of the lesion was not a sure sign of malignancy. The purpose of this study was to evaluate the effectiveness of ^{18}F-FDG-PET/CT in the characterization of SPN based on the analysis of the most recent data in the literature.

Methods: We analyzed systematically the studies in 5 years (from 2016 to 2020), considering sensitivity, specificity and diagnostic accuracy. The reference values have established, beyond which the data have deemed significant.

Results: ^{18}F-FDG-PET/CT showed sensitivity, specificity and diagnostic accuracy values between 37.8% and 100%, 23.4% and 98.3%, 79.2% and 84.0% respectively. The data collected were very heterogeneous but, analyzing the value curves and the linear curves it was evident that the specificity levels of PET/CT decreased with the increase in the number of patients enrolled in the different experiences.

Conclusions: ^{18}F-FDG-PET/CT represents a valid tool in the diagnostic path of SPN but it cannot replace biopsy in the characterization of lesion until a direct correlation between standardized uptake value and the degree of malignancy is demonstrated.

Keywords: Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT); performance status; solitary pulmonary nodule (SPN); analytic review

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Introduction

If the role of fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is indisputable in the follow-up of lung cancer, whether or not subjected to surgical resection, many perplexities arise in the evaluation of a solitary pulmonary nodule (SPN), especially in lesions with minimal solid component. In fact, the doubts concern the reliability of the maximum standardized uptake value (SUVmax) in relation to the histological type and size of the tumor (1-4). Many authors agree that ^{18}F-FDG-PET/CT shows high sensitivity but the data are still heterogeneous regarding specificity (5,6). The availability of increasingly sophisticated equipment and the need to formulate a preoperative diagnosis as quickly as possible, put us in front of the following questions: does ^{18}F-FDG PET/CT represents an essential step in the diagnostic path of SPN? What has changed in the last 5 years? These issues are essential when considering the

budgets reduction in healthcare and the cost of the functional imaging in relation to the expected diagnostic benefit. These arguments and the attempt to provide an answer to the questions, prompted us to conduct an analytical evaluation of the most recent data in the literature. We present the following article in accordance with the PRISMA-ScR reporting checklist (available at https://asj.amegroups.com/article/view/10.21037/asj-22-2/rc).

Methods

The search carried out using a combination of words, relevant Medical Subject Headings (MeSH) terms and appropriate filters; the strategy was developed in MEDLINE (via PubMed) between 2016 and 2020. We used as search terms: "^{18}F-FDG PET/CT AND evaluation AND solitary pulmonary nodule". Based on the eligibility criteria (articles in English that report data relating to sensitivity, specificity and diagnostic accuracy of the ^{18}F-FDG PET/CT in the evaluation of pulmonary nodules), the studies were evaluated by two independent authors who also analyzed the literature and assessed the dissimilarities; any biases were discussed and resolved. A flow chart was created with the included and excluded items. The experiences that contained overlapping data were discussed. Any discrepancies were resolved by consensus after extensive discussion. The following elements were extracted from each study, if available: first author surname, year of publication, sensitivity (%), specificity (%) and diagnostic accuracy (%). In the analysis the characteristics of the patients were not considered but only those of the nodules. Furthermore, we only entered the data relating to solid pulmonary nodules not considering subsolid nodules or pure ground glass since they have different problems compared to the solid nodule as regards the role of PET/CT. Data extrapolated from the selected articles were inserted in a calculation software that allowed us to more easily evaluate the individual parameters both independently and as a function of the variations of the others. We focused on the impact of the number of procedures and on sensitivity and specificity values.

Results

One hundred and eight results were found and, after removing the duplicates and non-English articles, 100 articles were identified. After reading the abstract, 68 studies out of 108 were excluded because of irrelevance. Of the remaining 40 articles, only 10 (7-16) were considered relevant after evaluating the content of the full text and included in the data analysis (*Figure 1*). Information on 3,324 patients undergoing to ^{18}F-FDG-PET/CT leaded the choice of the following parameters (*Table 1*): (I) sensitivity, ranged from 77.05% and 98.00%; (II) specificity, ranged from 23.40% and 98.35%; (III) diagnostic accuracy, ranged from 79.20% and 84.00%. Extreme values (maximum and minimum) were not considered statistically relevant. Instead, we considered the system of curves of the respective values; ^{18}F-FDG-PET/CT shows limits in terms of specificity on larger cohorts, going from 85.00% on a sample of 50 patients to 39.80% on a sample of 1,188 patients. On the other hand, sensitivity remains constantly high and without significant variations. In fact, on 50 patients it stands at values equal to 84.00% while in the largest cohort it is equal to 90.10% (*Figure 1*). Furthermore, sorting the parameters according to the year of publication of the relative studies no statistically significant data were noticed (*Figure 2*). In fact, in order to obtain a statistical evaluation on homogeneous data we focused on the values of specificity and sensitivity in relation to the number of non-small cell lung cancer (NSCLC) patients. Others parameters studied in several articles contributed to a heterogeneity of the research and therefore were not included to reduce the statistical bias that make the analysis ineffective. In the large study groups, the specificity of ^{18}F-FDG PET/CT is extremely low (*Figure 3*); these data were even more evident when we extrapolated the respective linear curves (*Figure 4*).

Discussion

The ^{18}F-FDG PET/CT has become prominent as a method of SPN evaluation in recent years although its usefulness is unclear. In fact, what is the use of knowing if a patient has increased metabolic activity of lesion suspected for lung cancer when a pulmonary nodule that persists on CT control at 3–6 months is a priority surgical indication? In this situation, the study of the mediastinum through a preoperative "endobronchial ultrasound" is also indicated and, in case of resection of diagnosed bronchogenic carcinoma, systematic nodal dissection is recommended (17,18). Many authors argue that ^{18}F-FDG-PET/CT provides reliable information especially in nodules with dimensions >12 mm (19-21) but the studies are often in conflict due to the lack of uniformity of the data (22,23). On the basis of recent studies, we did not consider it appropriate to refer to the role of ^{18}F-FDG-PET/CT in the

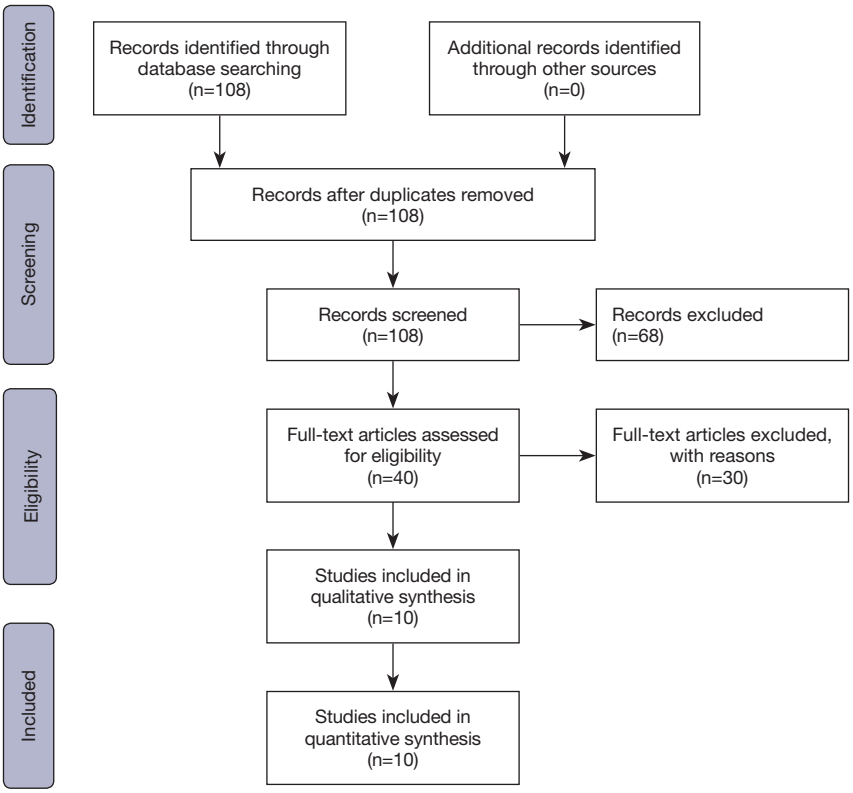

Figure 1 Flow chart of the selected articles.

Table 1 Selected studies and related parameters

Author	Number of patients	Sensitivity	Specificity	Diagnostic accuracy
Huang 2016	50	84.00%	85.00%	84.00%
Purandare 2017	191	94.40%	34.70%	79.50%
Hou 2018	88	83.30%	62.50%	79.20%
Taralli 2019	148	79.00%	81.80%	N/A
Kirienko 2018	534	91.60%	66.40%	N/A
Maiga 2018	1,188	90.10%	39.80%	N/A
Tang 2019	228	77.05%	98.35%	N/A
Şengöz 2019	78	98.00%	91.70%	N/A
Honguero Martinez 2021	305	94.60%	23.40%	N/A
Niyonkuru 2020	514	96.00%	48.70%	N/A

evaluation of subsolid nodules as, in this context, it has little use (24). Suh *et al.* (25) analyzed retrospectively 855 patients with NSCLC which radiologically showed itself as subsolid nodules with a solid component equal to or less than 3 cm. Comparing the preoperatory data with the postoperative ones, the ^{18}F-FDG-PET/CT displayed several limits in the diagnosis and lymph node staging, obtaining a low positive sensitivity and predictive value, equal to 44% and 9.6% respectively. Ruilong *et al.* (26) performed a meta-analysis starting from 356 articles and obtaining useful results

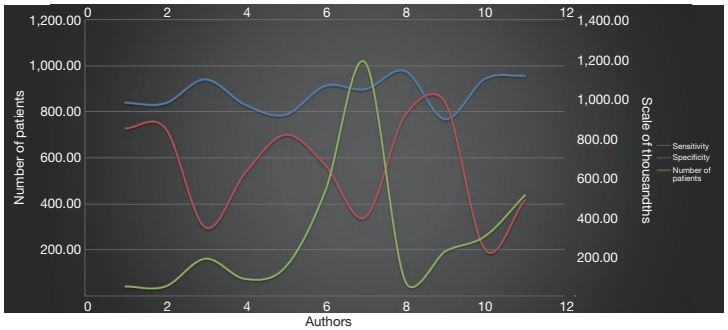

Figure 2 Graph with curves relating to the studies ordered according to the year of publication.

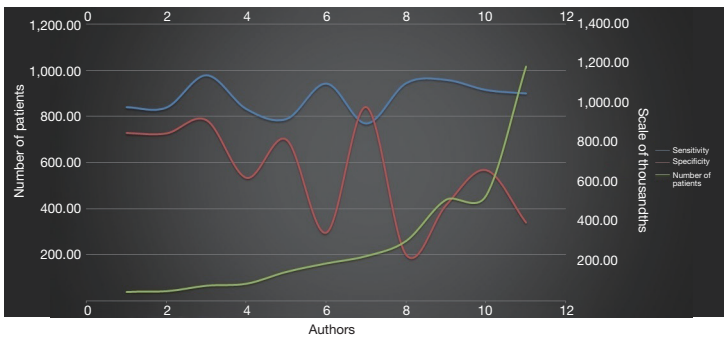

Figure 3 Graph with curves relating to the studies ordered according to the number of patients.

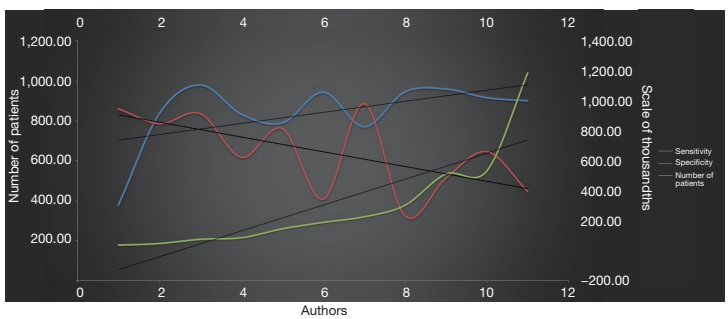

Figure 4 Linear value curves. Black lines are linear representation of average values.

only on 12 of these. Authors noticed a high sensitivity and specificity, equal to 82% and 81% respectively, but underlining the wide range of specificity with values between 58% and 100%. Consequently, must be reconsidered the role of ^{18}F-FDG-PET/CT in the diagnostic process of the pulmonary nodule in the light of the most recent scientific evidences and above all on sufficiently numerous study groups. A recent meta-analysis by Li *et al.* (27), aimed at quantifying sensitivity and specificity out of 21 studies and a total of 1,557 pulmonary nodule patients, showed unsatisfactory sensitivity and specificity values of ^{18}F-FDG-PET/CT, 0.89 [95% confidence interval (CI): 0.87–0.91] and 0.70 (95% CI: 0.66–0.73) respectively. Furthermore, Authors underlined that tendency to give false negatives does not allow it to be considered a substitute for biopsy. Similarly, our analysis showed that studies with a large number of patients enrolled provide reliable results. In addition, we experienced that extreme values of the parameters considered do not provide precise indications on the usefulness of this imaging technique and therefore

have no statistical significance. In order to obtain a correct interpretation of data, it is necessary to enter into the system all available values by determining the creation of the respective curves. The calculation software allowed us to plot the curves of the relative parameters on a graph and the lack of homogeneity of the data emerged if considered findings by publication chronology. On the contrary, by plotting the curves with the data ordered according to the number of patients enrolled, the interesting limits of ^{18}F-FDG-PET/CT have highlighted. In fact, we noted high values of specificity only in studies with a smaller sample (in the large study groups specificity decreased constantly) while high levels of sensitivity were confirmed regardless the number of patients. We think that patient selection and data heterogeneity represent important biases in statistical analysis of results. Therefore, it is necessary to study large samples, for statistically homogenize data and reduce the interpretation errors. Anyway, evidences suggest that biopsy is still mandatory today in the characterization of lung lesions; ^{18}F-FDG-PET/CT may have a role in directing biopsy sampling more precisely and improving the diagnostic accuracy than CT alone (28).

Conclusions

^{18}F-FDG-PET/CT certainly represents a valid tool in the evaluation of pulmonary nodules. However, having considerable specificity limits it is necessary to carefully clean and homologate the data to acquire reliable results. Hence, it is an excellent integrative tool in the diagnostic process but cannot replace biopsy until will be demonstrated a valid correlation between SUVmax and the histological type of the lesion.

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Footnote

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