

Diagnostic value of ^{18}F -fluorodeoxyglucose positron emission tomography for pancreatic neuroendocrine tumors with reference to the World Health Organization classification

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Received February 23, 2009; Accepted August 6, 2009

DOI: 10.3892/ol_00000029

Abstract. The 2004 classification of the World Health Organization (WHO) has demonstrated an efficacy for prediction of the prognosis of pancreatic neuroendocrine tumors. This study aimed to assess the predictive value of preoperative ^{18}F -fluorodeoxyglucose positron emission tomography (FDG-PET) in relation to the 2004 WHO criteria. The histology of 21 pancreatic endocrine tumors resected at our hospital was reviewed and the tumors were classified according to the 2004 WHO criteria. FDG-PET findings were analyzed by comparing the findings with CT scans. FDG uptake was positive in 10 primary endocrine tumors (47%), but no uptake was seen in 11 tumors. In relation to the 2004 WHO classification, 1 out of 8 well-differentiated tumors with benign behavior was positive by PET (12.5%), 4 out of 7 well-differentiated tumors with uncertain behavior were positive (57%) and 4 low-grade malignant tumors were positive (100%). According to the WHO criteria, the rate of positive FDG uptake increased as the malignant potential increased. The metastases of low-grade malignant tumors also showed a positive FDG uptake. In conclusion, from our limited experience, FDG-PET appears to be useful for identifying pancreatic neuroendocrine tumors with a higher malignant potential. In addition, FDG-PET can detect distant metastases and may contribute to better staging of advanced disease.

Introduction

Pancreatic neuroendocrine tumors (PNETs) account for 1-2% of pancreatic tumors. PNETs grow more slowly compared with

pancreatic cancer and can metastasize a number of years after resection. PNETs usually show strong enhancement by contrast medium on computed tomography (CT) and are detected at a smaller size in comparison with pancreatic cancer (1). Along with the technical progression and improvement of the spatiotemporal resolution of CT, small asymptomatic tumors are increasingly being detected. Consequently, a reliable classification system is needed. Several authors have attempted to develop staging and grading systems to predict the malignant potential of PNETs (2-4). In these studies, benign or malignant PNETs have usually been defined from macroscopic features, such as tumor size and the presence of distant metastasis, or from histopathological features. In one study, malignant PNETs were defined as tumors with nodal or distant metastases at the time of surgery or those producing such metastases during follow-up (3). In contrast, histopathological criteria for PNETs have been suggested as a useful prognostic tool (4).

The current World Health Organization (WHO) classification of PNETs (5) was developed from an earlier proposal by Capella *et al* (6). The WHO classification is based on stage-related criteria (size and the presence of metastasis) and grade-related criteria (mitotic rate, perineural and vascular invasion, and Ki-67 proliferative index). According to these criteria, PNETs are classified into 4 groups: well-differentiated PNETs of benign behavior (WHO1a), well-differentiated PNETs of uncertain behavior (WHO1b), well-differentiated pancreatic endocrine carcinomas (WHO2) and poorly differentiated pancreatic endocrine carcinomas (WHO3). An increasing number of studies have indicated that this classification is valuable for prediction of the prognosis of PNETs (7-9). However, this classification requires a histopathological examination and cannot predict the malignant potential before surgery. Moreover, a tool for assessing the malignant potential after surgery is also required for the long-term follow-up of patients.

^{18}F -fluorodeoxyglucose (FDG) is the glucose analog most commonly used for PET imaging in the field of oncology, and has a very high sensitivity for many types of tumors especially rapidly growing and aggressive malignancies (10). FDG uptake by tumor cells is related to regional blood flow, reflects high glucose metabolism and is also linked to cellular

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Key words: pancreatic endocrine neoplasm, fluorodeoxyglucose positron emission tomography, World Health Organization classification

proliferative activity (11). Accordingly, tumors with a high FDG uptake appear to be more aggressive and are generally associated with a less favorable prognosis (10). The usefulness of FDG-PET for the diagnosis of PNETs also depends to some extent on the grade and aggressiveness of the tumor. It is well known that PNETs are mostly well-differentiated and slow-growing tumors; thus, these tumors may not take up FDG (10,12-15). Many studies have suggested that ^{111}In -octreotide (a somatostatin analog) is the PET tracer that is favored for PNETs rather than FDG because of its higher sensitivity (13,16). However, ^{111}In -octreotide does not provide information regarding the malignant nature of the tumor, unlike FDG.

A detailed comparison of FDG uptake with the malignant potential of PNETs classified according to the WHO criteria has yet to be performed. The primary aim of this study was to evaluate the role of preoperative ^{18}F -FDG-PET in patients with proven PNETs to assess the malignant potential of these tumors compared with the current WHO classification. We also examined whether FDG uptake was able to detect metastases before surgery.

Materials and methods

Twenty-one patients (9 males and 12 females, aged 28-61 years) with cytologically or histologically proven neuroendocrine tumors were preoperatively investigated by FDG-PET at our institution, between January 2005 and December 2007. PNETs measuring <0.5 cm in diameter (microadenomas), those with >10 mitoses per 10 high-powered field (HPF) and those with widespread necrosis (poorly differentiated endocrine carcinomas) were excluded.

The 21 patients underwent dynamic CT to verify the exact location of the tumor before assessing FDG uptake. Eleven patients had signs, symptoms or histopathological findings consistent with sporadic gastrinoma ($n=2$), glucagonoma ($n=1$), insulinoma ($n=7$) and somatostatinoma ($n=1$), including 3 patients with multiple endocrine neoplasia type I (MEN-I). The size of the primary tumor ranged from 0.6 to 6.7 cm (resected specimens) and the distant metastases found in 5 patients ranged from 0.5 to 8.2 cm on CT scans at the time of FDG-PET.

FDG-PET was performed by injecting 10-12 mCi of ^{18}F -FDG after an overnight fast. The blood glucose level was measured just before tracer administration and was <140 mg/ml in the 21 patients. For quantitative analysis, the maximum standardized uptake value (SUVmax) was calculated at the sites of suspected tumor foci on CT scans. Positive uptake of FDG was defined as the focal uptake with an SUVmax of ≥ 3.0 .

Histopathology was reviewed by two independent pathologists at our institution. The information recorded included the tumor diameter, the presence of vascular or perineural invasion, the Ki-67 index and the number of mitoses per 10 HPF. Nodal status was also recorded, as well as the presence or absence of any distant metastases at presentation.

The WHO classification of PNETs separates well-differentiated endocrine neoplasms from carcinomas on the basis of macroscopic local invasion and/or the presence of metastases. Well-differentiated endocrine tumors are further divided into those with benign (WHO1a) or uncertain behavior (WHO1b) on the basis of size (<2 or ≥ 2 cm), the number of mitoses per HPF, the percentage of Ki-67-positive cells (at a cut-off value of

2%) and the presence or absence of vascular and/or perineural invasion. Tumors with distant metastasis or local invasion are categorized as WHO2 and tumors with a high mitotic rate (>10 mitoses per 10 HPF) are categorized as poorly differentiated endocrine tumors (WHO3).

Clinical data (gender, age, symptoms at diagnosis and laboratory data), pathological data (tumor size, nodal or liver involvement, Ki-67 value and WHO classification) and the FDG-PET uptake score were analyzed. Qualitative data were compared by the Chi-square and Fisher's exact test when necessary. Statistical analyses were performed with the JMP version 5.0 software and a $P<0.05$ was defined as significant.

Results

The tumors of 11 patients (4 males and 7 females with an average age of 47.7 years) were negative for FDG uptake (7 insulinomas, 1 gastrinoma, 1 glucagonoma and 2 non-functioning tumors), including the 3 MEN-I patients (Table I). The tumors of the other 10 patients (4 males and 6 females with an average age of 52.9 years) were positive for FDG uptake (1 gastrinoma, 1 somatostatinoma and 8 non-functioning tumors; Table II). The positive and negative primary tumors, including benign and metastatic tumors, were detectable by CT scan at presentation. Details of the patient characteristics, the results of FDG-PET and the WHO classification are shown in Tables I and II.

According to the WHO classification, 9 patients (43%) had WHO1a tumors, 7 patients (33%) had WHO1b tumors and 5 patients (24%) had WHO2 tumors. Within the WHO2 category, 2 patients had nodal metastases and 3 patients had distant metastases, including 1 patient with extrapancreatic extension to the spleen.

Tumors with a positive FDG uptake were more malignant according to the WHO classification. When the classification was compared with the SUVmax value no significant correlation was noted (data not shown), but when the tumors were classified as positive on FDG-PET (SUVmax >3.0), half of the positive tumors (5/10) were categorized as WHO2, 4/10 were WHO1b and only 1 was WHO1a. In contrast, the 11 FDG-PET-negative tumors (SUVmax <3.0) did not include any in the WHO2 category, with 3 being WHO1b and 8 being WHO1a; thus, these lesions were significantly less malignant ($P=0.009$; Fisher's exact test) (Fig. 1A).

There was a trend for FDG-positive tumors to be larger at diagnosis (Fig. 1B), although this trend was not significant. The median size of the FDG-positive tumors was 2.0 cm (range 0.7-6.7 cm) and that of the FDG-negative tumors was 1.5 cm (range 0.7-2.2 cm). The Ki-67 score was higher in the FDG-positive group than in the negative group (2.23 vs. 1.76%), but the difference was not significant. The mitotic rate per 10 HPF was <2 in the FDG-positive and-negative tumors, showing no difference between the two groups. There was also no difference of perineural and vascular invasion. Macroscopic invasion or distant metastasis at diagnosis was frequent in the FDG-positive tumors (5/10, 50%), but was not found (0/11, 0%) in the FDG-negative tumors ($p=0.009$; Fig. 1C).

When FDG uptake occurred at metastatic sites (Table I) the primary tumor was also positive, suggesting inheritance of the characteristics of the primary by the metastatic lesion. The

Table I. PET-negative pancreatic neuroendocrine tumors.

Gender	Age	SUVmax (primary)	SUVmax (metastasis)	Diameter (mm)	Ki-67 score	Proliferation	Ne	V	Gross invasion	WHO classification
F	28	1.2	No metastasis	7	<1.0%	1/10 HPF	-	-	-	WHO1a
F	33	1.5	No metastasis	10	<2.0%	0-1/10 HPF	-	-	-	WHO1a
F	36	0.8	No metastasis	15	0.3%	<2/10 HPF	-	-	-	WHO1a
F	48	0.4	No metastasis	16	1.0%	0-1/10 HPF	-	-	-	WHO1a
F	54	2.2	No metastasis	15	<1.0%	<2/10 HPF	-	-	-	WHO1a
F	65	0.6	No metastasis	8	1.3%	<2/10 HPF	-	-	-	WHO1a
M	38	2.8	No metastasis	9	<1.0%	<2/10 HPF	-	-	-	WHO1a
F	61	0.5	No metastasis	25	<1.0%	1/10 HPF	-	-	-	WHO1b
M	47	1.2	No metastasis	22	<2.0%	<2/10 HPF	-	-	-	WHO1b
M	58	2.6	No metastasis	15	5.0%	0/10 HPF	-	-	-	WHO1b
M	59	0.3	No metastasis	13	<2.0%	<2/10 HPF	+	-	-	WHO1b

WHO1a, well-differentiated endocrine tumor, benign behavior; WHO1b, well-differentiated endocrine tumor, uncertain behavior; Ne, perineural invasion; V, vascular invasion.

Table II. PET-positive pancreatic neuroendocrine tumors.

Gender	Age	SUVmax (primary)	SUVmax (metastasis)	Diameter (mm)	Ki-67 score	Proliferation	Ne	V	Gross invasion	WHO classification
F	53	8.80	No metastasis	7	<2%	<2/10 HPF	-	-	-	WHO1a
F	61	41.0	No metastasis	28	<1%	0/10 HPF	-	-	-	WHO1b
M	47	6.90	No metastasis	40	<2%	<1/10 HPF	-	-	-	WHO1b
M	50	18.0	No metastasis	17	3-5%	2/10 HPF	-	-	-	WHO1b
M	55	5.80	No metastasis	20	0.2-0.3%	0-1/10 HPF	-	-	-	WHO1b
F	38	9.40	9.4	35	<1%	0/10 HPF	-	-	LN met	WHO2
F	49	5.20	3.2	15	2-3%	0/10 HPF	-	-	Liver met	WHO2
F	52	4.30	6.2	8	1-2%	<2/10 HPF	-	-	LN met	WHO2
F	69	3.50	4.1	10	5% (primary) 30% (liver met)	4/10 HPF	+	+	Liver met/ spleen	WHO2
M	55	5.20	3.2	67	3%	0-1/10 HPF	-	+	Liver met	WHO2

WHO1a, well-differentiated endocrine tumor, benign behavior; WHO1b, well-differentiated endocrine tumor, uncertain behavior; WHO2, well-differentiated endocrine tumor, low-grade malignancy; LN met, lymph node metastasis; liver met, liver metastasis; Ne, perineural invasion; V, vascular invasion.

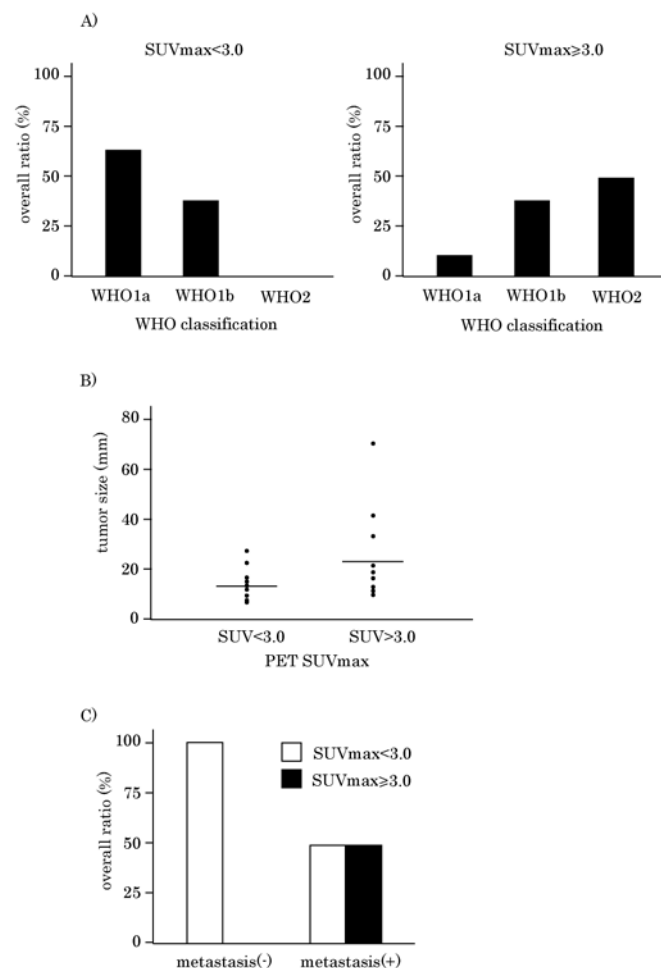


Figure 1. WHO classification in PET-positive and -negative tumors. (A) Left panel, percentage of WHO1a, 1b and 2 tumors with SUVmax <3.0; right panel, percentage of WHO1a, 1b and 2 tumors with SUVmax ≥3.0. WHO2 tumors were positive for FDG uptake ($p=0.009$). (B) SUVmax and tumor size. Pathological examination showed that the PET-positive tumors had a larger diameter, but that the difference was not significant. (C) Metastatic status and FDG uptake. None of the tumors with FDG uptake <3.0 showed metastasis at resection.

SUVmax of the metastatic site was higher (median 6.20) compared with that of the primary site (median 5.02), implying an increased malignant potential of metastases. However, not all of the metastases detected by CT were identified by FDG-PET, suggesting a higher sensitivity of CT scanning for the detection of metastasis. These findings imply that the follow-up of PNET patients with FDG-PET would require concomitant CT scanning.

Discussion

FDG is the most commonly used PET tracer in the field of oncology and has a high sensitivity for many types of tumors, especially rapidly growing and aggressive malignancies (10). FDG is taken up by tumor cells and converted to FDG-6-phosphate by glycolytic enzymes, after which it remains trapped in the tumor (17). A good correlation between the glycolytic rate of tumor cells and tumor proliferation has been shown for some neoplasms, including pancreatic cancer

(18-20). However, few studies have analyzed the usefulness of FDG-PET for the diagnosing and restaging of PNETs. An Italian study showed that FDG-PET was significantly more likely to be positive in patients who had rapidly growing or aggressive PNETs with distant metastases (13). Despite the good correlation of positive FDG uptake with the aggressiveness of PNETs, a detailed analysis of PET positivity vs. histopathology has been shown to be insufficient.

In 2004, a WHO classification of PNETs was proposed which has been examined for its validity as a predictor of prognosis in several previous studies (7-9). Although the outcome of WHO1b tumors is still a matter of controversy, the predictive value is excellent for WHO1a and WHO2 tumors. In this respect, the WHO classification is better than other systems based on the detection of necrosis and the number of mitoses alone (4).

In the present study, we examined 21 patients with histologically classified PNETs by FDG-PET. PNETs with a high FDG uptake were significantly more likely to have a higher malignant potential according to the WHO classification and indeed, all of the WHO2 tumors were FDG-positive. On the other hand, only 1 out of 8 WHO1a tumors was positive for FDG uptake, suggesting that tumors with less aggressive behavior have a lower glucose metabolism. In addition to the level of glucose metabolism, tumor size appears to be an important factor for detection by PET. The FDG-positive tumors had a larger average size (2.2 vs. 1.7 cm; Fig. 1B), implying that a large enough tumor cell mass as well as biological aggressiveness is necessary for FDG uptake to be detected by PET.

It is interesting that a positive FDG uptake (SUVmax >3.0) by the primary tumor was related to risk of metastasis. In our study, primary tumors with metastases at resection showed a positive FDG uptake at the time of admission (Fig. 1C). In other words, if the FDG-PET of a primary tumor is negative, it is likely that this tumor will have no metastases. Although the detection rate of metastases by CT scanning is higher, FDG-PET is unique in the sense that it predicts the potential for metastasis of the primary tumor. Thus, FDG-PET may be useful for detecting unsuspected distant metastases when performed with concomitant dynamic CT.

As for FDG uptake by metastatic tumors, patients with metastases showed an uptake of FDG at some point, but not all of the metastases were identified by FDG-PET. Failure to detect metastases were due to tumor size or the existence of a subpopulation of tumor cells with an altered glucose metabolism. FDG-PET therefore was less sensitive for identifying metastases compared with CT in our study.

In conclusion, ^{18}F -FDG-PET is highly accurate for the identification of low-grade malignant neuroendocrine tumors (WHO classification) prior to surgical intervention. Uptake of FDG by the primary tumor is therefore useful for predicting its aggressiveness and potential for metastasis.

References

1. Rha SE, Jung SE, Lee KH, Ku YM, Byun JY and Lee JM: CT and MR imaging findings of endocrine tumor of the pancreas according to WHO classification. *Eur J Radiol* 62: 371-377, 2007.
2. Modlin IM and Sandor A: An analysis of 8305 cases of carcinoid tumors. *Cancer* 79: 813-829, 1997.

3. Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA and Cameron JL: Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. *J Gastrointest Surg* 2: 472-482, 1998.
4. Hochwald SN, Zee S, Conlon KC, Colleoni R, Louie O, Brennan MF and Klimstra DS: Prognostic factors in pancreatic endocrine neoplasms: an analysis of 136 cases with a proposal for low-grade and intermediate-grade groups. *J Clin Oncol* 20: 2633-2642, 2002.
5. Heitz PU, Komminoth P, Perren A, Klimstra DS, Dayal Y, Bordi C, Lechagon J, Centeno BA and Kloppel G: Tumours of the endocrine pancreas. In: *Pathology and Genetics of Tumours of Endocrine Organs* (World Health Organization Classification of Tumours). DeLellis RA, Lloyd RV, Heitz PU and Eng C (eds). IARC Press, Lyon, pp177-182, 2004.
6. Capella C, Heitz PU, Hofler H, Solcia E and Kloppel G: Revised classification of neuroendocrine tumors of the lung, pancreas and gut. *Digestion* 55: 11-23, 1994.
7. Bettini R, Boninsegna L, Mantovani W, Capelli P, Bassi C, Pederzoli P, Delle Fave GF, Panzuto F, Scarpa A and Falconi M: Prognostic factors at diagnosis and value of WHO classification in a mono-institutional series of 180 non-functioning pancreatic endocrine tumours. *Ann Oncol* 19: 903-908, 2008.
8. Schmitt AM, Anlauf M, Rousson V, Schmid S, Kofler A, Riniker F, Bauersfeld J, Barghorn A, Probst-Hensch NM, Moch H, Heitz PU, Kloppel G, Komminoth P and Perren A: WHO 2004 criteria and CK19 are reliable prognostic markers in pancreatic endocrine tumors. *Am J Surg Pathol* 31: 1677-1682, 2007.
9. Ferrone CR, Tang LH, Tomlinson J, Gonen M, Hochwald SN, Brennan MF, Klimstra DS and Allen PJ: Determining prognosis in patients with pancreatic endocrine neoplasms: can the WHO classification system be simplified? *J Clin Oncol* 25: 5609-5615, 2007.
10. Reske SN and Kotzerke J: FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, 'Onko-PET III', 21 July and 19 September 2000. *Eur J Nucl Med* 28: 1707-1723, 2001.
11. Bombardieri E, Aktolun C, Baum RP, Bishof-Delaloye A, Buscombe J, Chatal JF, Maffioli L, Moncayo R, Mortelmans L and Reske SN: FDG-PET: procedure guidelines for tumour imaging. *Eur J Nucl Med Mol Imaging* 30: BP115-BP124, 2003.
12. Adams S, Baum R, Rink T, Schumm-Drager PM, Usadel KH and Hor G: Limited value of fluorine-18 fluorodeoxyglucose positron emission tomography for the imaging of neuroendocrine tumours. *Eur J Nucl Med* 25: 79-83, 1998.
13. Pasquali C, Rubello D, Sperti C, Gasparoni P, Liessi G, Chierichetti F, Ferlin G and Pedrazzoli S: Neuroendocrine tumor imaging: can 18F-fluorodeoxyglucose positron emission tomography detect tumors with poor prognosis and aggressive behavior? *World J Surg* 22: 588-592, 1998.
14. Eriksson B, Bergstrom M, Orlefors H, Sundin A, Oberg K and Langstrom B: Use of PET in neuroendocrine tumors. In vivo applications and in vitro studies. *Q J Nucl Med* 44: 68-76, 2000.
15. Eriksson B, Bergstrom M, Sundin A, Juhlin C, Orlefors H, Oberg K and Langstrom B: The role of PET in localization of neuroendocrine and adrenocortical tumors. *Ann NY Acad Sci* 970: 159-169, 2002.
16. Pawlikowski M and Melen-Mucha G: Somatostatin analogs from new molecules to new applications. *Curr Opin Pharmacol* 4: 608-613, 2004.
17. Pacak K, Eisenhofer G and Goldstein DS: Functional imaging of endocrine tumors: role of positron emission tomography. *Endocr Rev* 25: 568-580, 2004.
18. Sperti C, Pasquali C, Chierichetti F, Ferronato A, Decet G and Pedrazzoli S: 18-Fluorodeoxyglucose positron emission tomography in predicting survival of patients with pancreatic carcinoma. *J Gastrointest Surg* 7: 953-959, 2003.
19. Vansteenkiste JF, Stroobants SG, Dupont PJ, De Leyn PR, Verbeken EK, Deneffe GJ, Mortelmans LA and Demedts MG: Prognostic importance of the standardized uptake value on (18) F-fluoro-2-deoxy-glucose-positron emission tomography scan in non-small-cell lung cancer: An analysis of 125 cases. *Leuven Lung Cancer Group. J Clin Oncol* 17: 3201-3206, 1999.
20. Downey RJ, Akhurst T, Gonen M, Vincent A, Bains MS, Larson S and Rusch V: Preoperative F-18 fluorodeoxyglucose-positron emission tomography maximal standardized uptake value predicts survival after lung cancer resection. *J Clin Oncol* 22: 3255-3260, 2004.