

18F-FDG PET/CT rarely provides additional information other than primary tumor detection in patients with pulmonary carcinoid tumors

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Abstract:

AIM: The purpose of this study was to assess the contribution of ¹⁸F-fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/Computed Tomography (CT) in detection and staging of pulmonary carcinoid tumors.

METHODS: A total of 22 patients with pulmonary carcinoid tumors (14 typical, 8 atypical) were reviewed in this retrospective study. PET/CT images of all patients were evaluated for primary tumor as well as metastatic regional lymph nodes, bone and other distant metastases. PET/CT positivity of primary tumors was determined by visual interpretation. Tumor size, SUVmax and Hounsfield Unit (HU) values of the tumors were used to test for differences between tumor groups (typical carcinoids and atypical carcinoids).

RESULTS: SUVmax of carcinoids ranged from 1.24 to 11.1 (mean, 5.0; median, 2.67). The mean largest diameter of primary tumors was 2.7 ± 1.3 cm, ranging from 1 to 5.5 cm. The overall sensitivity of FDG PET/CT for detection of pulmonary carcinoid tumors was 81.8%. Tumor size, SUVmax and Hounsfield Unit (HU) values of the atypical carcinoids were higher than those for typical carcinoids. However, the results were not statistically meaningful ($P > 0.05$). The sensitivity and specificity of FDG PET/CT in the detection of mediastinal and hilar lymph nodes metastases were 25% and 83% respectively. One patient had bone metastasis.

CONCLUSION: Although FDG PET/CT can be a useful tool for the detection of pulmonary carcinoid tumors and distant metastasis, it cannot discriminate typical carcinoids from atypical ones and absence of an FDG avid lesion cannot exclude pulmonary carcinoid tumors. Moreover, PET/CT is not a reliable tool in the staging of mediastinal and hilar lymph nodes especially for those patients with typical carcinoids.

Key words:

FDG PET/CT, pulmonary carcinoid tumor, synchronous pulmonary carcinoids

Pulmonary carcinoids are rare malignant tumors, comprising 1-5% of all primary lung cancers.^[1] These tumors were categorized as low-grade typical carcinoids or intermediate-grade atypical carcinoids.^[2,3] While about 10-20% of pulmonary carcinoids are atypical carcinoids; the remaining 80-90% are typical carcinoids.^[1,4]

Anatomical imaging methods such as chest radiography and computed tomography (CT) are essential in the diagnosis of pulmonary carcinoid tumors. Pulmonary carcinoid tumors usually appear as a smooth, spherical, ovoid or slightly lobulated nodule having calcification or ossification in approximately 30% of cases on computed tomography (CT) scans. Approximately 80% of them are located in the central airways and accompanying evidence of bronchial obstruction such as atelectasis or obstructive pneumonitis can be seen frequently.^[4]

Although ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed

tomography (CT) have been widely used in the staging, restaging, follow-up and response of many malignancies, the use of PET/CT scan for detection and management of pulmonary carcinoids is controversial.^[5] In this study, we aimed to assess the contribution of FDG PET/CT in detection and staging of pulmonary carcinoids.

Methods

Patients

We retrospectively evaluated data from 22 patients (14 males and 8 females; mean age, 46 ± 14 years; age range, 21-68 years) with histopathologically proven pulmonary carcinoid tumors diagnosed between January 2010 and December 2012. Primary tumors underwent complete resection. Systematic lymph node dissection (LND) or sampling was performed during surgery. Pulmonary carcinoids were classified as atypical or typical tumors according to the criteria of the World Health Organization/International Association for the

study of Lung Cancer classification scheme on histopathological evaluation.^[6] The demographic data including age, gender and histological findings were recorded for all patients. This study was approved by the ethics committee.

FDG PET/CT imaging

PET/CT imaging was performed forty-five to sixty minutes after intravenous injection of 259-518 MBq (7-14 mCi) of FDG with a Siemens Biograph 6 HI-REZ integrated PET/CT scanner (Siemens Medical Solutions, Knoxville, TN, USA). All patients fasted for at least 6 hours before PET/CT imaging without water restriction. The blood glucose levels of patients were confirmed to be less than 180 mg/dL before FDG injection. PET/CT data was acquired from the top of skull to the upper thigh with the arms up position. The maximum standardized uptake value (SUVmax) corrected for body weight was computed by standard methods from the activity in the most intense voxel in the three-dimensional tumor region from the transaxial whole body images on attenuation-corrected PET/CT images. Iodinated intravenous (IV) CT contrast material was used in only four of 22 patients.

FDG PET/CT analysis

All PET/CT images were retrospectively evaluated by two experienced nuclear medicine physicians and one radiologist. All primary tumors were reviewed for CT features such as tumor location, existence of tumor calcification, existence of findings of endobronchial obstruction (atelectasis or consolidation). PET/CT positivity was determined using visual interpretation according to the following criteria: a) FDG uptake of primary tumor was compared with that of mediastinum in patients without endobronchial obstruction, b) in the presence of obstruction, FDG activity of tumor was compared with that of atelectasis or consolidation. Differentiation of primary tumor from atelectasis/consolidation or mediastinum was categorized as "easy" or "difficult". Easily differentiated tumors were considered as PET positive. PET/CT images of all patients were also evaluated for metastatic mediastinal and hilar lymph nodes, bone and other distant metastases. Lymph nodes were considered as positive if there was a FDG uptake higher than the surrounding mediastinal blood pool.

Quantitative assessment

In addition to visual assessment, SUVmax of all primary tumors, longest tumor size and SUVmax of each mediastinal and hilar nodes were recorded. Non-contrast mean attenuation measurements (in Hounsfield Unit, HU) for 18 patients obtained from the CT images of PET/CT were assessed. HU values of primary tumors were not measured in the remaining four of 22 patients who received IV iodinated contrast material on CT imaging.

Statistical analysis

The Mann-Whitney U test was used to test for differences between tumor sizes, SUVmax and HU values and tumor groups (typical carcinoids and atypical carcinoids). The Spearman's rank correlation test was used to test the hypothesis that quantifiable data (SUVmax, HU, primary tumor size) of the patients with typical carcinoids and atypical carcinoids differ from each other. All quantitative values are given as mean \pm standard deviation (SD). A statistically significant difference was defined as a *P*-value $<$ 0.05.

Results

Clinical and histopathological data

Complete resection was done for all of 22 patients. Twenty one of the 22 patients had thoracotomy for primary tumor resection within one month after PET/CT imaging. Lobectomy was performed for one patient after treatment with bronchoscopic cryotherapy and six cycles of chemotherapy. According to pathological examination, the tumors were typical carcinoids in 14 (63.64%) and atypical carcinoids in 8 patients (36.36%). There were synchronous multiple pulmonary carcinoid tumors in two patients (one typical, one atypical). There were multiple tumorlets in one patient who had typical carcinoid tumor in the right lung accompanying bronchioloalveolar cell carcinoma (BCA) in the left lung. Of the eight patients with atypical carcinoid tumors, one showed oncocyctic changes in the tumor specimens.

While 16 of 22 carcinoids were located in the central bronchial system, 6 of 22 carcinoids were located in peripheral bronchial system. All of the six peripheral tumors were typical carcinoids. All of the eight patients with atypical carcinoids had the primary tumor located in the central bronchial system [Table 1].

Sixteen of 22 patients (72.7%) had postsurgical follow-up at our institution. Mean observation time was 13 months (range, 1-25 months). Other than one progressive patient with multiple bone and liver metastasis detected by PET/CT, none of the patients died or showed progression during the follow-up period.

FDG PET/CT findings

The FDG PET/CT findings of 22 patients with pulmonary carcinoids are given in Table 2. SUVmax of carcinoids ranged from 1.24 to 11.1 (mean, 5.0; median, 2.67). The mean largest size of primary tumors was 2.7 ± 1.3 cm, ranging from 1 to 5.5 cm. There was a marked correlation between the SUVmax values and tumor sizes (*P* = 0.010). There was accompanying obstructive pneumonia or atelectasis distal to endobronchial tumor in 16 of 22 patients. Activity of primary tumors were not easily discriminated from atelectasis or consolidation (*n* = 2) or mediastinal blood pool (*n* = 2) for four patients (three typical, one atypical carcinoids). These four patients were interpreted

Table 1: Patient characteristics, pathological data and measurements of PET/CT findings

	Histology		P-value [§]	Overall
	Typical	Atypical		
Patients				
Mean age (years) \pm SD	48 \pm 12.6	41.8 \pm 16.8		45.8 \pm 14.2
Female (<i>n</i>)	7	1		8
Male (<i>n</i>)	7	7		14
Primary tumor location				
Peripheral (<i>n</i>)	6	0		6
Central (<i>n</i>)	8	8		16
Mean SUVmax \pm SD	4.7 \pm 2.2	5.6 \pm 3.3	ns*	5 \pm 2.6
Mean tumor size \pm SD (cm)	2.46 \pm 1.2	3.2 \pm 1.3	ns	2.7 \pm 1.3
Mean HU \pm SD	52 \pm 8.6	53 \pm 5.2	ns	52.4 \pm 7.3
FDG PET/CT sensitivity for primary tumor detection (%)	78.5	87.5		81.8

HU = Hounsfield Unit, *not significant, [§]correlation between patients with typical and atypical carcinoids

Table 2: PET/CT findings of pulmonary carcinoid tumors

Case no	Histology	CT findings			FDG PET findings		
		Size (cm)	Calcification	HU	SUVmax		Visual evaluation*
					Carcinoids	Atelectasis or consolidation	
1	Typical	3.5	Yes	58	4.1	2.7	Easy
2	Atypical	5	No	59	6.7	1.3	Easy
3	Typical	1.7	No	54	3.1	No distinctive uptake	Difficult
4	Atypical	2	No	51	4	2.7	Difficult
5	Typical	1.5	No	N/A	2.4	—	Easy
6	Atypical	4.5	Yes	54	2.8	5.1	Easy
7	Atypical	1	No	48	2.4	2.9	Easy
8	Typical	2.4	No	36	7.1	No distinctive uptake	Easy
9	Typical	2.9	No	55	4.7	5.2	Easy
10	Typical	1.1	No	N/A	1.2	—	Difficult
11	Atypical	3.7	Yes	N/A	3.8	No distinctive uptake	Easy
12	Atypical	4.2	No	60	11.1	11.2	Easy
13	Typical	4.4	Yes	55	7.1	2.2	Easy
14	Typical	1.7	No	40	4.8	—	Easy
15	Typical	2.2	No	55	5.7	—	Easy
16	Typical	1.5	No	N/A	3.3	5.1	Difficult
17	Typical	5.5	Yes	44	5	2.5	Easy
18	Atypical	3	No	53	3.8	2.0	Easy
19	Typical	1.8	No	54	4.9	2.7	Easy
20	Typical	2	Yes	66	2.55	2.1	Easy
21	Atypical	2.8	No	46	10.4	—	Easy
22	Typical	2.3	No	56	9.7	—	Easy

N/A = not available (patients who received IV iodinated contrast material), — = There were no atelectasis or consolidation, *differentiation of carcinoids from atelectasis/consolidation or mediastinum

as false negatives. The remaining 18 of 22 (81.8%) pulmonary carcinoids that had distinctive activity from adjacent lung tissue or mediastinum were interpreted as true positives.

The overall sensitivity of FDG PET/CT for detection of pulmonary carcinoid tumors was 81.8%. Although tumor size, SUVmax and HU values of the atypical carcinoids were higher than typical carcinoids, the results were not statistically meaningful for each comparison ($P > 0.05$) [Table 1].

The PET/CT showed distant metastasis in only one patient with bone metastases on the sternum.

Assessment of lymph nodes

Of the 22 patients, 20 also had hilar and mediastinal lymphadenectomy on surgery. Systematic LN dissection was performed in 19 patients. A hundred and fourteen mediastinal and hilar stations were dissected in these patients. Lymph nodes were completely removed from these stations. The right lower paratracheal nodes (level 4R) and subcarinal nodes (level 7) were sampled in a patient with a right-sided tumor. A total 116 lymph node stations were evaluated histopathologically. Metastases were diagnosed histopathologically in four of 116 stations in four individual patients. Histologic and imaging results are shown in Table 3. Twenty of 116 lymph nodes stations were found to be FDG-avid on PET/CT. However, only one of 20 FDG positive lymph nodes was proven to be metastatic on histopathological examination. The remaining 19 FDG false positive lymph nodes were revealed as reactive lymphoid proliferation and/or anthracosis ($n = 18$) or silicosis

Table 3: Results of FDG-PET/CT and histopathological findings of lymph nodes in 20 patients who underwent lymph node dissection during surgery

	Lymph node metastasis (+)		Lymph node metastasis (-)		Total
	Atypical	Typical	Atypical	Typical	
PET/CT (+)	1	0	8	11	20
PET/CT (-)	3	0	31	62	96
Total	4	0	39	73	116

($n = 1$) on histopathological examination. The SUVmax value of positive lymph node stations were ranging between 1.95 and 4.37, mean \pm SD: 3.04 ± 0.69 . SUV max of the metastatic lymph node was 2.46. All of the patients with lymph node metastases had atypical carcinoid tumors. None of the patients with typical carcinoid tumors had metastatic lymph nodes on histopathological examination. The sensitivity, specificity, positive and negative predictive values, false-positive and false-negative rates of PET/CT in detecting mediastinal and hilar lymph node metastases on a per-nodal station basis were 25, 83, 5, 96.8, 16.9 and 75% respectively.

Discussion

The present study revealed that the detection rate of FDG PET/CT imaging for pulmonary carcinoid tumors was 81.8%. Erasmus *et al.*^[7] reported that FDG PET had a low sensitivity (14.2%) for detecting pulmonary carcinoid tumors in seven patients. However, several other reports that included a larger

number of patients and large-size tumors indicate that FDG PET or PET/CT have a higher sensitivity similar to our results.^[8-11] There were some limitations of FDG PET/CT for evaluating pulmonary carcinoid tumors: (a) low FDG affinity of especially small carcinoid tumors; (b) FDG uptake of these endobronchial tumors may be obscure from intense FDG uptake of distal obstructive atelectasis. Kayani *et al.*^[12] reported the PET/CT results of 18 patients with pulmonary neuroendocrine tumors comparing the performance of ⁶⁸Ga-DOTATATE, a novel selective somatostatin receptor 2 PET ligand, and FDG in the detection of pulmonary neuroendocrine tumors. They showed that FDG uptake was more intense than the ⁶⁸Ga-DOTATATE uptake in a collapsed lung distal to endobronchial carcinoid tumor. However, in 14 (87.5%) of 16 carcinoids with accompanying distal atelectasis or consolidation, the activity of the tumor could be successfully separated from these paranchimal lesions in our study [Figure 1].

Some authors noticed that histologic type and lymph-node involvement were the most important prognostic factors for pulmonary carcinoid tumors.^[13] Reactive hilar or mediastinal lymph node hyperplasia may be seen due to recurrent pneumonia on patients with carcinoid tumors.^[14] Confirming this data, there were a lot of anthracosis and reactive lymphoid hyperplasia in lymph nodes in the present study. Due to high ratio of false negativity and false positivity in the staging of mediastinal lymph nodes in the pulmonary carcinoid tumors, LN dissection should be preferred in all patients.

It was shown that there was a positive correlation between the tumor size and SUVmax in lung cancer.^[15] Similarly, our study revealed that SUVmax of the primary carcinoid tumor has a positive correlation with the tumor diameter for 22 patients. It was reported that FDG uptake correlates well with Glut-1 expression.^[16] Ozbudak *et al.*^[17] revealed that Glut-1 was observed in 7% (3/46) of typical carcinoids and 21% (6/29) of the atypical carcinoids. It is expected that there is higher FDG uptake in atypical carcinoids than typical carcinoids. Daniels *et al.*,^[9] reported that atypical carcinoids were more likely to be PET true positive than were typical carcinoids (80% versus 72.7%, respectively). Similar to these reports, although there is no statistically significant difference, mean SUVmax, tumor size

and CT density were higher in atypical carcinoids than typical carcinoids. It seems that differentiation of atypical carcinoids from typical ones according to PET/CT findings is almost impossible. Future studies with a larger group of patients may yield more satisfactory results.

Synchronous multiple pulmonary carcinoids are extremely unusual cases.^[18,19] There were two patients with synchronous multiple pulmonary carcinoid tumors in our study group. The incidence of multiple pulmonary carcinoid tumors may be greater than expected. Also there were multiple tumorlets, pulmonary carcinoid and bronchioloalveolar carcinoma in the same patient. Tumorlets are nodular aggregates of neuroendocrine cells with a diameter of less than 0.5 cm. The morphology of tumorlets is similar to that of carcinoid tumors. Carcinoid tumors may be seen in patients with multiple tumorlets.^[20] In the presence of multiple pulmonary nodules, especially those with low FDG affinity, synchronous pulmonary carcinoids and/or tumorlets should be considered in the differential diagnosis.

Conclusion

Although FDG PET/CT can be a useful tool for the detection of pulmonary carcinoid tumors and distant metastasis, it cannot discriminate typical carcinoids from atypical ones and absence of an FDG avid lesion cannot exclude pulmonary carcinoid tumors. Moreover, PET/CT is not a reliable tool in the staging of mediastinal and hilar lymph nodes, especially for those patients with typical carcinoids.

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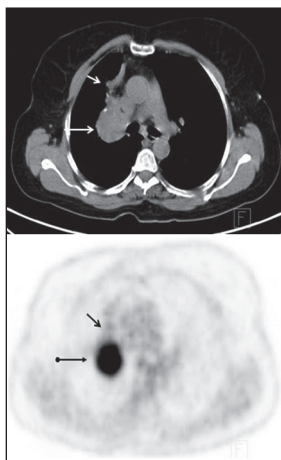


Figure 1: Typical carcinoid tumor (Case no. 13). Axial PET/CT image shows high FDG uptake in the central lobulated mass with punctate calcifications (*long arrow*). There was atelectasis with low FDG uptake at the right upper lobe (*short arrow*)

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