Systematic Review and Meta-Analysis

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The utility of ^{18}F-FDG and ^{68}Ga-DOTA-Peptide PET/CT in the evaluation of primary pulmonary carcinoid

A systematic review and meta-analysis

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Abstract

Background: Pulmonary carcinoids (PC) are histologically classified into typical carcinoid (TC) and atypical carcinoid (AC). The diagnosis of pulmonary carcinoid and possibly the differentiation between TC and AC could make a significant effect on the treatment planning as well as prognosis.[1] Several studies have explored the utility of ^{68}Ga-DOTA-Peptide (^{68}Ga-labelled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-peptide) and ^{18}F-flurodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) in the evaluation of primary pulmonary carcinoids. Therefore, we performed a meta-analysis to evaluate the diagnostic accuracy and prediction efficiency of histological subtypes of these two imaging modalities in primary PC.

Methods: Relevant studies were identified by searching PubMed, Web of Science, and EMBASE published from 2006 to 2016. Two authors extracted characteristics of patients and their lesions using predefined criteria.

Results: Fourteen studies comprising 352 patients were included in this meta-analysis. The pooled sensitivity of ^{68}Ga-DOTA-Peptide and ^{18}F-FDG PET/CT in detecting pulmonary carcinoid were 90.0% (95% CI = 82.0–95.0%; $P = .07$; $I^2 = 49.6\%$) and 71.0% (95% CI = 66.0–76.0%; $P < .001$; $I^2 = 59.3\%$), respectively. An SUVmax ratio between ^{68}Ga-DOTA-Peptide and ^{18}F-FDG higher than the cutoff value of 4.28 was predictive of TC with 89.3% sensitivity and 100% specificity (AUC, 96.4%; 95% CI, 91.1–100%). The ratio of tumor uptake to atelectatic lung uptake was significantly higher for ^{68}Ga-DOTA-peptide (2.5–91, mean 30.5 ± 28.1) than for ^{18}F-FDG (0.3–10.3, mean 2.1 ± 2.3) ($P < .001$).

Conclusions: Both ^{68}Ga-DOTA-peptide and ^{18}F-FDG are highly sensitive in detecting pulmonary carcinoid, while ^{68}Ga-DOTA-peptide is more sensitive than ^{18}F-FDG (90.0% vs 71.0%). The SUVmax ratio was an accurate predictor of the histopathologic variety of the carcinoid tumor, and ^{68}Ga-DOTA-peptide was better than ^{18}F-FDG in cases with atelectasis.

Abbreviations: ^{18}F-FDG = ^{18}F-fluorodeoxyglucose, ^{68}Ga-DOTA-Peptide = ^{68}Ga-labelled [1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid]-peptide, AC = atypical carcinoid, CI = confidence interval, CT = computed tomography, PC = pulmonary carcinoids, PET = positron emission tomography, SUV = standardized uptake value, TC = typical carcinoid.

Keywords: ^{18}F-FDG, ^{68}Ga-DOTA-peptide, PET/CT, pulmonary carcinoid

1. Introduction

Pulmonary carcinoids (PC) are rare malignant neoplasms, accounting for 2–5% of all lung tumors, with an approximate annual incidence of 2.3–2.8 cases per million of the population.[2] For the purpose of clinical decision making, the pre-operative staging for these tumors is crucial. Surgical resection is the gold standard of treatment for pulmonary carcinoid, the range of local resection and systematic lymph nodes resection depend mainly upon cyto/histology characteristics diagnosing typical or atypical carcinoid.[3] With the development of functional imaging evaluation using nuclear medicine techniques during last two decades, physicians have more confidence in the challenging clinical decision-making process for such rare entities.[4–6] Positron emission tomography (PET), using different tracers, has potential in the work-up process of pulmonary carcinoids.[7–9] 18-Fluoro-deoxyglucose (^{18}FDG) was one of the first tracers developed in oncology.[10,11] Its role in lung neuroendocrine malignancies is considered more powerful in poorly-differentiated lung NETs compared to the pulmonary carcinoids.[12–15] Approximately, 80% of pulmonary carcinoids were found to express somatostatin receptors by immunohistochemistry.[16,17] Based on this, 68-gallium-radiolabelled PET (^{68}Ga-DOTA-PET)

Editor: Michael Masoomi.

YJ and GH contributed equally to this work.

This report was supported by the National Natural Sciences Foundation of China (No. 81371588; No. 81101074).

All authors report no conflicts of interest in this study.

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Medicine (2019) 98:10(e14769)

Received: 26 November 2018 / Received in final form: 24 January 2019 / Accepted: 7 February 2019

http://dx.doi.org/10.1097/MD.0000000000014769

tracers for functional NET imaging have emerged as potentially useful tools. These include (^{68}Ga-DOTA0-Tyr3) octreotate (^{68}Ga-DOTATATE), (^{68}Ga-DOTA0-Tyr3) octreotide (^{68}Ga-DOTATOC, ^{68}Ga-EDOTREOTIDE), and (^{68}Ga-DOTA0-1NaI3) octreotide (^{68}Ga-DOTANOC).[18,19] And the role of these new imaging techniques in patients with pulmonary carcinoid remains unclear.[20]

To our knowledge, the performance of ^{18}F-FDG and ^{68}Ga-DOTA-Peptide in the evaluation of primary pulmonary carcinoid has yet to be determined. The aims of this meta-analysis were to retrospectively evaluate and compare the role of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT in the preoperative workup of a group of patients with proven pulmonary carcinoid and to assess the utility of various functional indicators obtained with the 2 tracers in predicting the histological characterization of pulmonary carcinoids, that is, typical versus atypical.

2. Materials and methods

2.1. Ethics statement

Because all analyses were based on previously published studies, no patient consent and ethical approval were required.

2.2. Search strategy

We searched published reports in the PubMed, EMBASE, and Web of Science using the following keywords: "^{18}F-fluorodeoxyglucose or FDG or ^{18}F-FDG" and "Ga or gallium or ^{68}Ga" and "carcinoid tumors or tumor, carcinoid or carcinoids or neuroendocrine tumors or neuroendocrine" and "lung or pulmonary or bronchial or bronchopulmonary". We placed no restrictions on the language or date of publication.

2.3. Inclusion and exclusion criteria

The inclusion criteria were as follows:

(1) ^{68}Ga-DOTA-peptide PET/CT and/or ^{18}F-FDG PET/CT performed in patients with pulmonary carcinoid tumors;
(2) providing sufficient data to calculate sensitivity.

The exclusion criteria were:

(1) review articles, cases, editorials or letters, comments, conference proceedings, preclinical studies, animal studies;
(2) articles only concerning about the impact of ^{68}Ga-DOTA-peptide or ^{18}F-FDG PET/CT on the post-surgical assessment;
(3) studies only evaluating tumor grading;
(4) duplicate data.

2.4. Data abstraction and quality assessment

Two researchers independently extracted the required information from the selected reports in a standardized manner. We collected the following information from each article: first authors name, year of publication, country of origin, patient characteristics (mean age, sex, number of patients with pulmonary carcinoid performing ^{68}Ga-DOTA-peptide or ^{18}F-FDG PET/CT), type of pulmonary carcinoid evaluated, technical parameters (device and radiopharmaceutical used, image analysis and reference standard used), and study design.

Two independent reviewers evaluated the methodology of the selected studies using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. The QUADAS-2 tool primarily assesses four domains: risk of bias in patient selection; index test; reference standard; and the timing of the reference test.[21] We resolved discrepancies by consensus.

2.5. Statistical analysis

We evaluated the diagnostic performance of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT in the evaluation of pulmonary carcinoid using OR values and the corresponding 95% CIs.

In this study, we only calculated the sensitivity of ^{68}Ga-DOTA-peptide and ^{18}F-FDG, because most of the studies only included patients with pathologically confirmed pulmonary carcinoids. Sensitivity of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT were calculated on a patient-based analysis. The sensitivity was determined from the number of true positive and false negative results obtained from individual studies. We used a random effect model for statistical pooling of the data. Pooled data are presented with 95% confidence intervals (95% CI). Dispersion of sensitivity, with their respective 95% CIs, was displayed in a forest plot.

An estimate of the area under the curve (AUC) for the receiver operating curve (ROC) was also calculated to evaluate the prediction efficiency of SUVmax ratio (SUVmax between ^{68}Ga-DOTA-peptide and ^{18}F-FDG) and SUVmax of ^{18}F-FDG in the discrimination of typical carcinoid and atypical carcinoid. Independent-samples t test was performed to compare the ratios of tumor uptake to atelectatic lung uptake between ^{68}Ga-DOTA-peptide and ^{18}F-FDG.

Heterogeneity among those eligible studies was assessed by the I^2 test, with $I^2 > 50\%$ suggesting mild heterogeneity among studies. When I^2 index was higher than 50%, a random-effect model was used; otherwise, a fixed-model was used. In this meta-analysis, possible sources of heterogeneity were explored by sensitivity analysis, with results sub-classified according to methodological or clinical characteristics.

All statistical analyses were performed using Meta-disc 1.4 software and SPSS version 21. For P value, the level of statistical significance was set to 5%.

3. Results

3.1. Study identification and selection

Figure 1 shows the process of selecting studies for the meta-analysis. We obtained 688 articles through the initial search, 130 of which were duplicates. About 512 studies were excluded based on title and abstract review. Thirty-two literatures were excluded with reason as no original data. Finally, 14 studies, comprising a total sample size of 352 patients with proven pulmonary carcinoid met all the inclusion criteria, and they were included in this meta-analysis.[1,4–6,9–11,14,16,17,19,20,22,23]

3.2. Study characteristics and quality assessment

The main characteristics of the included studies are presented in Table 1. The studies were performed in the following countries: one in UK, two in India, one in Turkey, four in Italy, three in USA, one in Sweden, one in Germany, and one in South Korea. Most of the studies were retrospective (13/14). The risk of bias was unclear for patient selection in 4 studies, which did not provide information regarding consecutive enrollment.[10,11,19,20] For the index test and reference standard, the risk of bias was low in all 14 studies. For flow and timing, only 2 studies reported time intervals between PET/CT examinations and pathological

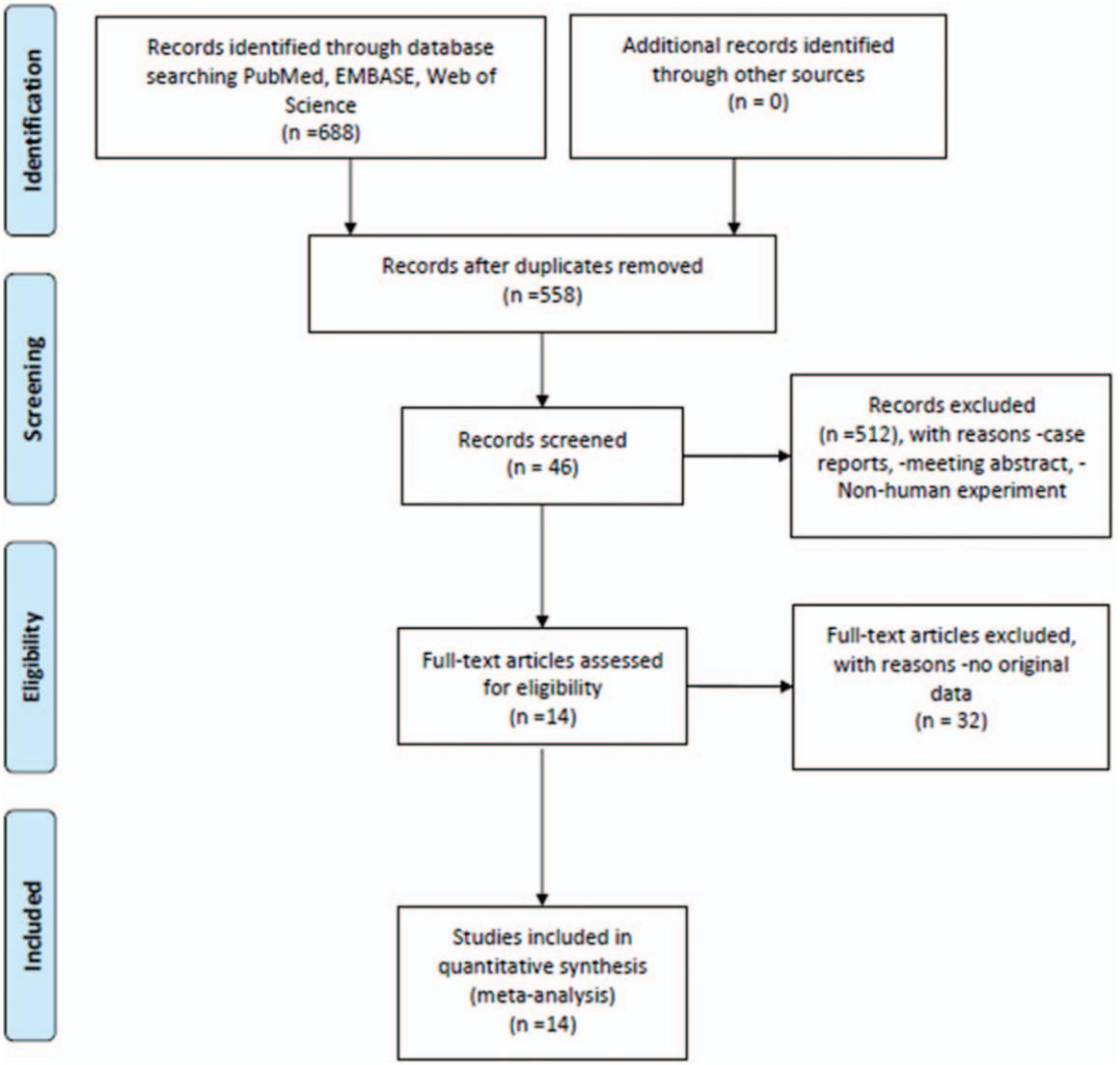

Figure 1. The process of selecting studies for the meta-analysis.

confirmations. All studies used histopathological diagnosis as a reference standard. The applicability of the included studies was adequate and all classified as low.

3.3. Pooled diagnostic performance of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT

The sensitivity of ^{68}Ga-DOTA-peptide in the detection of pulmonary carcinoid ranged from 79% to 100%, with pooled estimates of 90.0% (95% CI = 82.0–95.0%; $P < .1$; $I^2 = 49.6\%$). The sensitivity of ^{18}F-FDG PET/CT in the detection of pulmonary carcinoid was reported to range from 52% to 100%, with pooled estimates of 71.0% (95% CI = 66.0–76.0%; $P < .001$; $I^2 = 59.3\%$) (Figs. 2 and 3).

3.4. Subgroup analysis of TC versus AC

Seven studies in our meta-analysis, consisting of 104 subjects, had detailed data like SUVmax values of ^{68}Ga-DOTA-peptide or ^{18}F-FDG PET/CT. We also calculated the ratio between SUVmax of ^{68}Ga-DOTA-peptide PET/CT and SUVmax of ^{18}F-FDG PET/CT (SUVmax ratio). By matching the SUVmax ratio and the SUVmax values of ^{18}F-FDG PET/CT with histologic subtypes, we performed a subgroup analysis of TC versus AC. In those studies comparing the performance of ^{68}Ga-DOTA-peptide and ^{18}F-FDG, typical carcinoids revealed apparently higher SUVmax on ^{68}Ga-DOTA-peptide PET/CT (SUVmax range 8.2–118, mean SUVmax 36.5 ± 21.6) compared with atypical carcinoids (SUVmax range 1.1–18.5, mean SUVmax 9 ± 5.6, $P < .002$). The ratios of SUVmax on ^{68}Ga-DOTA-peptide PET/CT to that on ^{18}F-FDG PET/CT were significantly higher in typical carcinoids (1.22–30, mean 13.1 ± 7.3) than atypical carcinoids (0.19–3.97, mean 1.7 ± 1.5) ($P < .001$). An SUVmax ratio higher than the cutoff value of 4.28 was predictive of TC with 89.3% sensitivity and 100% specificity (AUC, 96.4%; 95% CI, 91.1–100%) (Fig. 4). In ^{18}F-FDG studies, the SUVmax values of AC (SUVmax range 1.7–14.5, mean SUVmax 6.0 ± 3.4) was higher than that of TC (SUVmax range 0.8–16.0, mean SUVmax 3.7 ± 2.6, $P < .05$). An

Table 1

The main characteristics of the included studies.

Study/years of publication	Country	Patients	Median age (range) (years)	% Female	Device and radiopharmaceutical used	Type of pulmonary carcinoid evaluated	Design	Reference standard
Tatci 2014	Turkey	22	NR	36.4%	^{18}F-FDG	14 typical carcinoid 8 atypical carcinoid	Retrospective	Histopathological diagnosis
Venkitaraman 2014	India	26	NR	NR	^{68}Ga-DOTATOC ^{18}F-FDG	21typical carcinoid 5 atypical carcinoid	Prospective	Histopathological diagnosis
Kayani 2009	UK	13	56	55.6%	^{18}F-FDG ^{68}Ga-DOTATATE	11 typical carcinoid 2 atypical carcinoid	Retrospective	Histopathological diagnosis
Ambrosini 2009	Italy	11	NR	45.5%	^{68}Ga-DOTANOC	NR	Retrospective	Histopathological diagnosis
Daniels 2007	USA	16	NR	NR	^{18}F-FDG	11 typical carcinoid 5 atypical carcinoid	Retrospective	Histopathological diagnosis
Lococo 2014	Italy	33	65	63.6%	^{18}F-FDG 68Ga-DOTA-peptide	23 typical carcinoid 10 atypical carcinoid	Retrospective	Histopathological diagnosis
Jindal 2011	India	20	NR	45%	^{18}F-FDG 68Ga-DOTATOC	13 typical carcinoid 7 atypical carcinoid	Retrospective	Histopathological diagnosis
Moore 2013	USA	29	NR	89.7%	^{18}F-FDG	23 typical carcinoid 6 atypical carcinoid	Retrospective	Histopathological diagnosis
Gasparri 2015	Italy	97	NR	NR	^{18}F-FDG	65 typical carcinoid 32 atypical carcinoid	Retrospective	Histopathological diagnosis
Uhlén 2016	Sweden	36	NR	66.7%	^{18}F-FDG	31 typical carcinoid 5 atypical carcinoid	Retrospective	Histopathological diagnosis
Kruger 2006	Germany	13	NR	NR	^{18}F-FDG	12 typical carcinoid 1 atypical carcinoid	Retrospective	Histopathological diagnosis
Stefani 2013	Italy	25	61	88%	^{18}F-FDG	24 typical carcinoid 1 atypical carcinoid	Retrospective	Histopathological diagnosis
Chong 2007	South Korea	7	NR	NR	^{18}F-FDG	2 typical carcinoid 5 atypical carcinoid	Retrospective	Histopathological diagnosis
Kayani 2008	USA	4	NR	NR	^{18}F-FDG ^{68}Ga-DOTATATE	4 typical carcinoid 0 atypical carcinoid	Retrospective	Histopathological diagnosis

^{18}F-FDG = ^{18}F-fluorodeoxyglucose, ^{68}Ga-DOTANOC = ^{68}Ga-labelled-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-1-Nal3-octreotide, ^{68}Ga-DOTATATE = ^{68}Ga-labelled-1,4,7,10-tetraazacyclododecane-NI,NII,NIII,NIIII-tetraacetic acid (D)-Phe1-thy3-octreotate, ^{68}Ga-DOTATOC = ^{68}Ga-labelled-1,4,7,10-tetraazacyclododecane-N,N′,N″,N‴-tetraacetic acid-D-Phe1-Tyr3-octreotide, NR = not reported.

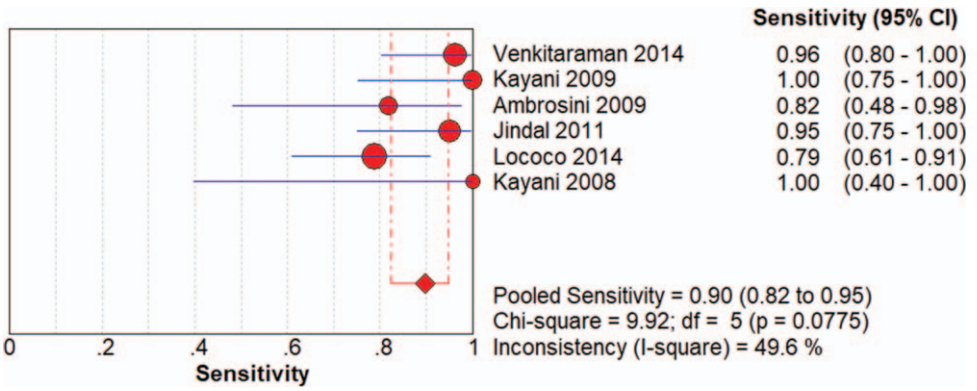

Figure 2. Forest plots for sensitivity of ^{68}Ga-DOTA-peptide PET/CT in evaluation of pulmonary carcinoid.

SUVmax of ^{18}F-FDG PET/CT higher than the cutoff value of 3.7 was predictive of AC with 73.9% sensitivity and 65.4% specificity (AUC, 73.3%; 95% CI, 62.2–84.4%).

3.5. Uptake of ^{68}Ga-DOTA-peptide and ^{18}F-FDG in atelectatic lung

Obstructive pneumonia or collapsed lung distal to endobronchial tumor was found in 21 subjects from 2 literatures, showing mild ^{68}Ga-DOTA-peptide uptake (SUVmax = 1.2–3.3, mean SUVmax 1.85 ± 0.80) and more intense ^{18}F-FDG uptake (SUVmax = 0.7–18.2, mean SUVmax 4.4 ± 4.2). The ratio of tumor uptake to atelectatic lung uptake was significantly higher for ^{68}Ga-DOTA-peptide (2.5–91, mean 30.5 ± 28.1) than for ^{18}F-FDG (0.3–10.3, mean 2.1 ± 2.3) ($P < .001$).

4. Discussion

Several studies have compared the diagnostic role of ^{68}Ga-DOTA-peptide PET/CT to that of ^{18}F-FDG PET/CT in patients with pulmonary carcinoid. However, many of these studies have limited power and analyzed only small numbers of patients. In order to

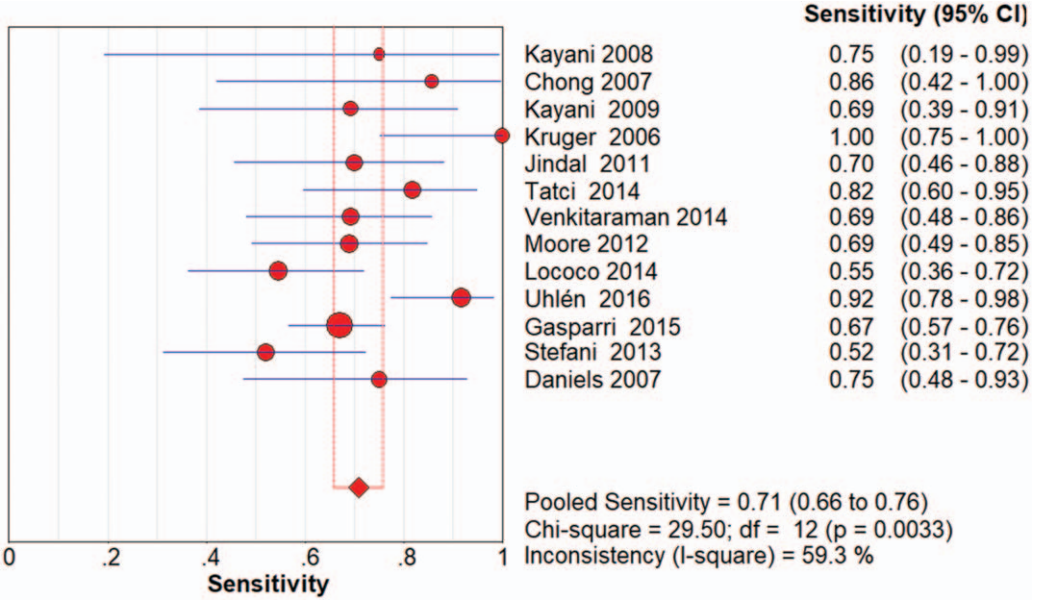

Figure 3. Forest plots for sensitivity of ^{18}F-FDG PET/CT in detecting pulmonary carcinoid.

derive more robust estimates of the diagnostic performance of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT in patients with pulmonary carcinoid, we pooled published studies. In this meta-analysis, we chose to calculate pooled sensitivity on a per patient-based analysis (instead of a per lesion-based or a per region-based analysis) because most of the authors have adopted this criterion.

When the detection rate of pulmonary carcinoid with the 2 methods was assessed, ^{68}Ga-DOTA-peptide was confirmed providing better overall sensitivity than ^{18}F-FDG PET/CT (90.0% vs 71.0% DR, respectively). Four studies in this meta-analysis comparing the performance of two tracers in detecting pulmonary carcinoids all indicated the superiority of ^{68}Ga-DOTA-peptide over ^{18}F-FDG, which was in line with our pooled result. Their different uptake mechanisms bears principal responsibility for different behavior of ^{68}Ga-DOTA-peptide and ^{18}F-FDG.[22] Pulmonary primary carcinoids are subclassified as typical and atypical carcinoids.[22] Concerning the different histopathological features and prognosis of these two subtypes, the distinction between TC and AC before treatment is clinically vital. The surgical management was affected by histological subtype of pulmonary carcinoid. According to recent evidences, the surgical strategy of TC should plan to perform nonanatomic resection with lymph node sampling, while for AC, the surgical planning was anatomic resection with radical lymphadenectomy.[24] Typical carcinoids have been found to have a better prognosis than atypical carcinoids. Two studies by Jindal et al and Lococo et al co-relate the histology of pulmonary carcinoids with the uptake patterns of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT and their SUV ratios.[19,22] The uptake patterns of AC and TC on ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT are different, which can be explained by their different metabolic mechanisms. The increased somatostatin receptor expression and slow metabolism of TC may contribute to the more intense uptake on ^{68}Ga-DOTA-peptide and relatively low uptake on ^{18}F-FDG PET/CT, whereas atypical carcinoid revealed significant uptake on ^{18}F-FDG PET/CT but poor uptake on ^{68}Ga-DOTA-peptide PET/CT due to its more aggressive nature and decreased somatostatin receptor expression.

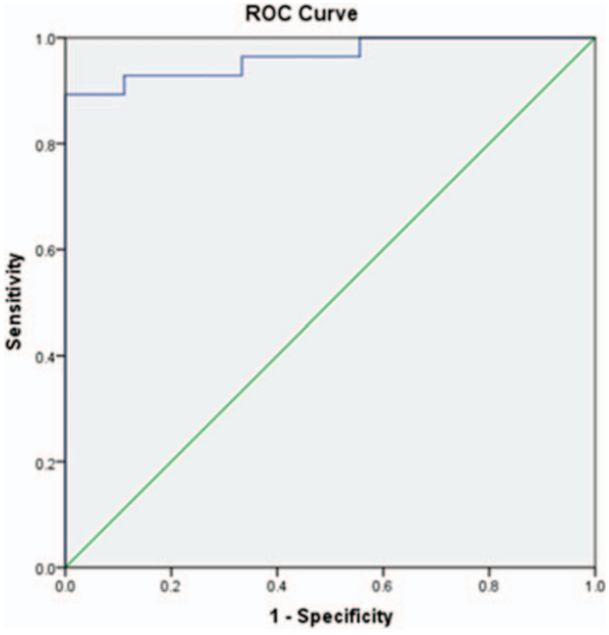

Figure 4. Accuracy of SUVmax ratio in distinguishing TC from AC, the ROC curves analysis.

Seven studies in our meta-analysis presented detailed SUVmax data of ^{18}F-FDG or ^{68}Ga-DOTA-peptide.[6,9,10,16,17,19,23] When we matched PET/CT findings with histological subtypes and performed a subgroup analysis of TC versus AC, we found that the SUVmax ratio between ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT was a valuable indicator in predicting the histological type. The typical carcinoids revealed apparently higher SUVmax on ^{68}Ga-DOTA-peptide PET/CT (SUVmax range 8.2–118, mean SUVmax 36.5 ± 21.6) compared with atypical carcinoids (SUV-

max range 1.1–18.5, mean SUVmax 9 ± 5.6, $P < .002$). By calculating the ratios of SUVmax on ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT, we made an interesting observation. The ratios were significantly higher in typical carcinoids (1.22–30, mean 13.1 ± 7.3) than atypical carcinoids (0.19–3.97, mean 1.7 ± 1.5) ($P < .001$). A SUVmax ratio higher than the cutoff value of 4.28 was predictive of TC with 89.3% sensitivity and 100% specificity, making itself an accurate semiquantitative index in identifying TC from AC (AUC, 96.4%; 95% CI, 91.1–100%), which was similar to the result of Lococo et al reporting that the SUVmax ratio was accurate in identifying TC (AUC, 0.90; 95% CI, 0.79–1.00) with a cutoff value of 1.19 optimizing sensitivity (82.6%) and specificity (90%).[22] When a lesion showed avidity for both imaging tools, we suggest the use of SUVmax ratio to allow a distinction between TC and AC accurately. If a tumor is ^{18}F-FDG positive and ^{68}Ga-DOTA-peptide negative, we tend to think that it is an atypical one; on the contrary, we consider it as a typical one. Although final diagnosis of pulmonary carcinoid was made through histopathologic examination by either bronchoscopy or percutaneous biopsy, nonetheless these non-invasive imaging methods could also provide information substantially aiding in the prediction of the histopathologic subtype of carcinoids and reliably guide the investigator.[19] The combined use of ^{68}Ga-DOTA-peptide and ^{18}F-FDG plays a great role in distinguishing between TC and AC, and therefore helps to make the best therapeutic method in the clinic.

Besides SUVmax ratio, the prediction efficiency of SUVmax value on ^{18}F-FDG was also evaluated in this meta-analysis. The SUVmax cutoff value of ^{18}F-FDG that best separated typical carcinoids from atypical carcinoids was 3.7, with 73.9% sensitivity and 65.4% specificity (AUC, 73.3%; 95% CI, 62.2–84.4%). Areas under the curve of SUVmax cutoff value for ^{18}F-FDG (73.3%) was smaller than that for SUVmax ratio (96.4%), thus making the SUVmax value of ^{18}F-FDG not as a good predictor as SUVmax ratio in differentiation of histological subtype. According to the study of Mamede et al, a close correlation between Glut-1 expression and ^{18}F-FDG uptake was observed, and the elevated level of Glut-1 expression was reported to be related closely with malignancy.[25] Ozbudak et al investigated the GLUT-1 expression in pulmonary neuroendocrine carcinomas, and 7% (3/46) of typical carcinoid, and 21% (6/29) of atypical were found to have GLUT-1 expression.[26] We can tell from those researches that the number of typical carcinoids with FDG avidity was not significantly fewer compared to that of atypical carcinoids. Moore et al reported a cutoff SUVmax value of 6 or greater for differentiating typical from atypical carcinoid, the corresponding sensitivity, specificity and AUC was not available.[4] Through literature retrieval, Moore et al also found that 36% of atypical carcinoids and 20% of typical carcinoids had an SUVmax of 6 or greater, therefore it is not reliable using the cutoff SUVmax value of 6 or greater in the differentiation of typical and atypical carcinoids. The SUVmax value of ^{18}F-FDG might not be used to reliably distinguish more aggressive atypical carcinoids from less aggressive typical carcinoids.

About 21 patients from 2 studies in our meta-analysis had collapsed lung distal to the tumor.[10,16] We observed that ^{68}Ga-DOTA-peptide was superior to ^{18}F-FDG in identifying endobronchial tumor from adjacent atelectasis correctly. The ratio of tumor uptake to atelectatic lung uptake was significantly higher for ^{68}Ga-DOTA-peptide (2.5–91, mean 30.5 ± 28.1) than for ^{18}F-FDG (0.3–10.3, mean 2.1 ± 2.3) ($P < .001$). Kayani et al first described high accumulation of ^{18}F-FDG in collapsed lung distal to endobronchial carcinoids secondary to obstructive pneumonitis.[16] Due to the high tracer uptake of collapsed lung, sometimes even higher than nearby tumor, it may be difficult to delineate tumor boundaries. As a glucose analog, ^{18}F-FDG is not specific for tumor. Increased activity can also be seen in inflammation or infection by reason of glycolytic activity in leukocytes, whereas ^{68}Ga-DOTA-peptide, as a somatostatin analog, revealed selective uptake on carcinoid tumor and little uptake for collapsed lung, with the cause attributed to low level expression of somatostatin receptor on inflammatory cells. ^{68}Ga-DOTA-peptide might be a valuable tool in discrimination between tumor and atelectasis. The application of ^{68}Ga-DOTA-peptide should be taken into consideration when it comes to the diagnosis of suspected carcinoid tumor accompanying adjacent atelectasis or obstructive pneumonia. In the experience of Zidi et al in 20 patients of bronchial carcinoid tumor, 75% subjects were reported showing signs of atelectasis on the plain chest X-ray.[27] However, study concerning the application of ^{68}Ga-DOTA-peptide or ^{18}F-FDG PET/CT in patients with pulmonary atelectasis secondary to bronchial carcinoid tumor is still few, and we crave for more related data to support our viewpoint.

Some limitations exist in this meta-analysis. Most studies included are retrospective in nature, containing only confirmed diagnosis of pulmonary carcinoid. Therefore, a selection bias may occur as the diagnosis was already made at the time of the patient selection. Additionally, the specificity of studies was not available due to the lack of false positive and true negative data. Studies evaluating the role of ^{68}Ga-DOTA-peptide or ^{18}F-FDG PET/CT in discriminating carcinoid tumor from atelectasis are too small. Methodological concerns and study design may have influenced the results of the different studies including the use of different diagnostic criteria for positive pulmonary carcinoid among studies.

5. Conclusion

^{68}Ga-DOTA-peptide was superior to ^{18}F-FDG in terms of the detection rate of pulmonary carcinoids. The SUVmax ratio of ^{68}Ga-DOTA-peptide and ^{18}F-FDG was an accurate predictor of the histopathologic variety of the carcinoid tumor compared with the SUVmax on ^{18}F-FDG-PET/CT alone. The combination of ^{68}Ga-DOTA-peptide and ^{18}F-FDG PET/CT findings was a reliable tool in preoperative assessment. The diagnostic efficiency of ^{68}Ga-DOTA-peptide was considered better than ^{18}F-FDG in those cases accompanying adjacent atelectasis.

Author contributions

Data curation: Yuanyuan Jiang, Guozhu Hou.
Formal analysis: Yuanyuan Jiang, Guozhu Hou.
Funding acquisition: Wuying Cheng.
Methodology: Wuying Cheng.
Project administration: Wuying Cheng.
Resources: Wuying Cheng.
Software: Yuanyuan Jiang.
Writing – original draft: Yuanyuan Jiang, Guozhu Hou.
Writing – review & editing: Yuanyuan Jiang, Guozhu Hou.

References

[1] Gasparri R, Rezende GC, Fazio N, et al. Fluorodeoxyglucose positron emission tomography in pulmonary carcinoid tumors. Q J Nucl Med Mol Imaging 2015;59:446–54.
[2] Morandi U, Casali C, Rossi G. Bronchial typical carcinoid tumors. Semin Thorac Cardiovasc Surg 2006;18:191–8.

[3] Rizzardi G, Marulli G, Bortolotti L, et al. Sleeve resections and bronchoplastic procedures in typical central carcinoid tumours. Thorac Cardiovasc Surg 2008;56:42–5.
[4] Moore W, Freiberg E, Bishawi M, et al. FDG-PET imaging in patients with pulmonary carcinoid tumor. Clin Nucl Med 2013;38:501–5.
[5] Uhlén N, Grundberg O, Jacobsson H, et al. ^{18}F-FDG PET/CT diagnosis of bronchopulmonary carcinoids versus pulmonary hamartomas. Clin Nucl Med 2016;41:263–7.
[6] Krüger S, Buck AK, Blumstein NM, et al. Use of integrated FDG PET/CT imaging in pulmonary carcinoid tumours. J Intern Med 2006;260:545–50.
[7] Lococo F, Treglia G, Cesario A, et al. Functional imaging evaluation in the detection, diagnosis, and histologic differentiation of pulmonary neuroendocrine tumors. Thorac Surg Clin 2014;24:285–92.
[8] Jindal T, Kumar A, Venkitaraman B, et al. Role of (68)Ga-DOTATOC PET/CT in the evaluation of primary pulmonary carcinoids. Korean J Intern Med 2010;25:386–91.
[9] Stefani A, Franceschetto A, Nesci J, et al. Integrated FDG-PET/CT imaging is useful in the approach to carcinoid tumors of the lung. J Cardiothorac Surg 2013;8:223.
[10] Tatci E, Ozmen O, Gokcek A, et al. 18F-FDG PET/CT rarely provides additional information other than primary tumor detection in patients with pulmonary carcinoid tumors. Ann Thorac Med 2014;9:227–31.
[11] Venkitaraman B, Karunanithi S, Kumar A, et al. Role of 68Ga-DOTATOC PET/CT in initial evaluation of patients with suspected bronchopulmonary carcinoid. Eur J Nucl Med Mol Imaging 2014;41:856–64.
[12] Abgral R, Leboulleux S, Déandreis D, et al. Performance of (18) fluorodeoxyglucose-positron emission tomography and somatostatin receptor scintigraphy for high Ki67 (≥10%) well-differentiated endocrine carcinoma staging. J Clin Endocrinol Metab 2011;96:665–71.
[13] Park CM, Goo JM, Lee HJ, et al. Tumors in the tracheobronchial tree: CT and FDG PET features. Radiographics 2009;29:55–71.
[14] Daniels CE, Lowe VJ, Aubry MC, et al. The utility of fluorodeoxyglucose positron emission tomography in the evaluation of carcinoid tumors presenting as pulmonary nodules. Chest 2007;131:255–60.
[15] Pattenden HA, Leung M, Beddow E, et al. Test performance of PET-CT for mediastinal lymph node staging of pulmonary carcinoid tumours. Thorax 2015;70:379–81.
[16] Kayani I, Conry BG, Groves AM, et al. A comparison of 68Ga-DOTATATE and 18F-FDG PET/CT in pulmonary neuroendocrine tumors. J Nucl Med 2009;50:1927–32.
[17] Chong S, Lee KS, Kim BT, et al. Integrated PET/CT of pulmonary neuroendocrine tumors: diagnostic and prognostic implications. AJR Am J Roentgenol 2007;188:1223–31.
[18] Sollini M, Erba PA, Fraternali A, et al. PET and PET/CT with 68gallium-labeled somatostatin analogues in non GEP-NETs tumors. TheScientificWorldJournal 2014;2014:194123.
[19] Jindal T, Kumar A, Venkitaraman B, et al. Evaluation of the role of [18F]FDG-PET/CT and [68Ga]DOTATOC-PET/CT in differentiating typical and atypical pulmonary carcinoids. Cancer Imaging 2011;11: 70–5.
[20] Ambrosini V, Castellucci P, Rubello D, et al. 68Ga-DOTA-NOC: a new PET tracer for evaluating patients with bronchial carcinoid. Nucl Med Commun 2009;30:281–6.
[21] 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;155:529–36.
[22] Lococo F, Perotti G, Cardillo G, et al. Multicenter comparison of 18F-FDG and 68Ga-DOTA-peptide PET/CT for pulmonary carcinoid. Clin Nucl Med 2015;40:e183–9.
[23] Kayani I, Bomanji JB, Groves A, et al. Functional imaging of neuroendocrine tumors with combined PET/CT using 68Ga-DOTA-TATE (Dota-DPhe1,Tyr3-octreotate) and 18F-FDG. Cancer 2008;112: 2447–55.
[24] Okoye CC, Jablons DM, Jahan TM, et al. Divergent management strategies for typical versus atypical carcinoid tumors of the thoracic cavity. Am J Clin Oncol 2014;37:350–5.
[25] Mamede M, Higashi T, Kitaichi M, et al. [^{18}F]FDG uptake and PCNA, Glut-1, and hexokinase-II expressions in cancers and inflammatory lesions of the lung. Neoplasia 2005;7:369–79.
[26] Ozbudak IH, Shilo K, Tavora F, et al. Glucose transporter-1 in pulmonary neuroendocrine carcinomas: expression and survival analysis. Mod Pathol 2009;22:633–8.
[27] Zidi A, Douira W, Hantous-Zannad S, et al. [Imaging of bronchial carcinoid tumors: 20 cases]. Rev Pneumol Clin 2006;62:380–5.