^{18}F-FDG PET/CT can be used to detect non-functioning pancreatic neuroendocrine tumors

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Received June 10, 2014; Accepted July 17, 2014

DOI: 10.3892/ijo.2014.2570

Abstract. ^{18}F-Fluorodeoxyglucose positron emission tomo-graphy and computed tomography (^{18}F-FDG PET/CT) has limited value in well-differentiated neuroendocrine tumors. The value of ^{18}F-FDG PET/CT in non-functioning pancreatic neuroendocrine tumors, which are often poorly differentiated, malignant, and present at an advanced stage, was also thought to be limited. This study was performed to evaluate the clinical value of ^{18}F-FDG PET/CT in assessing non-functioning pancreatic neuroendocrine tumors. From January 2010 to February 2014, a comparable large cohort of patients (31 cases) with non-functioning pancreatic neuroendocrine tumors from Shanghai Cancer Center underwent ^{18}F-FDG PET/CT scans. Demographics and clinical characteristics were retrospectively collected and analyzed for all the patients. Twenty-eight of 31 (90.3%) patients with non-functioning endocrine pancreatic tumors had an elevated ^{18}F-FDG uptake (SUVmax ≥2.5). In addition, ^{18}F-FDG PET/CT visualized 38 of 42 (90.5%) distant metastatic lesions. The ^{18}F-FDG uptake had significant association with tumor size (P=0.012) and TNM stage (P=0.004). The application of ^{18}F-FDG PET/CT has changed the management of 8 cases (8/31, 25.8%). In conclusion, ^{18}F-FDG PET/CT plays an important role in detecting and staging non-functioning pancreatic neuroendocrine tumors.

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Key words: pancreatic neuroendocrine tumor, non-functioning pancreatic neuroendocrine tumor, ^{18}F-FDG, PET/CT, TNM stage

Introduction

Neuroendocrine tumors (NETs) are a diverse group of neoplasms characterized by their endocrine secretion and histologic features and are often well-differentiated and slow-growing (1). They most commonly occur in the gastro-enteropancreatic tract, but are also found in the lung and the rest of the body (1,2). Pancreatic neuroendocrine tumors (PNETs) are rare neoplams; in 2004, their incidence was 0.22 per 100,000 in the United States (3). PNETs are classified clinically as either functioning or non-functioning based on their clinical endocrine manifestations (4). Most PNETs (90%) are non-functioning (3). Unlike functioning PNETs such as insulinomas and gastrinomas, non-functioning PNETs are often malignant and usually present at a late stage, often including a huge mass, local invasion, and distant metastases (5-7).

Modern cancer care highly depends on imaging technologies. For general imaging, positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}F-FDG) is a powerful and common functional imaging technique that can provide information about the functional and metabolic characteristics of malignancies, tumor stage, therapeutic response, and tumor recurrence (8). The advent of combined ^{18}F-FDG PET with computed tomography (^{18}F-FDG PET/CT) allows anatomic correlation and exact localization of lesions (9). Unfortunately, FDG PET has limited value for imaging gastroenteropancreatic NETs and only tumors with low differentiation and high proliferative activity have demonstrated an elevated FDG uptake (10-13). In contrast to functioning PNETs, which are usually well differentiated and slow growing, non-functioning PNETs are often found incidentally or through symptoms caused by their enlargement or metastatic spread; they are often malignant and usually present at an advanced stage (14). Therefore, it is reasonable to infer that non-functioning PNETs could be detected by ^{18}F-FDG PET. However, there is currently no published evidence of ^{18}F-FDG PET/CT in evaluating non-functioning PNETs, and generally ^{18}F-FDG PET/CT is considered to have limited value in assessing non-functioning PNETs (10-13). Moreover, ^{18}F-FDG PET/CT is not recommended to detect non-functioning pancreatic neuroendocrine tumors by the newest edition of NCCN guideline (15).

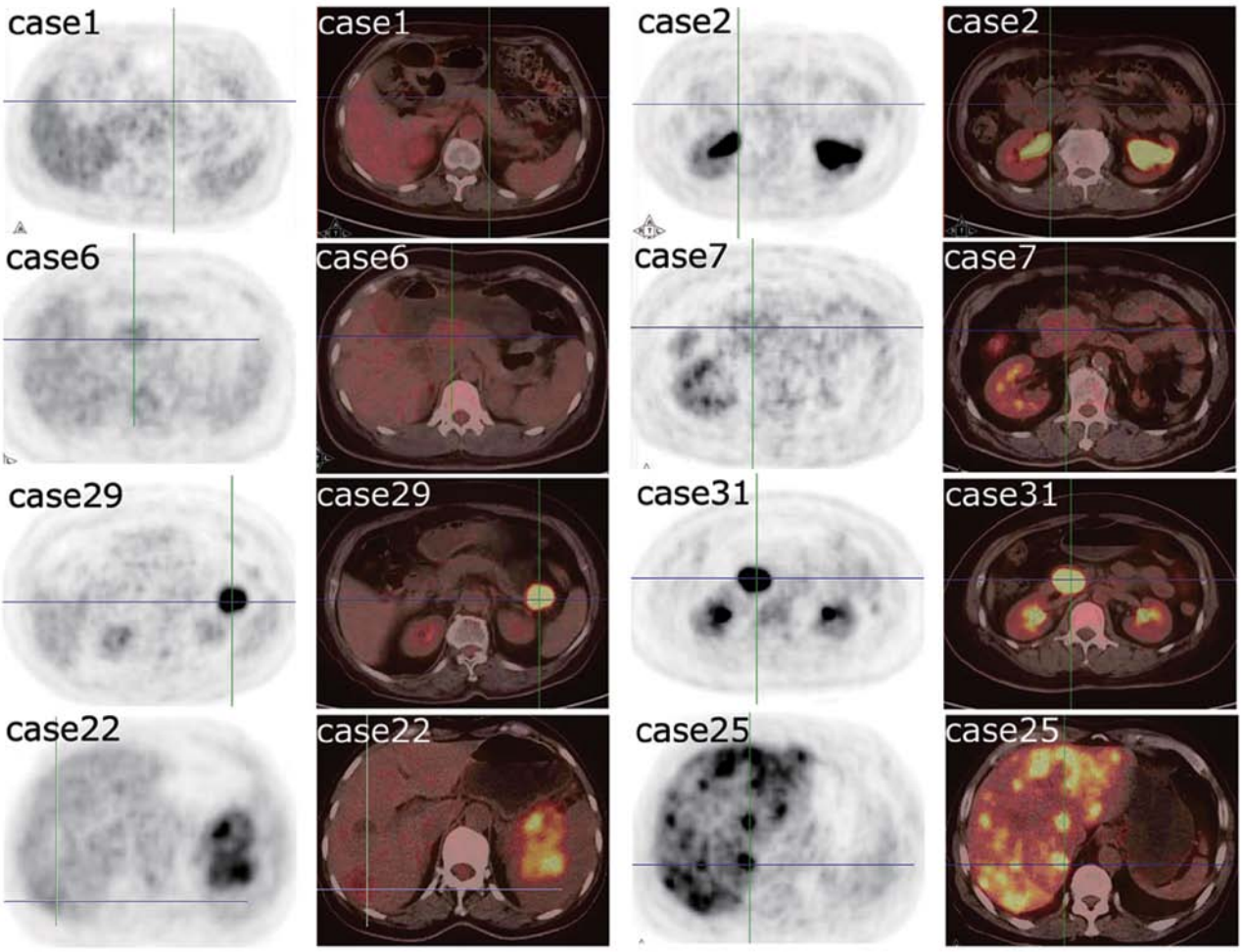

Figure 1. Representative ^{18}F-FDG uptake and PET/CT scan images in patients with non-functioning PNETs. Primary non-functioning PNETs showed no (cases 1 and 2), mild (cases 6 and 7), and intense (cases 29 and 31) ^{18}F-FDG accumulation. ^{18}F-FDG uptake was observed in liver metastatic lesions of 2 patients with non-functioning PNETs (cases 22 and 25).

In the present study, we evaluated the utility of whole-body ^{18}F-FDG PET/CT in the detection and staging of non-functioning PNETs.

Materials and methods

Patients. This study retrospectively reviewed 31 patients with PNETs referred to Shanghai Cancer Center, Shanghai, China (single institution) who underwent ^{18}F-FDG PET/CT from January 2010 to February 2014. One patient underwent transcatheter arterial chemoembolization before PET/CT scan. Tumor size was measured intraoperatively or by contrast-enhanced CT scan for patients without operation. The resected or biopsy tissues were prepared for histological and immunocytochemistry examination (cell cycle-associated Ki-67 antigen, insulin and gastrin). The functioning category of PNETs was determined by clinical symptoms and immunocytochemistry examination. The TNM staging of PNETs was determined according to the newest edition of the AJCC Cancer Staging Handbook (15). Tumor grade was defined as low grade (G1), intermediate grade (G2), and high grade (G3) according to the NCCN guidelines (15). The study protocol conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki, and was approved by the ethics boards of Fudan University Shanghai Cancer Center. Written informed consent was obtained from all the patients participating in the study.

The whole-body ^{18}F-FDG PET/CT protocol. The whole-body FDG PET/CT was performed as previously described (16). Briefly, ^{18}F-FDG was made automatically by cyclotron (Siemens CTI RDS Eclipse ST; Knoxville, TN, USA) using an Explora FDG4 module. All patients had been fasting for ≥6 h and at the time of the tracer injection, normal glucose plasma levels were confirmed. Scanning was started 60 min after intravenous administration of the tracer (7.4 MBq/kg). The images were acquired on a Siemens biograph 16HR PET/CT scanner with a transaxial intrinsic spatial resolution of 4.1 mm. CT scanning was first initiated from the proximal thighs to the head, with 120 kV, 80-250 mA, pitch 3.6, and rotation time 0.5 sec. A PET emission scan that covered the identical transverse field of view was carried out immediately after CT scanning. PET image data were reconstructed iteratively by using the CT data to attenuate correction.

Image interpretation. The image interpretation was performed as previously described (16). Two experienced nuclear medicine physicians independently assessed the data for each patient.

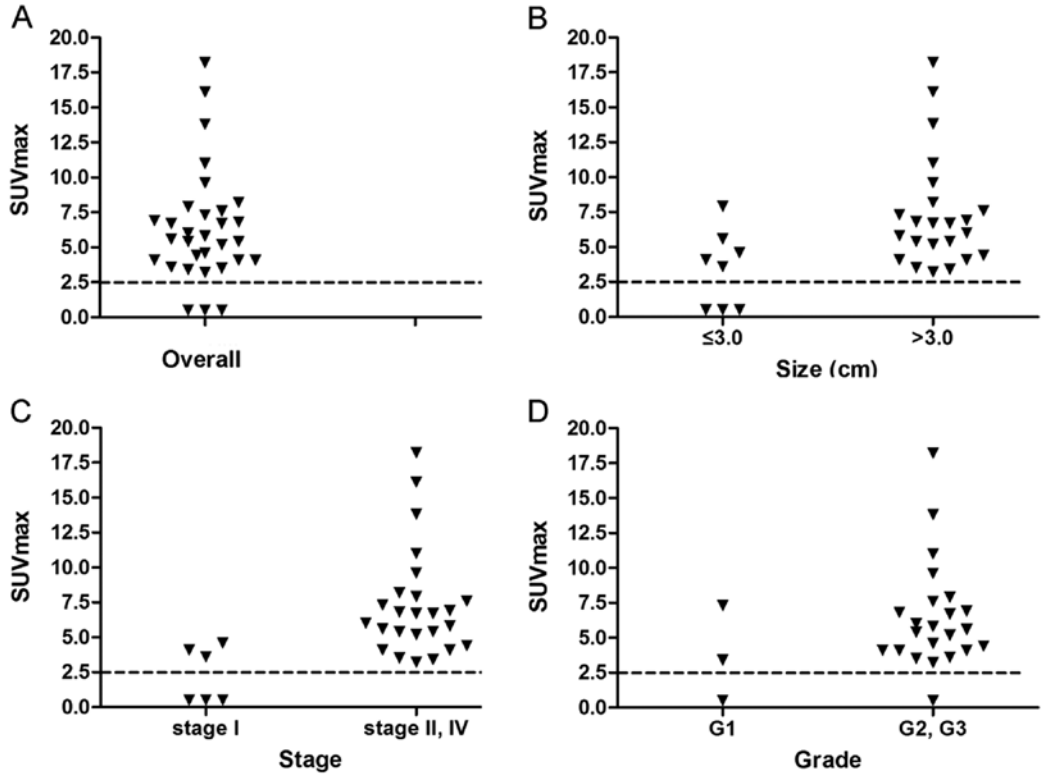

Figure 2. Overall distribution of SUVmax in non-functioning PNETs (A) and distribution of SUVmax according to (B) size (P=0.012), (C) TNM stage (P=0.004), and (D) tumor grade (P=0.222).

The reviewers reached a consensus in cases of discrepancy. Image review and manipulation was carried out on a multimodality computer platform (Syngo; Siemens). Quantification of metabolic activity was acquired using the standardized uptake value (SUV) normalized to bodyweight, and the maximum SUV (SUVmax) for each lesion was calculated. A PET lesion was considered as positive if the SUVmax was ≥2.5 (16). For the detection of distant metastases, we adopted the same functional criteria (SUVmax ≥2.5). Suspicious lesions detected by CT scans, such as nodules in the liver or the peritoneum, were also included for follow-up in order to confirm whether they were false-negative cases of PET/CT. Images were independently interpreted and compared with the histopathologic findings at surgery (5 patients) or with serial imaging and clinical follow-up findings (7 patients).

Statistical analysis. Demographics and clinical characteristics of patients with or without SUVmax of the primary tumor >2.5 were compared using Fisher's exact probability test. The statistical software used was StataSE11.0 (StataCorp, College Station, TX, USA). A P-value of <0.05 was considered statistically significant.

Results

The study group consisted of 31 cases with non-functioning PNETs and ^{18}F-FDG PET/CT detected 28 (90.3%) primary lesions (Figs. 1 and 2). The study cohort included 16 women and 15 men, age range 25-77 years (median age, 48 years) (Table I). In the subgroup of patients aged ≤50 years, 100% patients had SUVmax ≥2.5, which was similar to that of the subgroup of patients aged >50 years (78.6%) (Table II). The percentage of patients with SUVmax ≥2.5 was similar for women and men (93.8 and 86.7%, respectively). Thirteen lesions were located at the head of the pancreas and 18 at the body and tail of the pancreas. Size of lesions ranged from 1.4 to 10.0 cm (mean ± SD, 4.9±2.3 cm). In 8 cases of tumor size ≤3.0 cm, 62.5% of patients had SUVmax ≥2.5. However, in 23 cases of tumor size >3.0 cm, all the patients (100.0%) had SUVmax ≥2.5 (Fig. 2B). According to the AJCC TNM staging system, 6 patients had stage I tumors, 12 had stage II, and 13 had stage IV tumors. All 25 patients with stage II and IV tumors had SUVmax ≥2.5, compared with only 50.0% of patients with stage I tumors (Fig. 2C). Of all 26 cases with grade information, 3 cases had G1 tumors, 16 had G2 tumors, and 7 cases had G3 tumors. The percentage of SUVmax ≥2.5 in the cases with G1 tumors was lower than that of the cases with G2 and G3 tumors (66.7 and 95.7%, respectively) (Fig. 2D).

For all 12 patients with stage IV tumors (liver metastases of case 15 were resected before PET/CT examination), 42 distant metastatic lesions were found and confirmed by biopsy or serial imaging and clinical follow-up findings (Table III). Thirty-eight (90.5%) lesions had a SUVmax ≥2.5 during PET/CT scans and only 4 (9.5%) lesions demonstrated normal ^{18}F-FDG distribution. Eight of the 31 (25.8%) cases of PNETs had changed their clinical management based on results of the ^{18}F-FDG PET/CT examinations. Among these 8 cases, 4 cases underwent one-stage resection for both the primary tumor and distant metastases and 4 cases abandoned curative surgery and underwent systematic treatments.

Table I. Patient characteristics.

Patient	Age (years)	Gender	Location	Size (cm)	TNM stage	Grade	SUVmax[a]
1	62	F	Body	2.0	I	G1	(-)
2	64	M	Head	2.0	I	G2	(-)
3	63	M	Head	3.0	I	Unknown	(-)
4	52	F	Head	6.0	II	G2	3.2
5	30	M	Body	4.0	II	G1	3.4
6	65	F	Head	10.0	IV	G2	3.5
7	31	F	Head	3.0	I	G2	3.6
8	66	F	Body	4.0	II	G2	4.1
9	46	F	Body	2.5	I	G3	4.1
10	44	F	Body	4.0	IV	G2	4.1
11	29	F	Body	5.1	IV	G2	4.4
12	47	M	Head	3.0	I	G2	4.6
13	43	M	Body	5.0	II	G3	5.2
14	68	F	Head	8.0	IV	G2	5.4
15	71	M	Tail	3.5	IV	Unknown	5.4
16	49	M	Head	2.0	II	G2	5.6
17	42	M	Body	5.0	II	G3	5.8
18	52	M	Body	5.0	II	G2	6
19	42	M	Head	5.0	II	G3	6.7
20	41	M	Head	5.4	IV	Unknown	6.7
21	48	M	Head	10.0	IV	G3	6.8
22[b]	48	F	Tail	8.0	IV	G2	6.9
23	58	M	Body	5.7	IV	G1	7.3
24	56	F	Tail	9.0	IV	G2	7.6
25	67	M	Tail	1.4	IV	G3	7.9
26	28	F	Tail	4.1	IV	Unknown	8.2
27	25	F	Tail	4.0	II	G2	9.6
28	47	M	Body	8.0	IV	G3	11
29	77	F	Tail	4.0	II	G2	13.8
30	66	F	Head	6.0	II	Unknown	16.1
31	45	F	Head	5.0	II	G2	18.2

[a]SUVmax of primary tumor. [b]The patient underwent transcatheter arterial chemoembolization before PET/CT examinations. SUVmax, maximum standardized uptake value. (-), these patients presented no abnormal FDG uptake.

Discussion

Imaging technologies are essential to detect non-functioning PNETs and guide their treatment. At present, because of the high expression of somatostatin receptors on NET cells, somatostatin receptor scintigraphy with ^{111}In octreotide is a standard functional imaging technique in the detection and staging of NETs (11,17). However, poorly differentiated or aggressive NETs with high proliferative rates may not be localized on ^{111}In octreotide scanning (17). Kisker *et al* (17) found that somatostatin receptor scintigraphy visualized only 4 of 10 cases with non-functioning PNETs, which are often poorly differentiated and aggressive. In another study, Rickes *et al* (18) showed that the sensitivity and specificity of somatostatin receptor scintigraphy for diagnosing PNETs was 54 and 81%, respectively. Therefore, additional functional imaging modalities are needed to detect non-functioning PNETs.

The application of ^{18}F-FDG PET in the detection of NETs depends on the grade of tumor differentiation and the biological characteristics of the tumor (10). NETs are mostly well-differentiated and low-malignancy tumors and ^{18}F-FDG PET frequently fails to visualize them (10). However, ^{18}F-FDG accumulation is often observed in less-differentiated NETs with high proliferative activity (10,19). It has been reported that tumors with increased FDG accumulation appear more aggressive and correlate with poor prognosis (20). Because a great proportion of non-functioning PNETs are poorly differentiated with high proliferative activity, it is reasonable to infer

Table II. SUVmax of primary tumor, patient demographics and clinical characteristics.

Characteristic	SUVmax <2.5	SUVmax ≥2.5	% (SUVmax ≥2.5/total)	P-value
Age				0.081
≤50	0	17	100.0	
>50	3	11	78.6	
Gender				0.600
Male	2	13	86.7	
Female	1	15	93.8	
Location				0.558
Head	2	11	84.6	
Body/tail	1	17	94.4	
Size (cm)				0.012
≤3.0	3	5	62.5	
>3.0	0	23	100.0	
TNM stage				0.004
I	3	3	50.0	
II, IV	0	25	100.0	
Grade[a]				0.222
G1	1	2	66.7	
G2, G3	1	22	95.7	
Total	3	28	90.3	

[a]Twenty-six cases had tumor grade information. SUVmax, maximum standardized uptake value.

Table III. SUVmax in distant metastases.

Patient[a]	Site of distant metastasis	SUVmax
6	1 liver	-
10	2 liver	-
11	3 lung, 3 distant lymph nodes	2.9-5.8
14	1 liver	-
20	3 liver	4.3-6.8
21	4 liver, 1 lung, 2 peritoneum	3.0-6.2
22	2 liver	2.8,3.1
23	2 peritoneum, 1 distant lymph nodes	4.5-7.8
24	1 liver	3.5
25	6 liver	3.1-12.2
26	3 liver	3.5-8.6
28	1 liver, 6 peritoneum	2.5-7.0
	% (SUVmax ≥2.5/total)	90.5%

[a]Two liver metastases of case 15 were resected before PET/CT examination. SUVmax, maximum standardized uptake value; (-), no abnormal ^{18}F-fluorodeoxyglucose uptake.

that they can be detected by ^{18}F-FDG PET. However, there has been no published evidence of ^{18}F-FDG PET in detecting non-functioning PNETs.

In the present study, we showed that 90.3% of non-functioning PNETs can be visualized by ^{18}F-FDG PET/CT, indicating that ^{18}F-FDG PET/CT can be employed to detect non-functioning PNETs. The implication ^{18}F-FDG PET/CT in PNETs changed the clinical management of 8 cases. In addition, ^{18}F-FDG PET/CT was found to accumulate in 90.5% of distant metastatic lesions, suggesting that ^{18}F-FDG PET/CT can be used to stage non-functioning PNETs. Other PET imaging agents, such as ^{11}C-5-hydroxytryptophan (^{11}C-5-HTP) and ^{68}Ga-DOTA-Tyr3-octreotide, have been used to detect NETs with promising results (13,21-23). For example, in 2011, Naswa *et al* (16) showed that ^{68}Ga-labeled [1, 4, 7, 10-tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid]-1-NaI(3)-octreotide (^{68}Ga-DOTA-NOC) PET/CT had a sensitivity of 78.3 for primary tumor and 97.4% for metastases in gastroenteropancreatic NETs, findings that are similar to our study using ^{18}F-FDG PET/CT. However, these imaging agents are still not widely applied in clinical practice compared with ^{18}F-FDG PET/CT.

Because the uptake of ^{18}F-FDG in NETs is closely related to differentiation status and tumor stage (10,12,13,19), we also examined whether tumor size, tumor grade, and TNM stage affect the uptake of ^{18}F-FDG. We found that the uptake of ^{18}F-FDG in PNETs was significantly associated with tumor size and TNM stage, indicating that ^{18}F-FDG PET can be used to detect and stage non-functioning PNETs. In addition, although there was no significant association between increased ^{18}F-FDG uptake and tumor grade, we found that

FDG-PET/CT may aid in the diagnosis and staging of PNETs with G2 and G3 tumors (SUVmax ≥2.5, G1, 66.7%, G2 and G3, 95.7%, respectively, P=0.222).

In conclusion, ^{18}F-FDG PET/CT can be used to detect, stage, and conduct surveillance of non-functioning PNETs. In the detection stage, ^{18}F-FDG PET/CT can be applied to a fully evaluated tumor burden to guide treatments, especially for curative and cytoreductive surgery. It also can be used to assess therapeutic response including cytotoxic chemotherapy and targeted therapy and monitor disease recurrence. However, further systematic analyses with even larger study populations will be needed to confirm the role of ^{18}F-FDG PET/CT in the clinical management of non-functioning PNETs.

Acknowledgements

This study was supported in part by the Sino-German Center (GZ857), by the Science Foundation of Shanghai (13ZR1407500), by the Shanghai Rising Star Extension Program (12QH1400600), by the Fudan University Young Investigator promoting program (20520133403) and by the National Science Foundation of China (grant nos. 81101807, 81001058, 81372649, 81372653 and 81172276).

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