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Comparison of endoscopic ultrasound guided fine needle aspiration and PET/CT in preoperative diagnosis of pancreatic adenocarcinoma

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ABSTRACT

Background: Endoscopic ultrasound guided fine needle aspiration (EUS-FNA) is the procedure of choice to investigate and sample pancreatic masses for the preoperative diagnosis of pancreatic ductal adenocarcinoma (PDAC). The role of ^{18}fluoro-deoxyglucose positron emission tomography/computed tomography (PET/CT) in PDAC is debated. This study evaluates the role of EUS-FNA as compared to PET/CT in the preoperative evaluation of PDAC.

Methods: Preoperative evaluation by PET/CT and EUS-FNA was performed on 25 patients with pancreatic solid lesions, who underwent a subsequent Whipple procedure or partial pancreatic resection.

Results: This series included 19 PDACs and 6 non-PDACs including 1 metastatic breast ductal adenocarcinoma, 2 low grade neuroendocrine tumors, 2 chronic pancreatitis and 1 gastrointestinal tumor abutting the pancreas. EUS-FNA correctly diagnosed 18 of 19 PDACs, 1 metastatic breast ductal adenocarcinoma and all 5 of the other non-PDAC cases. One case of well differentiated PDAC was negative on EUS-FNA. PET/CT provided excellent size and was positive in 14 of 19 PDACs and the metastatic breast ductal adenocarcinoma. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for EUS-FNA in diagnosis of selected pancreatic tumors were 91%, 100%, 100%, 50% and 92%, respectively, while they were 65%, 100%, 100%, 20% and 68% for PET/CT, respectively.

Conclusions: Compared to PET/CT, EUS-FNA has a higher sensitivity and accuracy for preoperative diagnosis of PDAC. However, PET/CT provides excellent size, volume and stage information. A combination of both PET/CT and EUS will better help guide diagnosis and treatment of pancreatic adenocarcinoma.

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Introduction

Pancreatic cancer is the fourth leading cause of cancer death in the USA. In 2015, the estimated incidence of pancreatic cancer in the United States was 48,960 cases, and an estimated 40,560 patients died from the disease [1]. Despite developments in detection and management of pancreatic cancer, only about 7% of

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patients will be alive 5 years after diagnosis. This low rate is partly because 80–85% of patients present with advanced, unresectable disease [2]. Thus, successful therapy depends to a great extent on early diagnosis. Currently, tri-phasic pancreatic-protocol CT is the imaging procedure of choice for the initial evaluation, which provides about 80% accuracy for prediction of resectability [3]. Tissue biopsy is recommended to confirm the radiological findings and to rule out benign pancreatic lesions including mass-like autoimmune pancreatitis. A biopsy of the pancreatic mass is most often accomplished by means of endoscopic ultrasound guided fine needle aspiration (EUS-FNA) [3,4]. The sensitivity of EUS-FNA for solid pancreatic masses ranges from 64% to 96% in meta-analyses, with a specificity of over 95% [5,6]. Traditionally, 90% of primary solid pancreatic malignant tumors are shown to be pancreatic ductal carcinoma (PDAC) [7,8], but with the increasing use of imaging that detects smaller lesions, PDAC accounts for only 60%–70% [9].

Positron emission tomography/computed tomography (PET/CT), an advanced noninvasive imaging technique, is extensively used for tumor staging and detection of distant metastases [10–12]. PET/CT is based on the increased uptake and metabolism of glucose by tumor cells compared with normal cells. PET/CT images are analyzed visually and semi-quantitatively by calculating maximum standardized uptake values (SUVs). A focal uptake above SUV thresholds (e.g. SUV >2.5) is generally considered positive, although the setting of positive value varies among different medical centers [13]. However, the SUV threshold for cancer diagnosis can be raised to 3.0 to achieve a positive predictive value of 1.0 [14]. Although the National Comprehensive Cancer Network (NCCN) notes that in the diagnosis of PDAC, PET/CT is not superior to CT due to the image resolution and contrast issues [15], the role of PET/CT in the pre-operative diagnosis of PDAC is still under debate [16].

In the present study, we evaluated the impact of PET/CT on the preoperative evaluation of patients with solid pancreatic masses. The results of PET/CT were compared to both EUS-FNA and the gross and microscopic findings of the resected pathologic specimens.

Materials and methods

This retrospective study was approved by the Cedars-Sinai Medical Center's Institutional Review Board. A computer based search was used to identify patients who underwent both PET/CT and EUS-FNA of solid pancreatic masses and subsequent pancreatic resections between July 2008 and Jan 2013. Two interventional gastroenterologists (SL and LJ) performed the vast majority of biopsies during this entire period. Patients' demographic data, pre-operative PET/CT and EUS-FNA, and pathology of surgical resections were obtained from the electronic medical record (Table 1).

EUS-FNA was performed by using Olympus array echoendoscopes. The patients underwent EUS procedures with monitored anesthesia care (MAC). The sampling was performed by using a 22 or 25-gauge FNA or FNB (fine needle biopsy) needle at the discretion of the endoscopists. The aspirates were expelled onto slides, smeared, and air-dried or fixed in 95% alcohol. An on-site cytopathologist was present to evaluate smears for adequacy and preliminary diagnosis. Fixed smears were stained with Papanicolaou technique. Papanicolaou-stained slides as well as hematoxylin-eosin stained cell block sections available were used for evaluation to render a final cytologic diagnosis [17]. PET/CT scans were acquired with on a whole-body 64-slice PET/CT scanner (Biograph-64 TruePoint PET/CT; Siemens Medical, Erlangen, Germany) in our institution. After fasting for at least 6 h, patients received an intravenous injection of FDG. Dose of 18F-FDG was calculated based on body mass, using a reference of 370 MBq for 65 kg and not exceeding 555 MBq. Approximately 60 min after injection, CT imaging from the eyebrows to the mid thighs were performed with the following parameters: 0.5 s/rotation, 100 mA tube current, 120 kVp tube voltage, 5 mm slice thickness, and 4.25 mm slice interval.

Table 1
Patients' demographics, PET, EUS-FNA and histology of resection.

Patient No.	Age (yrs.)	sex	Neoadjuvant	PET SUV(max)	PET Tumor size [cm]	EUS-FNA diagnosis	Tumor location	Tumor size [cm]	Grade	Resection diagnosis
1	58	F	Y	6.9	2.6	PDAC	head	MF[a]	1	PDAC
2	68	F	Y	9.6	2.1	PDAC	head	MF[a]	1	PDAC
3	74	M	N	1.7	n/a	PDAC	head	2.3	1	PDAC
4	63	M	Y	3.9	1.6	PDAC	head	MF[a]	2	PDAC
5	50	M	Y	10.9	2.6	PDAC	head	MF[a]	2	PDAC
6	69	F	N	2.0	n/a	PDAC	head	1.0	2	PDAC
7	79	M	N	2.6	n/a	PDAC	body	1.5	2	PDAC
8	75	F	N	5.9	3.3	PDAC	head	2.1	2	PDAC
9	72	M	N	2.2	n/a	PDAC	head	2.6	2	PDAC
10	82	F	N	3.0	2.4	PDAC	head	3.0	2	PDAC
11	64	F	Y	1.9	n/a	Benign	tail	3.2	2	PDAC
12	79	F	Y	3.3	4	PDAC	head	4.6	2	PDAC
13	83	F	N	8.7	3	PDAC	tail	4.7	2	PDAC
14	71	F	N	5.3	4.1	PDAC	head	4.9	2	PDAC
15	73	M	Y	7.5	7.8	PDAC	tail	5.2	2	PDAC
16	58	F	N	10.4	1.7	PDAC	head	1.6	3	PDAC
17	74	F	N	3.5	2.5	PDAC	head	2.0	3	PDAC
18	73	M	N	8.0	2.2	PDAC	tail	3.5	3	PDAC
19	64	F	N	6.9	1.8	PDAC	tail	4.5	3	PDAC
20	50	F	N	10.3	1.7	Metastatic breast duct cancer	tail	1.9	3	Metastatic breast cancer
21	70	M	N	2.7	n/a	Mild atypical epithelial cells	head	n/a	n/a	chronic pancreatitis
22	57	M	N	2.9	n/a	Negative	head	n/a	n/a	chronic pancreatitis
23	51	F	N	2.9	n/a	Negative	tail	2.0	low grade	GIST abuts the pancreas
24	60	F	N	2.3	n/a	PNET	tail	1.4	low grade	PNET
25	41	F	N	2.8	n/a	PNET	head	2.0	low grade	PNET

[a] Only microscopic foci of the tumor present after neoadjuvant therapy; n/a: PET SUV<3.0, no tumor identified by imaging study.

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PET images were acquired using 4 mm slice thickness and 3 min emission scan/position. Acquired images were then reconstructed and evaluated using the oncology software, Velocity Advanced Imaging (Varian, Palo Alto, CA). 18-F FDG uptake was measured by the standard uptake value (SUV), which represents the radioactivity of the tissue for a given time, mass and initial tracer injection. The maximum uptake value (SUVmax) was used to characterize the tumor metabolic activities for a given volume of interested. In our center, a nodular FDG uptake with a SUV superior to 3.0 was typically considered as malignant. The PET-defined tumor size was measured as the average diameter of the volume of interest with SUV >3.0 in tumor regions.

Based on clinical presentations and an indeterminate preliminary cytologic diagnoses, the patients were further subjected to core needle biopsies. All patients underwent surgical excisions of the pancreatic lesions. The specimens were fixed in 10% formalin, processed in paraffin-embedded blocks, and hematoxylin-eosin-stained sections were available for histopathologic evaluation.

Diagnostic performances of EUS and PET/CT for the tumor diagnosis and staging were determined by calculating sensitivity and specificity, accuracy, negative (NPV) and positive (PPV) predictive values for each investigation, respectively. The 95% confidence interval was calculated. Student's *t*-Test and McNemar's exact test were performed. $P < 0.05$ was considered statistically significant.

Results

Twenty-five patients met criteria (Table 1). They consisted of 10 males and 15 females, with a median age 71 years (age range: 42–86 years). Nineteen of the twenty-five patients (76%) were found to have PDAC and 1 metastatic breast ductal adenocarcinoma. Among the 19 patients, 8 had neoadjuvant therapy. The remaining 5 patients had either low grade tumors or benign lesions including pancreatic neuroendocrine tumor (PNET) in 2 patients, gastrointestinal stromal tumor (GIST) in 1 patient and chronic pancreatitis in 2 patients.

PET/CT was positive in 14 of the 19 PDACs (Table 1), no metastatic foci was demonstrated in any case. EUS-FNA was positive in 18 of the 19 PDACs including all the 14 PET/CT positive cases. Of the 5 PET/CT-negative PDACs, four were moderately differentiated and one was well-differentiated, the latter was also negative on EUS-FNA. Examples of a PET/CT positive and FNA positive PDAC (Fig. 1), and of a PET/CT negative and EUS-FNA positive (Fig. 2) are shown.

In all 6 non-PDAC patients, PET/CT was negative except for the one with metastatic breast cancer. These include two with well differentiated pancreatic neuroendocrine tumors (PNET), which were both correctly diagnosed by EUS-FNA. Cytologically, there was a monotonous appearance of the tumor cells with plasmacytoid features, salt and pepper chromatin and inconspicuous nucleoli. The gross appearance of the tumor is solid with a tan cut surface and histologically the tumor was well differentiated neuroendocrine tumor, low grade. The PET/CT in the PNET was 2.3 and 2.8 respectively.

The sensitivity, specificity, positive predictive value, negative predictive value and accuracy for EUS-FNA in diagnosis of selected pancreatic tumors were 91%, 100%, 100%, 50% and 92%, respectively, while they were 65%, 100%, 100%, 20% and 68% for PET/CT, respectively. The sensitivity and accuracy of EUS-FNA were higher than that of PET/CT (Table 2). Both EUS-FNA and PET/CT showed 100% specificity and positive predictive value in our study. These findings suggest that EUS-FNA has an important role in the preoperative workup of solid pancreatic lesions.

We then compared the tumor size at PET/CT to the gross tumor size at resection. The tumor size was not able to be measured in four patients due to neoadjuvant therapy, including two well-differentiated PDACs and two moderately differentiated PDACs.

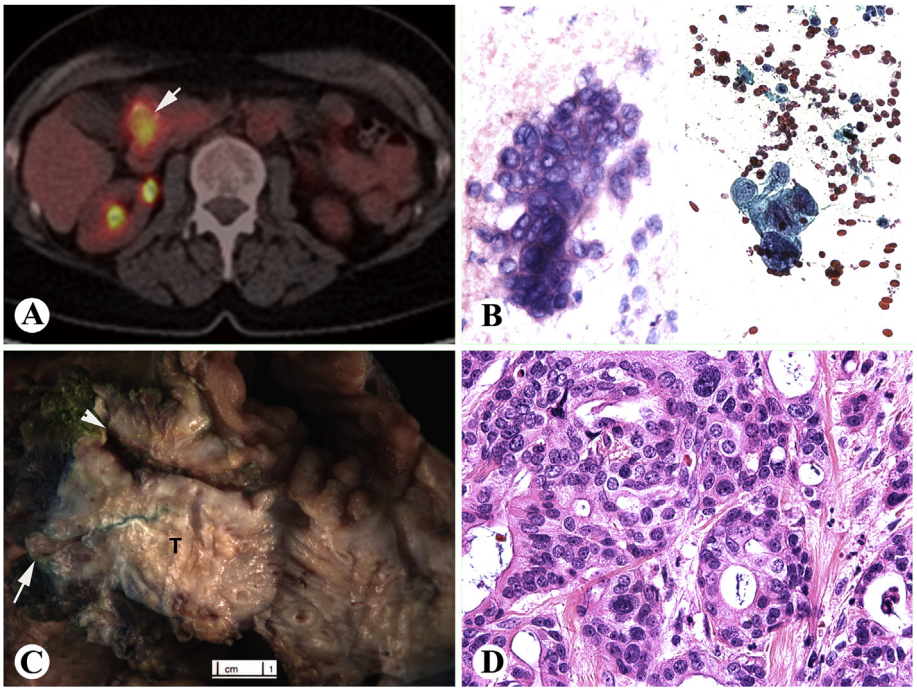

Fig. 1. Pancreatic head PDAC diagnosed by both PET/CT and EUS-FNA: A. the tumor (arrow) is PET-CT positive; B. EUS-FNA Diff-quick stained smear (left, ×400) and Pap-stained smear (right, ×400) show disarray of the cells with nuclear atypia and increased nuclear to cytoplasmic ratio; C. Grossly, bivalving of the pancreatic head through the common bile duct (arrow head) and pancreatic duct (arrow) showing a white to tan, ill-defined fleshy lesion (T) causing dilatation of the common bile duct and distal pancreatic duct; D. Histologically, the tumor is moderately differentiated adenocarcinoma with desmoplasia (×400).

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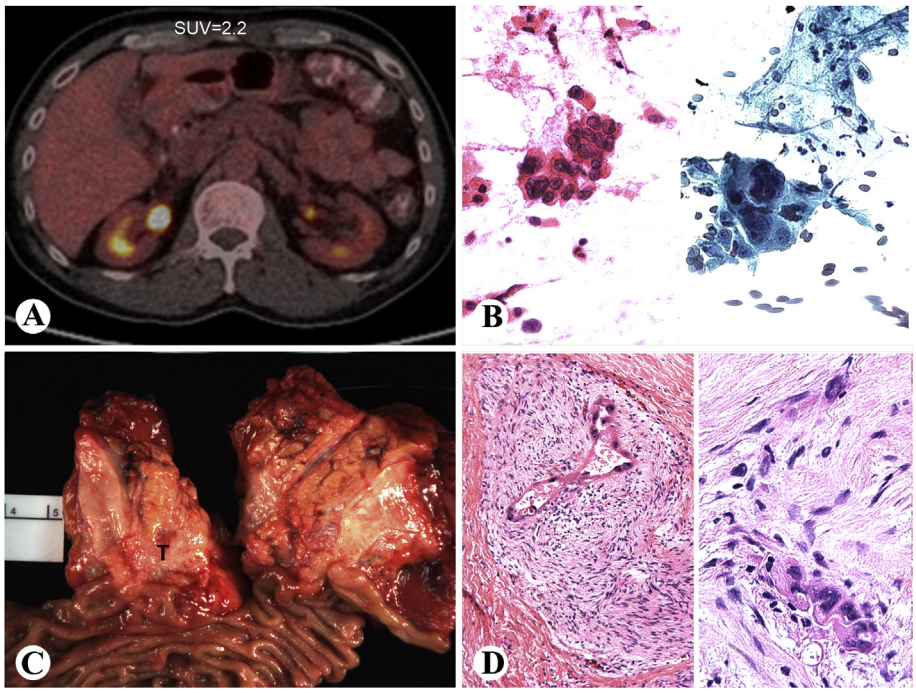

Fig. 2. Pancreatic head PDAC diagnosed by EUS-FNA: A, Negative PET-CT scan; B EUS-FNA HE stained smear (left, ×400) and Pap-stained smear (right, ×400) show nuclear enlargement, anisonucleosis and overlapping; C. Bivalving of the pancreatic head through the common bile duct and pancreatic duct showing an ill-defined fleshy lesion (T). D. Histologically, an atypical gland present in the nerve (left, ×200) and focus of atypical epithelial cells with nuclear atypia present in the fibrous tissue (right, ×400).

These four patients had microscopic foci of PDAC. These patients with PDAC who did not receive neoadjuvant therapy had an average tumor size by PET/CT of 2.98 cm, and the gross tumor size at resection was 3.11 cm. There was no significant difference by Student's *t*-Test (2.98 ± 0.81 Versus 3.11 ± 0.79, p = 0.81).

Discussion

Our study showed that compared to PET/CT, EUS-FNA has a higher sensitivity, negative predictive value and accuracy for preoperative diagnosis of PDAC, however, PET/CT provides excellent size and volume and staging information. A combination of PET/CT and EUS-FNA preoperatively may help better guide surgical decisions regarding resectability.

Since it was developed in 1992, EUS-FNA has emerged as the primary modality for cytopathologic confirmation of pancreatic cancer, especially for smaller lesions (<3 cm) [6,18,19]. It is also useful in patients with obstructive jaundice and no mass or an atypical/questionable mass seen on CT. The need for a preoperative biopsy before proceeding to surgery is still controversial; however, is considered mandatory in patients for whom neoadjuvant therapy is considered [20]. In our center, with a robust interventional gastroenterologist group, EUS-FNA is usually obtained prior to surgery, even for those patients with classical findings of PDACs for PDAC on imaging. On the basis of current literature, EUS-FNA has the best overall operating characteristics (sensitivity, specificity, diagnostic accuracy, and negative and positive predictive value), although these characteristics are variable depending on different centers. According to recent meta-analysis, the sensitivity and specificity of EUS-FNA were over 85% and 95% respectively [5,6]. The variation for EUS-guided FNA of the pancreas probably reflects the different levels of experience among institutions. The current study showed that in our center, the sensitivity, specificity, PPV, NPV and accuracy were 91%, 100%, 100%, 50% and 92% respectively for the diagnosis of pancreatic tumor, which has a higher sensitivity than recent studies. We contribute this to 1) the presence of experienced on-site cytopathologists for rapid onsite evaluation and 2) experienced EUS service in the large medical center. Recent studies showed that an on-site cytopathological evaluation reduces the number of inadequate FNA samples and improves the sensitivity and overall accuracy of EUS-guided FNA for the cytological diagnosis of solid pancreatic masses. Endoscopic ultrasound criteria for malignant tumor included hypoechoic inhomogeneous mass with irregular margins [21]. As EUS-FNA of pancreatic mass lesions are probably the most technically demanding EUS skills, a formal EUS-FNA training will also increase the diagnostic accuracy of solid pancreatic mass [22].

We had one false negative EUS-FNA PDAC case in our study. It is reported that at least 1 in 10 EUS-FNAs result in false-negative cytology [23]. Studies showed that the false negative cases are mostly due to contamination of duodenal or gastric epithelium during the procedure, that is, sampling error, rather than interpretative error [24]. The nature, consistency and location of the lesion, the site of FNA within a lesion and the needles used for biopsy also play significant roles in the quality of the specimen obtained for cytologic interpretation [25]. Recent studies suggested that a 25G needle is more sensitive than 22G in diagnosing

Table 2
Comparison of the sensitivity and specificity of EUS-FNA and PET/CT in preoperative diagnosis of the pancreatic tumors.

	EUS-FNA	PET/CT	p-value
Sensitivity (%)	91.3 (72.0–98.9)[a]	65.2 (42.7–83.6)[a]	0.031[b]
Specificity (%)	100	100	NA
Accuracy (%)	92.0 (74.0–99.0)[a]	68.0 (46.5–85.1)[a]	0.031[b]

[a] 95% CI.
[b] McNemar's test for related proportions.

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pancreatic malignancy [26–28]. Over all, a negative FNA diagnosis cannot override CT findings that demonstrate a probable pancreatic malignancy. A repeat EUS-FNA or core biopsy after communication with a cytopathologist may be necessary in these patients with high suspicion of malignancy to increase the diagnostic accuracy.

In recent years, PET/CT has been increasingly used in the diagnosis, staging, and post-treatment surveillance of many types of malignancy, such as colorectal cancer and pancreatic cancer [29]. The performance of PET/CT for the diagnosis of PDAC is reported to range between 85% and 100% for sensitivity, 67%–99% for specificity, and 85%–93% for accuracy [24]. In our study, the sensitivity and specificity were 65% and 100% respectively in diagnosing selected pancreatic tumor patients. PET/CT was not able to detect any non-PDAC patients including low grade tumors and chronic pancreatitis. This indicated that PET/CT may be better in diagnosing PDAC patients than non-PDAC patients. Both the strengths and weaknesses of PET/CT are evident for pancreatic cancer staging [16]. In patients with suspected PDAC, PET/CT has a high sensitivity for M staging, however, it has poor sensitivity for N staging because the regional lymph nodes are too close to the primary tumor with high signal intensity, and of low sensitivity to detect small lymph-nodes [13,30]. Another weakness of PET/CT is the variability of SUV value between different centers with different calculations, as shown by a recent study [31]. However, some centers are studying methods that may reduce variability, such as semiautomatic PET/CT analysis or automated FDG dose administration [32,33].

Studies have shown that there is statistically significant difference in the SUV value of PET/CT between patients with resectable and unresectable disease, and in overall survival between patients with high and low SUV [34,35]. In our study, because we chose patients who underwent surgery, we were not able to compare resectable and unresectable diseases. However, we found no significant difference between the tumor size at resection and the size of tumor measured from the PET/CT, which indicated that PET/CT can provide good size and volume information. This may be helpful for surgeons to make the surgical decision.

There are few studies that directly compared EUS-FNA and PET/CT scan in diagnosing pancreatic cancer. In a meta-analysis, the pooled sensitivity for PET/CT (88.4%) was higher than EUS-FNA (81.2%), however, the pooled specificity for EUS-FNA (93.2%) was significantly higher than PET/CT (83.1%). They concluded that, PET/CT was a highly sensitive and EUS-FNA was a highly specific modality in diagnosing patients with pancreatic cancer [36]. In our study, EUS-FNA has better sensitivity than PET/CT; however, the specificity of EUS-FNA is 100%, same to PET/CT, which we attributed to our relatively high setting of positive SUV and our experienced endoscopists and cytopathologists to detect cancer by EUS-FNA (Table 2). The advantage of our study over the previous studies is that the results of the resection provided a reference diagnosis, or 'gold standard', as all our patients underwent PET/CT, EUS-FNA and subsequent surgery.

In conclusion, we confirmed the high sensitivity and specificity of EUS-FNA, in a large institution with on-site experienced cytopathologists and subspecialist, expert endoscopists. Both EUS-FNA and PET/CT have 100% positive predictive value and specificity in our study. The sensitivity and accuracy of EUS-FNA are both higher than PET/CT. However, prior studies have described false positive FNA results, and particularly in centers with lesser degrees of experience, it may be useful in some situations to have a confirmatory positive PET/CT. Although PET/CT assists with benign versus malignant, it does not provide information on histologic type. PET/CT, however is non-invasive and provides accurate information on tumor size and tissue metabolic activities. We think that PET/CT and EUS play different roles during different conditions in diagnosing patients suspected with pancreatic cancer, and a combination of EUS-FNA and PET/CT preoperatively will increase the sensitivity and help surgeons to guide their surgical decision. As we have relatively low number of patients, more studies directly comparing EUS-FNA and PET/CT are needed to further reveal the role of EUS-FNA and PET/CT in the diagnosis and treatment of pancreatic cancer.

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