Hyperaccumulation of ^{18}F-FDG in order to differentiate solid pseudopapillary tumors from adenocarcinomas and from neuroendocrine pancreatic tumors and review of the literature

Zhi-wei Guan[1] PhD,
Bai-xuan Xu[1] MD,
Rui-min Wang[1] PhD,
Lu Sun[2] MD,
Jia-he Tian[1] MD

1. Department of Nuclear Medicine and
2. Department of Pathology, Chinese PLA General Hospital, Beijing, China

***

Keywords: Solid pseudopapillary tumor
- ^{18}F-FDG - Pancreatic ductal adenocarcinoma
- Neuroendocrine tumor

Correspondence address:
Jia-he Tian MD,
Fuxing Road 28,
Beijing, China. 100853
Email: 13718806573@139.com

Received:
22 March 2013
Accepted revised:
14 May 2013

Abstract

Solid pseudopapillary tumors (SPT) are rare, unique pancreatic tumors with benign entity and low malignant potential. Limited information is available in the literature reporting their accumulation of fluorine-18 fluoro deoxyglucose (^{18}F-FDG) using positron emission tomography/computed tomography (PET/CT). *The aim* of this retrospective study was to define the uptake-accumulation of ^{18}F-FDG PET/CT in a comparatively large cohort of SPT, and to compare their uptake with the uptake of ^{18}F-FDG in pancreatic ductal adenocarcinomas (PAC) and neuroendocrine tumors (PNET). Between June 2007 and January 2013, *18 pathologically proven SPT* were identified from the total of patients studied by PET/CT in our Center, including 13 women and 5 men, aging from 23 to 56 years old (mean age, 38.5 years). Malignant SPT was histologically classified using the WHO criteria. Eighty-six PAC patients and 28 PNET patients were also identified and included in this study for comparison. Positron emission tomography results were considered as positive if focal accumulation of ^{18}F-FDG exceeded the surrounding normal pancreatic tissue. Regions of interest were drawn on the pancreatic lesions, and the maximal standardized uptake values (SUVmax values) were calculated. The mean values of SUVmax were compared with independent-samples t test or with the nonparametric Mann-Whitney U method. Correlation of SUVmax values and tumor size were analyzed in cases of SPT. Receiver operating characteristics (ROC curve) were used to study the efficiency of SUV values for the differential diagnosis between SPT versus (vs) PAC and SPT vs PNET. A value of $P<0.05$ was considered statistically significant. *All SPT cases were ^{18}F-FDG-PET positive*, with SUVmax values ranging from 3.5-18.3. The SUVmax values of SPT had poor correlation with tumor size, and no significant difference by gender and age. Areas under the curve ROC were 0.619 and 0.526, respectively for the differentiation of SPT from PNET and PAC tumors. Five SPT tumors were malignant, and exhibited relatively low ^{18}F-FDG uptake (SUVmax range, 3.0-4.5) except a tumor after recurrence (SUVmax 17.7). Images of CT were of low dose and thus were not evaluated. *In conclusion,* our results suggest that SPT benign or malignant are consistently hyperaccumulating ^{18}F-FDG above SUVmax 3. Differentiation from PAC and PNET if only based on the higher SUVmax values was not possible but if based on lower SUVmax, of ≤2.6 (in 14%) and ≤2.5 (in 21.4%) of PAC and PNET, respectively, these pancreatic tumors could be differentiated from SPT.

Hell J Nucl Med 2013; 16(2): 97-102 *Epub ahead of print: 21 May 2013* *Published on line: 20 July 2013*

Introduction

Solid pseudopapillary tumors (SPT) of the pancreas are rare, accounting for 0.13%-2.7% of all pancreatic tumors [1]. As PET (PET/CT) is becoming more and more popular in pancreatic tumors detection, it is important to better understand the imaging characteristics of this rare tumor when interpreting the PET images of the pancreas. Currently, information about the metabolic feature of SPT is limited, with no more than 15 cases found in the literature [2-9]. The limited available information reveals that SPT has high uptake of 2-deoxy-2-[^{18}F]-fluoro-D-glucose (^{18}F-FDG), despite of its benign nature. So, based on the present knowledge of SPT, there are two questions. First, if SPT consistently have this kind of hyperaccumulation of ^{18}F-FDG in a cohort study. Second, if so, can SPT be differentiated from other solid pancreatic tumors such as ductal adenocarcinomas (PAC) or neuroendocrine tumors (PNET), which are the most common pancreatic tumors with very different prognosis.

We retrospectively studied 18 patients with pathologically proven of SPT selected from all patients who underwent ^{18}F-FDG PET/CT studies in our center during the last 5 years. We compared these patients with patients with histologically proven PNET and PAC of the pancreas with the aim to confirm the metabolic features of SPT and differentiate them from PAC and PNET of the pancreas using PET/CT.

Subjects and methods

This study was approved by the institutional Review Board of the Chinese PLA General Hospital. The requirement of informed consent from patients was waived due to the retrospective nature of the study.

We retrospectively reviewed the patients referred to this center for ^{18}F-FDG PET/CT studies between June 2007 and January 2013 to identify the patients of pathologically proven solid pancreatic tumors including SPT, PNET and PAC. Because PAC were much more common than SPT and PNET, the inclusion period for PAC ended in June 2012 rather than January 2013. Eighteen patients of SPT (5 men, 13 women; mean age, 38.5±11.9 years; range, 23-56 years) were included in the study. The PET/CT studies were done for staging in 9 cases, differential diagnosis in 7 cases, restaging in 1 case and primary tumor screening in 1 case according to the prescription of the clinical doctors. Pathological results were obtained from resection of the tumor in 13 cases and from fine needle biopsy in 5 cases. Eighty-six patients with PAC (53 men, 33 women; mean age, 61.4±10.8 years; range, 35-80 years) and 28 patients with PNET (16 men, 12 women; mean age, 50.9±10.4 years; range, 37-73 years) were included in the study and were compared with the SPT patients.

Before imaging, patients fasted for 6h and their blood glucose levels were as tested, below 7mmol/L. Positron emission tomography/CT scans were performed on a dedicated PET/CT scanner (Biograph Truepoint, Siemens) with 64-slice CT 60min after the intravenous injection of ^{18}F-FDG (5.55MBq/kg). The scan covered the trunk from skull base to midthigh. Attenuation correction was performed using a low-dose helical CT protocol (90mAs, 110kV, 0.9pitch) under normal breathing. The PET images were reconstructed using the true X method (3 iterations, 21 subsets), and postfiltered with a 5.0mm full width at half maximum (FWHM) in a matrix of 168. The attenuation corrected PET images, CT images and integrated PET-CT images were displayed in 3-dimensional planes. Positron emission tomography results were recorded as positive if any focal tracer accumulation exceeded normal regional tracer uptake in the pancreas [10]. Lesions outside the pancreas with focal ^{18}F-FDG accumulation higher than the surrounding normal tissues, if there was no other reasonable explanation, e.g. physical uptake, inflammation, other benign or secondary tumors, were diagnosed as metastases [11]. The region of interest was placed on the area with the highest ^{18}F-FDG uptake. The maximal standardized uptake value (SUVmax) was calculated. Images of PET/CT were reviewed by two nuclear medicine doctors experienced in PET/CT image reading. Disagreement was resolved by discussion between them.

The diagnosis of SPT was based on the histopathological examination as well as the immunohistochemical staining. Malignant SPT was classified according to the WHO criteria, including perineural invasion, angioinvasion, deep invasion into the surrounding tissue, and distant metastases.

Quantitative variables were expressed as means±standard deviations, and categorical variables were expressed as counts and proportions. Patients of SPT were classified

Table 1. *Clinical characteristics of the patients with SPT*

No.	Sex	Age	Tumor in pancreas	Tumor size(cm)	Tumor SUVmax	Management	Pathology
1	F	46	Neck	3.4	5.4	Resection	Benign
2	»	49	Uncinate process	2.0	4.2	Biopsy	»
3	»	25	Neck	5.5	7.5	Resection	»
4	»	56	Tail	8.5	4.0	»	»
5	M	37	Neck	2.4	8.2	»	»
6	F	23	Head	5.2	7.0	»	»
7	»	24	Neck	3.2	6.5	»	»
8	»	38	Head	2.0	4.1	Biopsy	»
9	»	30	Uncinate process	1.7	7.4	»	»
10	M	47	Head	2.6	18.3	Resection	»
11	F	50	Body	8.0	11.4	»	»
12	»	24	Tail	10	8.6	»	»
13	M	31	Head	4.5	7.6	»	»
14	»	56	Tail	5.0	3.5	Biopsy	Mal.(h. m.)
15	F	49	»	4.0	3.7	»	» »
16	»	26	Head	3.5	4.5	Resection	» (p. in.)
17	M	42	»	3.0	4.0	»	» (c. in.)
18	F	34	»	3.4	17.7	»	Recurrence

SPT: solid pseudopapillary tumors, Mal. h. m: malignant hepatic metastases, p.in: perineural invasion, c: capsule, M: male, F: female

Table 2. *Studies of SPT with ^{18}F-FDG information retrieved from the database of Medline and Embase*

Reference of study	Number of patients	Gender/age	Tumor size (cm)	SUVmax value
[2]	1	Female/40	3.5	2.6
[3]	2	»/31 »/37	5.8 5.3	4.2 3.0
[4]	1	»/16	1	3.6
[5]	6			0.9-42.8*
[6]	1	»/34	6.7	4.8
[7]	1	»/65	large	11.4
[8]	1	Male/58	2.4	4.4
[9]	2	»/58 »/75	12 4.5	3.4 negative
Total	15	F/M 12/2		

M: male, F: female, *One tumor was ^{18}F-FDG negative with the SUVmax value as 0.9

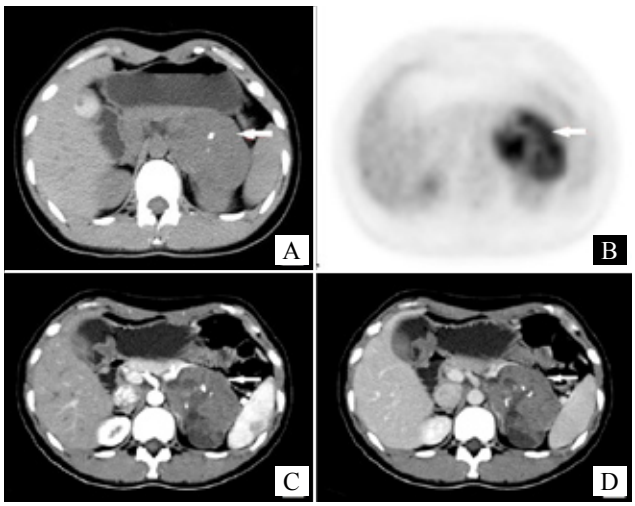


Figure 1. A pathology proven benign SPT located in the pancreatic tail (arrow) of a 26 years old woman showed avid ^{18}F-FDG uptake in the peripheral zone (B, solid white arrow, SUVmax of 7.5), corresponding to the solid part of the tumor enhanced after contrast administration (C-D). The spleen vessel was suppressed but not invaded.

into younger and elderly groups by comparing their mean age. Independent-samples t test was used to compare the SUVmax values between SPT groups defined by age and sex. Nonparametric Mann-Whitney U method was used to compare the SUVmax values between the tumor groups of SPT, PNET and PAC. Correlation between SUVmax value and tumor size (maximum diameter of the tumor) was analyzed by the method of linear regression. The ROC curve was used to analyze the efficiency of SUVmax value for differential diagnosis between SPT and PAC and also between SPT and PNET. A significant difference was indicated by $P<0.05$. Statistical analysis was performed using SPSS for Windows (version 11.5).

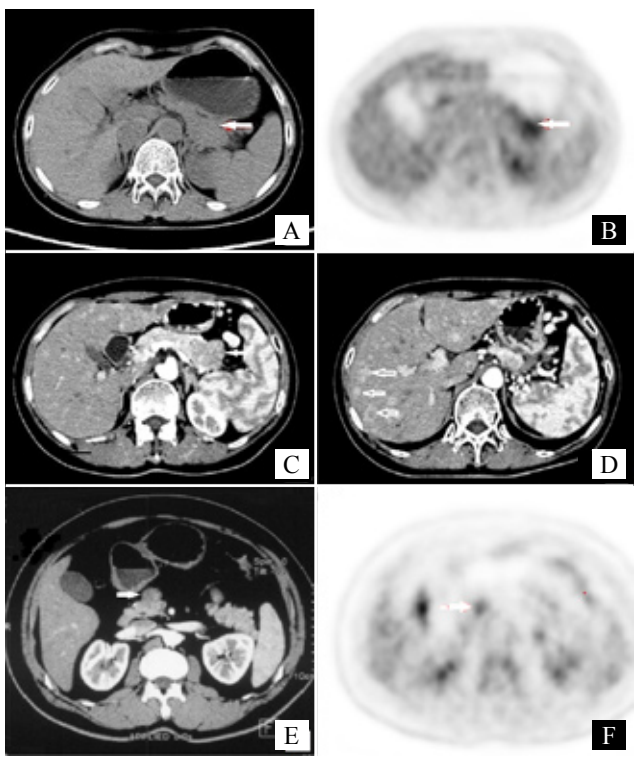


Figure 2. A pathology proven malignant SPT with hepatic metastasis located in the pancreatic tail of a 55 years old woman showed mild ^{18}F-FDG uptake with SUVmax value as 3.7 (B, solid white arrow), and exhibited hypoattenuation at the arterial phase after contrast administration (C, solid white arrow). The PET image failed to display the lesions in the liver which were identified as hyperenhanced small nodules or circles at the arterial phase after contrast administration (D, empty white arrows). Another pathology proven malignant SPT with capsule invasion located in the pancreatic neck of a 42 years old man exhibited hypovascular enhancement at the arterial phase after contrast administration (E, solid white arrow), and also showed mild ^{18}F-FDG uptake with SUVmax value as 4.0 (F, solid white arrow).

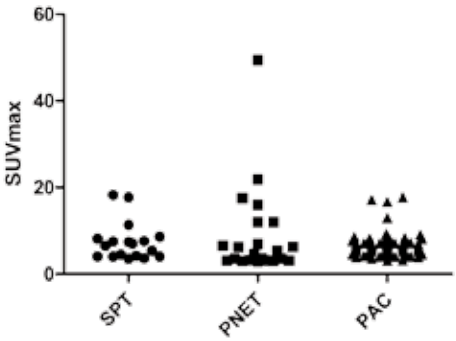


Figure 3. Scatter plot of SUVmax values in the 3 groups of pancreatic tumors.

Results

Our results showed that all SPT tumors exhibited positive ^{18}F-FDG uptake (Fig.1), with the SUVmax values varying from 3.5 to 18.3 (Table 1). Statistical results showed no correlation between the SUVmax value and the tumor size (r=0.002, P=0.994). Eight patients were much elder than the mean age, but their SUVmax values were not significantly different from those of the younger patients (P=0.632). Comparison of the values between male and female patients also showed no significant difference (P=0.683). According to the WHO criteria, 5 SPT tumors were classified as malignant because 2 had hepatic metastases confirmed on biopsy, 2 had microscopic capsule or perineural tumor invasion, and 1 had recurrence, 4 years after the primary tumor resection, confirmed by pathology.

The 2 malignant tumors with liver metastases were diagnosed in elderly patients and the SPT tumors were located in the tail of the pancreas. These tumors showed low ^{18}F-FDG uptake with the lowest SUVmax values of 3.5 and 3.7, respectively (Fig. 2). The hepatic metastases in one of these 2 patients were identified with slightly higher ^{18}F-FDG accumulation than the surrounding hepatic tissue.

The 2 malignant tumors with perineural and capsule invasion were both located in the pancreatic head and also exhibited relatively low ^{18}F-FDG uptake with the SUVmax values of 4 and 4.5, respectively (Fig. 2).

The tumor after recurrence showed high ^{18}F-FDG accumulation with a very high SUVmax value of 17.7.

No significant difference was found in general, between total SUVmax values of SPT and of PNET (P=0.209), or SPT and PAC (P=0.734) (Fig.3). For the differential diagnosis of SPT vs PNET and vs PAC by the SUVmax value, the ROC areas were 0.619 and 0.526, respectively (Fig. 4).

It was noticed that 74/86 PAC tumors (86%) had higher ^{18}F-FDG uptake with SUVmax between 3.1-17.7. A SUVmax of ≤2.6 (2-2.6) was noticed in 12 (14%) of PAC cases.

For PNET, tumors 22/28 (78.6%) patients had higher ^{18}F-FDG uptake with SUVmax 3-49.4. A SUVmax of ≤2.5 (1.2-2) was noticed in 6 (21.4%) of the 28 PNET patients.

Discussion

Hyperaccumulation of ^{18}F-FDG in SPT was first reported by other researchers in 2005 [2] and later by others (Table 2) [3-9]. From the database of Medline and Embase, 8 studies

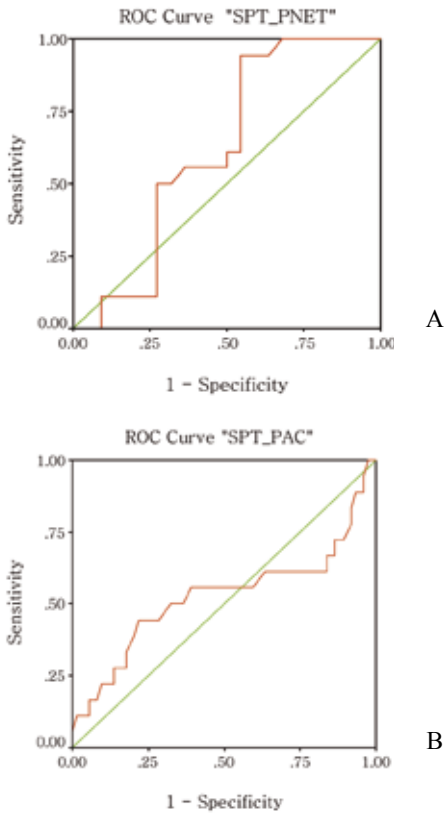


Figure 4. ROC curves of SUVmax to differentiate between all SPT vs all PNET (A) and vs all PAC tumors (B), the areas under curve were 0.619 and 0.526, respectively.

with a total of 15 cases of SPT were retrieved by using the keywords: "solid pseudopapillary tumor", "solid and cystic tumor", with "^{18}F-FDG". According to the literature, all 15 tumors except for 2 exhibited hyperaccumulation of ^{18}F-FDG, with SUVmax ranging from 2.6 to 42.8. It was not clear if the hyperaccumulation of the SPT was an arbitrary finding considering that most of the studies were case reports. In the present retrospective study we included 18 patients with SPT all of which exhibited hyperaccumulation of ^{18}F-FDG, while 14% of PAC and 21.4% of PNET patients did not. So, it was interesting that SPT, a type of tumor with largely benign character, could accumulate ^{18}F-FDG so markedly both at its benign and malignant state. As SPT predominantly occurs in young women [1], we showed that the SUVmax value was not affected by age or gender. There was a poor correlation between the SUVmax value and the tumor size. It is well known that glucose transporter-1 (Glut-1) and hexokinase-II (HK-II) play key roles in ^{18}F-FDG uptake and trapping in the tumor cells. Immunohistochemical staining showed that SPT tumor cells had poor expression of Glut-1 and moderate expression of HK-II, but were rich in mitochondria [3]. Cells with high density, rich in mitochondria, and the hypervascular nature of the tumor may contribute to the accumulation of ^{18}F-FDG in SPT tumor cells [3, 4]. Some PAC tumors may be negative in the ^{18}F-FDG PET scan or have very low SUVmax as in our study, because of their small size, or having small number of tumor cells and large amount of fibrous components [12]. Some PNET tumors may also be negative in the ^{18}F-FDG scan because well-differentiated tumors do not accumulate ^{18}F-FDG [13, 14].

Fluorine-18-FDG PET/CT has been shown to be useful in pancreatic cancer staging or in differential diagnosis between inflammation and pancreatic cancer [10, 11]. For differential diagnosis on pancreatic tumors, ^{18}F-FDG PET/CT plays only an additional role as dynamic CT and MRI examinations are usually the first choice. Different from ^{18}F-FDG PET, which reflects glucose metabolism of the tumor cells, CT and MRI reflect their anatomical structures and tumor components [15, 16]. In case of SPT, dynamic MRI seems more able than CT to display the pseudocapsule cystic changes, hemorrhage, as well as the progressively peripheral enhancement after contrast administration, which were the most important imaging features of SPT and helps to differentiate them from other pancreatic tumors such as PAC and PNET [16, 17]. From the clinical point of view, the differentiation of SPT from PAC or from PNET is quite important, because their prognosis and treatment are quite different. Patients with SPT can benefit from resection of both the primary tumor and metastatic lesions in case that SPT becomes malignant and metastatic [1, 18], with much better prognosis than PAC and PNET [19, 20]. Unfortunately, we found it impossible to differentiate between these kinds of tumors if only based on higher SUVmax values of more than 3.5. But still, it was important that SPT always exhibits hyperaccumulation of ^{18}F-FDG, while PAC and PNET may show lower SUVmax equal or lower than 2.6 in 14% and in 21.4% of cases, respectively.

In our study, the incidence of malignant SPT was 5/18, in good proportional agreement with previous studies [18, 21]. Malignant pancreatic tumors are more often found in old and male patients [21], and often located in the tail of the pancreas having a size of more than 6cm [22]. A relationship between SUV and histological malignancy was suggested according to a study of 14 patients, among which 6 underwent a ^{18}F-FDG PET scan [5]. In that study, tumors with microscopic venous and perineural invasion were found to have more increased ^{18}F-FDG uptake as compared with tumors without these characteristics. Our results seemed different, as the malignant tumors with local invasion and hepatic metastases exhibited relatively low uptake of ^{18}F-FDG compared with the tumors without the above characteristics. Furthermore, only the recurrent tumor 4 years after resection of the primary exhibited avid ^{18}F-FDG uptake. Considering the small number of malignant SPT patients in the previous as well as in our studies, further studies of ^{18}F-FDG-PET are needed to clarify the relationship between SUV and SPT potential for malignancy.

There were some limitations in our study. First, it was retrospective. Second, the SPT patient number was still small, though it is the largest till today reported cohort with ^{18}F-FDG PET/CT results. Third, we did not discuss the CT part of our PET/CT study, because the CT scan integrated in our PET/CT procedure was used mainly for attenuation and location using a very low dose, and thus with poor quality. Furthermore, we did not include the dynamic CT and MRI imaging results on our patients, because many such studies have already been reported, illustrating the radiological features of SPT as well as their differentiation from other pancreatic tumors [17, 23, 24]. Other PET tracers such as ^{68}Ga-DOTA-TOC, specific for somatostatin receptors in PNET and such as the ^{18}F-FLT specific for cellular proliferation in PAC patients, respectively, may help to differentiate between different pancreatic tumors [25, 26].

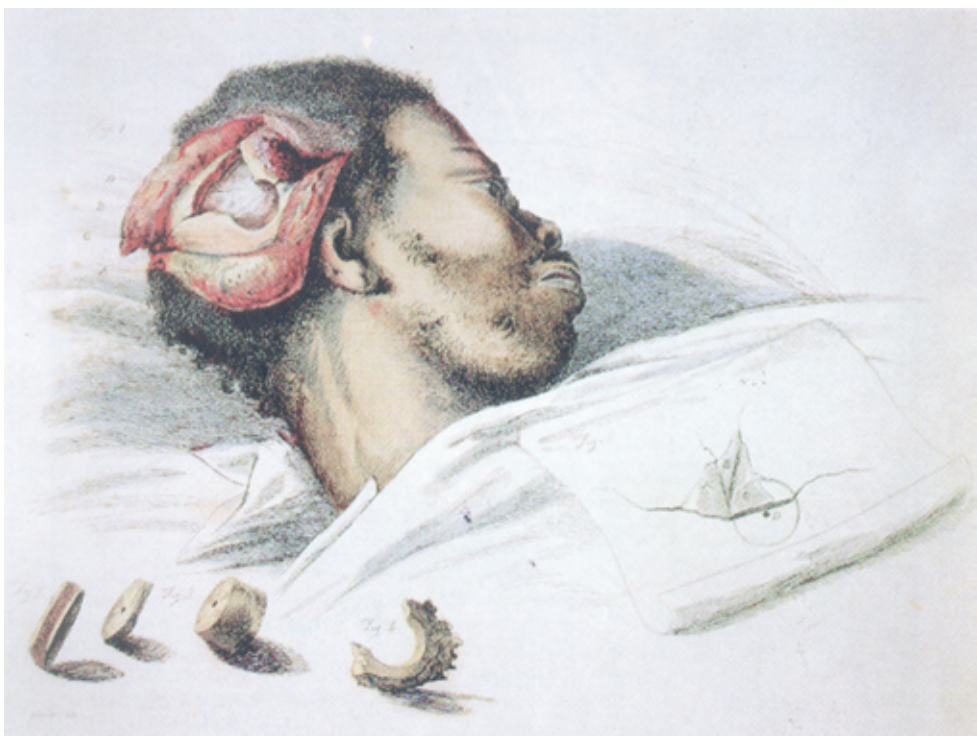
In conclusion, our study showed that SPT tumors either at a benign or malignant stage, hyperaccumulated ^{18}F-FDG PET, and was thus difficult to differentiate them from PAC and PNET if only based on high SUVmax. On the other hand, 14% of PAC tumors and 21.4 of PNET showed lower SUVmax of less or equal to 2.6 or to 2.5, respectively and in this aspect differed from SPT.

The authors declare that they have no conflicts of interest.

Bibliography

1. Papavramidis T, Papavramidis S. Solid pseudopapillary tumors of the pancreas: review of 718 patients reported in English literature. *J Am Coll Surg* 2005; 200: 965-72.
2. Lee JK, Tyan YS. Detection of a solid pseudopapillary tumor of the pancreas with F-18 FDG positron emission tomography. *Clin Nucl Med* 2005; 30: 187-8.
3. Sato M, Takasaka I, Okumura T et al. High F-18 fluorodeoxyglucose accumulation in solid pseudopapillary tumors of the pancreas. *Ann Nucl Med* 2006; 20: 431-6.
4. Shimada K, Nakamoto Y, Isoda H et al. F-18 fluorodeoxyglucose uptake in a solid pseudopapillary tumor of the pancreas mimicking malignancy. *Clin Nucl Med* 2008; 33: 766-8.
5. Nakagohri T, Kinoshita T, Konishi M et al. Surgical outcome of solid pseudopapillary tumor of the pancreas. *J Hepatobiliary Pancreat Surg* 2008; 15: 318-21.
6. Wu J. Solid pseudopapillary tumor of the pancreas: Imaging diagnosis and sifferentation. *Chinese J Med Imag Technol* 2009; 25: 642-5.
7. Uchida M. A case of solid pseudopapillary neoplasm presenting with strong fluorodeoxyglucose uptake on positron emission tomography mimicking malignancy. *Pancreatology* 2010; 10: 71.
8. Ishikawa T. A case of solid-pseudopapillary neoplasm, focusing on contrast-enhanced endoscopic ultrasonography. *J Med Ultrasonics* 2011; 38: 209-16.
9. Pasquali C. Frantz's Tumor of the pancreas in males. Report on two cases. *Europ J Surg Oncol* 2011; 37: S9.
10. van Kouwen MC, Jansen JB, van GH et al. FDG-PET is able to detect pancreatic carcinoma in chronic pancreatitis. *Eur J Nucl Med Mol Imaging* 2005; 32: 399-404.
11. Kauhanen SP, Komar G, Seppanen MP et al. A prospective diagnostic accuracy study of ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Ann Surg* 2009; 250: 957-63.
12. Higashi T, Saga T, Nakamoto Y et al. Diagnosis of pancreatic cancer using fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET)-usefulness and limitations in "clinical reality". *Ann Nucl Med* 2003; 17: 261-79.
13. Adams S, Baum RP, Hertel A et al. Metabolic (PET) and receptor (SPET) imaging of well- and less well-differentiated tumours: comparison with the expression of the Ki-67 antigen. *Nucl Med Commun* 1998; 19: 641-7.
14. Junik R, Drobik P, Malkowski B et al. The role of positron emission tomography (PET) in diagnostics of gastroenteropancreatic neuroendocrine tumours (GEP NET). *Adv Med Sci* 2006; 51: 66-8.
15. Buetow PC, Buck JL, Pantongrag-Brown L et al. Solid and papillary epithelial neoplasm of the pancreas: imaging-pathologic correlation on 56 cases. *Radiology* 1996; 199: 707-11.

16. Yao XJY, Zeng MRS, Yang B. Solid pseudopapillary tumor of the pancreas: cross-sectional imaging and pathologic correlation. *Pancreas* 2010; 39: 486-91.
17. Yu MH, Lee JY, Kim MA et al. MR imaging features of small solid pseudopapillary tumors: retrospective differentiation from other small solid pancreatic tumors. *Am J Roentgenol* 2010; 195: 1324-32.
18. Kim CW, Han DJ, Kim J et al. Solid pseudopapillary tumor of the pancreas: can malignancy be predicted. *Surgery* 2011; 149: 625-34.
19. Wray CJ, Ahmad SA, Matthews JB et al. Surgery for pancreatic cancer: recent controversies and current practice. *Gastronenterology* 2005; 128: 1626-41.
20. Franko J, Feng W, Yip L et al. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology and outcomes in 2,158 patients. *J Gastrointest Surg* 2010; 14: 541-8.
21. Kang CM, Kim KS, Choi JS et al. solid pseydopapillary tumor of the pancreas suggesting malignant potential. *Pancreas* 2006; 32: 276-80.
22. Yin Q, Wang M, Wang C et al. Differentation between benign and malignant solid pseydopapillary tumor of the pancreas by MDCT. *Eur J Radiol* 2012; 81: 3010-8.
23. Baek JH, Lee JM, Kim Sh et al. Small (<or-3cm) solid pseudopapillary tumors of the pancreas at multiphasic multidetector CT. *Radiology* 2010; 257: 97-106.
24. Sunkara S, Williams TR, Myers DT et al. Solid pseudopapillary tumours of the pancreas: spectrum of imaging findings with histopathological correlation. *Br J Radiol* 2012; 85: e1140-4.
25. Kumar R, Sharma P, Garg P et al. Role of ^{68}Ga-DOTATOC PET-CT in the diagnosis and staging of pancreatic neuroendocrine tumours. *Eur Radiol* 2011; 21: 2408-16.
26. von Forstner C, Egberts JH, Ammerpohl O et al. Gene expression patterns and tumor uptake of ^{18}F-FDG, ^{18}F-FLT and ^{18}F-FEC in PET/MRI of an orthotopic mouse xenotransplantation model of pancreatic cancer. *J Nucl Med* 2008; 49: 1362-70.



Anonymous: Brain surgery