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

Yuanyuan Jiang, MD$^{a,b}$, Guozhu Hou, MD$^{a,b}$, Wuying Cheng, MD$^{a,b,*}$

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 $^{18}$F-fluorodeoxyglucose (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 was 90.0% (95% CI = 82.0–95.0%; $P = 0.07$; $\hat{I}^2 = 49.6%$) and 71.0% (95% CI = 66.0–76.0%; $P < .001$; $\hat{I}^2 = 59.3%$), 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 = $^{18}$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)
tracers for functional NET imaging have emerged as potentially useful tools. These include (⁶⁸Ga-DOTA0-Tyr3) octreotate (⁶⁸Ga-DOTATATE), (⁶⁸Ga-DOTATOC), (⁶⁸Ga-EDOTREOTIDE), and (⁶⁸Ga-DOTATATE), (⁶⁸Ga-DOTANOC). And the role of these new imaging techniques in patients with pulmonary carcinoid remains unclear.

To our knowledge, the performance of ¹⁸F-FDG and ⁶⁸Ga-DOTA-Peptide in the evaluation of primary pulmonary carcinoid has yet to be determined. The aims of this meta-analysis were to evaluate ⁶⁸Ga-DOTA-Peptide in the evaluation of primary pulmonary carcinoid.

We included 14 studies. For the index test; reference standard; and the timing of the reference test, we resolved discrepancies by consensus.

2.5. Statistical analysis

We evaluated the diagnostic performance of ⁶⁸Ga-DOTA-peptide and ¹⁸F-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 ⁶⁸Ga-DOTA-peptide and ¹⁸F-FDG, because most of the studies only included patients with pathologically confirmed pulmonary carcinoids.

Sensitivity of ⁶⁸Ga-DOTA-peptide and ¹⁸F-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 efficacy of SUVmax ratio (SUVmax between ⁶⁸Ga-DOTA-peptide and ¹⁸F-FDG) and SUVmax of ¹⁸F-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 ⁶⁸Ga-DOTA-peptide and ¹⁸F-FDG.

Heterogeneity among those eligible studies was assessed by the I² test, with I² > 50% suggesting mild heterogeneity among studies. When I² 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.

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. 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

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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, $P < .05$).
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

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**Table 1**

| 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     | 21 typical carcinoid 5 atypical carcinoid | Prospective | Histopathological diagnosis |
| Kayani 2009                | UK      | 13       | 56                        | 55.6%   | $^{18}$F-FDG                       | 11 typical carcinoid 2 atypical carcinoid | Retrospective | Histopathological diagnosis |
| Ambrosini 2009             | Italy   | 11       | NR                        | 45.5%   | $^{68}$Ga-DOTATOC                 | 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 $^{68}$Ga-DOTA-peptide | 23 typical carcinoid 10 atypical carcinoid | Retrospective | Histopathological diagnosis |
| Jindal 2011                | India   | 20       | NR                        | 45%     | $^{18}$F-FDG $^{68}$Ga-DOTA-peptide | 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 |
| Ulhén 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-DOTATOC = $^{68}$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-N,N,N,N'-tetraacetic acid-D-Phe1-Tyr3-octreotide, NR = not reported.
derive more robust estimates of the diagnostic performance of \( ^{68} \text{Ga-DOTA-peptide} \) and \( ^{18} \text{F-FDG PET/CT} \) 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, \( ^{68} \text{Ga-DOTA-peptide} \) was confirmed providing better overall sensitivity than \( ^{18} \text{F-FDG PET/CT} \) (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 \( ^{68} \text{Ga-DOTA-peptide} \) over \( ^{18} \text{F-FDG} \), which was in line with our pooled result. Their different uptake mechanisms bears principal responsibility for different behavior of \( ^{68} \text{Ga-DOTA-peptide} \) and \( ^{18} \text{F-FDG} \).[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]

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

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 \( ^{18} \text{F-FDG} \) or \( ^{68} \text{Ga-DOTA-peptide} \).[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 \( ^{68} \text{Ga-DOTA-peptide} \) and \( ^{18} \text{F-FDG PET/CT} \) was a valuable indicator in predicting the histological type. The typical carcinoids revealed apparently higher SUVmax on \( ^{68} \text{Ga-DOTA-peptide PET/CT} \) (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. Ozbudak et al investigated the GLUT-1 expression in pulmonary neuroendocrine carcinomas, and 7% (3/46) of typical carcinoids, and 21% (6/29) of atypical were found to have significantly higher level of Glut-1 expression was reported to be related closely with malignancy.[25] Ozbudak et al investigated the GLUT-1 expression of somatostatin receptor on 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.

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