

[68Ga]Ga-DOTA-FAPI-04 and [18F]FDG PET/CT in the Assessment of Pancreatic Tumors: A Comparison Study

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Abstract

Purpose Pancreatic tumors are characterized by abundant desmoplasia including cancer-associated fibroblasts (CAFs) that express fibroblast activation protein (FAP). Gallium-68-labeled fibroblast-activating protein inhibitor (FAPI) is promising probe for positron emission tomography/computed tomography (PET/CT) imaging of various types of cancers. This work aims to compare the diagnostic performances of [⁶⁸Ga]Ga-DOTA-FAPI-04 and [¹⁸F]FDG PET/CT in detecting primary pancreatic tumors and metastasis prospectively.

Methods We collected patients with pancreatic tumors during May 1 to August 1, 2020. All the patients underwent [⁶⁸Ga]Ga-DOTA-FAPI-04 and [¹⁸F]FDG PET/CT within 5 days at diagnosis, recurrence detection or therapeutic evaluation. The clinical information, PET/CT image characteristics, maximum standardized uptake (SUV_{max}) value of pancreatic tumors and metastases, target-to-background ratio (TBR) of the liver metastases were collected for analysis. The pathological results or follow-up clinical diagnostic results were obtained.

Results A total of 45 patients (18 females and 27 males; median age of 62.4 years; range: 42 - 84 years) were enrolled for analysis, including 37 patients with pancreatic cancers and 8 patients with other types of pancreatic tumors. [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT detected abnormal pancreatic uptake in 36 patients (97.30%) with a SUV_{max} of 14.0 ± 5.4 (range 5.4 to 25.1), while 34 patients (91.89%) with abnormal pancreatic uptake with a SUV_{max} of 7.6 ± 3.9 (2.9 to 20.4) were detected by [¹⁸F]FDG PET/CT. Moreover, [⁶⁸Ga]Ga-DOTA-FAPI-04 detected more lymph nodes (LNs) and metastases than [¹⁸F]FDG. The SUV_{max} of [⁶⁸Ga]Ga-DOTA-FAPI-04 in LNs and TBR of liver metastases was higher than that of [¹⁸F]FDG (LNs: 6.1 ± 2.7 vs. 4.4 ± 1.6 , TBR: 5.0 ± 3.1 vs. 2.9 ± 1.4 $p < 0.0001$), respectively. [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT successfully unregulated the clinical stage in 2 patients, visualized recurrence in 1 patient, and detected residual active tumor tissues in 2 patients with discordant imaging results (FAPI⁺/FDG⁻). In addition, there was nearly no [⁶⁸Ga]Ga-DOTA-FAPI-04 or [¹⁸F]FDG uptake in pancreatic cystic neoplasms. Most of neuroendocrine neoplasms showed negligible [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake.

Conclusion Compared with [¹⁸F]FDG PET/CT, [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT detected pancreatic tumors and associated metastases with a higher sensitivity and SUV_{max} value. However, false-positive uptake of [⁶⁸Ga]Ga-DOTA-FAPI-04 in pancreatitis, cholangitis, some benign liver disease, and inflammatory LNs was also prominent.

Introduction

Pancreatic tumors consist of a heterogeneous group of lesions, such as adenocarcinoma, neuroendocrine neoplasms (NEN), and pancreatic cystic neoplasms. Pancreatic ductal adenocarcinoma (PDAC) accounts for above 85% and the incidence continues to increase over the past decade [1]. Unfortunately, the majorities of patients with PDAC are diagnosed with advanced stages. More than 80%

of the patients with surgery or adjuvant chemotherapy experienced recurrence in a short time [2]. The 5-year relative survival rate for PDAC was 3% when other organs were involved and the corresponding median survival was only 3 months without treatment [1, 3]. Consequently, accurate diagnosis, staging, and early detection of the recurrence or metastasis is essential in the precise management of pancreatic tumors.

In the clinical practice, contrast enhanced computerized tomography (CT) and magnetic resonance imaging (MRI) are mostly used for the diagnosis of pancreatic tumors [4]. They can detect metastatic lymph nodes (LNs) or liver metastases with high resolution. Compared with CT or MRI, positron emission tomography/computed tomography (PET/CT) imaging with [^{18}F]FDG is not recommended with high priority in the guideline, but it has great advantages in clinical staging, therapeutic evaluation, and detection of recurrence. Some studies have also demonstrated that [^{18}F]FDG uptake of pancreatic tumors is associated with poor prognosis [5–7]. However, its specificity is relative low due to that the false positive uptake in inflammatory diseases. And [^{18}F]FDG PET/CT has limited role in detecting LN involvement of PDAC [8]. Moreover, [^{18}F]FDG uptakes is generally low in some types of pancreatic NENs [9].

Cancer associated fibroblasts (CAFs) and extra-cellular fibrosis constitute nearly 90% of the tumor [10]. And the expression of fibroblast-activating protein (FAP) is relatively high on CAFs [11]. Recent studies have illustrated that ^{68}Ga -labeled FAP inhibitor (FAPI) is promising for noninvasively imaging of various types of tumors [12–14]. Furthermore, the high expression of FAP in some tumors is associated with poor prognosis and response to chemotherapy [15, 16]. Pancreatic cancer is one of the tumors with the highest desmoplastic reaction and intermediate radiolabeled-FAPI uptake. Röhrich *et al.* have showed that [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT could change the staging and detect the recurrences of pancreatic cancer with high sensitivity then CT [17]. One of the great advantages of [^{68}Ga]Ga-DOTA-FAPI-04 is the high tumor-to-background ratio (TBR), which may help to depict more primary and metastatic tumors. Therefore, [^{68}Ga]Ga-DOTA-FAPI-04 is a promising alternative to [^{18}F]FDG for the assessment of tumors with better performance.

To the best of our knowledge, there is no evidence demonstrating the differential diagnostic value of [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT and [^{18}F]FDG PET/CT in diagnosing pancreatic tumors. In this prospective study, we aim to investigate the diagnostic performances of sequential [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT in detecting primary pancreatic tumors and the metastases.

Materials And Methods

Patients selection and study design

The study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center (IRB protocol #ZS1810). All the subjects were provided written informed consent to receive [^{68}Ga]Ga-DOTA-

FAPI-04 PET/CT scanning. Patients were recruited from May 1 to August 1, 2020 at our hospital. The inclusion criteria were as follows: (1) patients with suspicious pancreatic tumors revealed by non-invasive imaging (CT, MR, or ultrasound); (2) patients with pancreatic cancer who have fulfilled chemotherapy within 1 month; (3) patients received surgery before and presented with elevated tumor markers. Exclusion criteria were: (1) the pancreatic tumor turned out to be metastatic lesion; (2) no abnormal uptake in post-surgical patients; (3) patients who can not fulfill [^{18}F]FDG or [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT scanning. The final diagnosis was determined by the pathological assessment of the surgically removed/biopsied tissues or clinical diagnosis based on radiological features, laboratory examinations, and clinical symptoms 6-month later.

Radiopharmaceuticals

Radiolabeling of [^{68}Ga]Ga-DOTA-FAPI-04 was performed according to the published method [12]. In brief, FAPI-04 was dissolved in NaAc solution, to which $^{68}\text{GaCl}_3$ was added. After pH adjustment with sodium acetate, the reaction mixture was heated to 100 °C for 10 min. [^{68}Ga]Ga-DOTA-FAPI-04 was processed by solid-phase extraction. The radiochemical purity was assessed by thin-layer chromatography (TLC). [^{18}F]FDG was manufactured by cyclotron (Siemens CTI, RDS Eclips ST, Knoxville, Tennessee, UA) at our department. The radiochemical purity of [^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG was both above 95%.

PET/CT scanning and image analysis

[^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT scans were conducted within 5 days. For [^{18}F]FDG PET/CT imaging, patients should fast for at least 6 h before the injection of [^{18}F]FDG (3.7 MBq/Kg) and the blood glucose levels should be less than 10 mmol/L. For [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT imaging, the injected activity was 132–187 MBq. The image acquisition was performed 60 min post-injection with the PET/CT scanner (Biograph 16 HR, Siemens Medical Systems, Erlangen, Germany). The spiral CT scan was conducted using a standardized protocol (120 kV, 140 mA, 3 mm slice thickness). Then PET scan was conducted with FlowMotion. PET data were reconstructed iteratively using an ordered-subset expectation maximization iterative reconstruction (OSEM) with CT data for attenuation correction.

[^{68}Ga]Ga-DOTA-FAPI-04 and [^{18}F]FDG PET/CT images were analyzed independently by two experienced nuclear medicine physicians by using the software (Taxus, Medivoly technology). Regions of interest (ROIs) were drawn and maximum standard uptake value (SUV_{max}) were automatically calculated in the ROI of the primary tumors, lymph nodes, and metastatic lesions.

Statistical analysis

All the statistical analyses were conducted using the Graphpad Prism7 software. [¹⁸F]FDG and [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake in the tumors, metastatic LNs, and distant metastases were compared using matched-pairs signed-rank test, respectively. Two-tailed *P* values < 0.05 was considered statistically significant.

Results

Clinical characteristics of the patients

Fifty-three patients were enrolled in the current prospective study. Eight patients were excluded for the analysis, five of which were with metastatic pancreatic tumors and three patients with no abnormal uptake. Finally, forty-five patients including 18 females and 27 males (median age of 62.4 years; range: 42–84 years) were included. Of the 45 patients, thirty-two patients received PET/CT scans for initial tumor diagnosis and staging, eight patients previously diagnosed with pancreatic cancer for therapy evaluation, and five patients for detecting the recurrence because of abnormally increased tumor markers. The scheme of the study was shown in Figure 1. Of the 45 patients, thirty-two were PDACs, three were intraductal papillary mucinous neoplasm (IPMN), two were benign lesions, two were NENs (one NET G2 and one NEC), one was autoimmune pancreatitis, and five patients were clinically diagnosed with pancreatic cancer after 6-month follow-up. Notably, one patient has two primary tumors (PDAC and lymphoma) simultaneously. The characteristics of the patients were shown in Table 1.

Table 1
The clinical characteristics of the enrolled patients

No. of patients		45
Age	Median (range)	62.4(42-84)
Sex	Men	27
	Female	18
Elevated tumor markers		
	CA199	30
	CA50	26
	CA242	20
	CA724	12
	CA125	16
	CEA	19
	NSE	2
Surgery	Post-surgery	7
	Pre-surgery	38
Disease type		
	Pancreatic cancer	37
	Benign lesions	2
	Autoimmune pancreatitis	1
	Neuroendocrine tumor	1
	Neuroendocrine carcinoma	1
	IPMN	3
Lesion location		
	Head	14
	Body	11
	Tail	13
Ways of diagnosis		
	Biopsy	22
	Surgery	13

Adverse event during the imaging studies

All the 45 patients tolerated well the [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT scanning. There were no drug-related pharmacologic effects or physiological responses. No abnormal symptoms were observed during and after the scanning.

Head-to-head comparison of [⁶⁸Ga]Ga-DOTA-FAPI-04 and [¹⁸F]FDG PET/CT in pancreatic cancer

We included 37 patients (32 patients with PDAC and 5 patients with clinically diagnosed malignancy) with [⁶⁸Ga]Ga-DOTA-FAPI-04 and [¹⁸F]FDG PET/CT imaging data for the analysis (Figure 2). Patient-based analysis was firstly conducted in this cohort. For the detection of primary pancreatic tumors, 34 patients (91.89%) were with abnormal [¹⁸F]FDG uptake ($SUV_{max} = 7.6 \pm 3.9$; range: 2.9–20.4) while elevated [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake was found in 36 patients (97.30%) ($SUV_{max} = 14.0 \pm 5.4$; range 5.4–25.1) accordingly. Two patients were with discordant results (FAPI⁺/FDG⁻). For the detection of LNs involvement, [¹⁸F]FDG PET/CT detected positive findings in 14 patients (37.83%). In comparison, whereas 19 patients (54.05%) with LN involvement were accurately diagnosed by [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT. The corresponding uptake in terms of SUV_{max} of the two tracers was 5.7 ± 1.4 and 8.0 ± 3.5 ($p < 0.0001$), respectively. A representative case was presented in Figure 3. When it comes to the metastatic lesions from PDAC, 18 patients with distant metastases had elevated [¹⁸F]FDG uptake ($SUV_{max} = 6.6 \pm 2.8$; range 3.5–13.8), 24 patients demonstrated FAPI-avid metastases with a higher SUV_{max} value (7.2 ± 3.3 , range 3.5–16) ($p < 0.0001$). However, no statistical difference was found between the uptake value ($p > 0.05$). These results demonstrate that PET/CT scanning with [⁶⁸Ga]Ga-DOTA-FAPI-04, but not [¹⁸F]FDG, detected more primary and metastatic PDAC lesions with increased uptake of the tracer.

For the lesion-based analysis, [¹⁸F]FDG PET/CT revealed 39 pancreatic tumors, 38 LNs, and 87 suspected lesions. The average SUV_{max} was 7.5 ± 3.7 (range 1.8–20.4), 4.4 ± 1.6 (range 2.0–7.9), and 5.8 ± 2.3 (range 3.0–13.8), respectively. [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT imaging detected 38 primary tumors with a higher SUV_{max} (13.5 ± 5.7 ; range 2.9–25.1, $p < 0.0001$). Strikingly, [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT delineated 67 LNs and 114 metastases. The SUV_{max} of [⁶⁸Ga]Ga-DOTA-FAPI-04 in LNs was higher than that of [¹⁸F]FDG (6.1 ± 2.7 vs. 4.4 ± 1.6 , $p = 0.0002$), but there was no statistical difference in the uptake of the two tracers in the metastases (5.8 ± 2.3 vs. 5.6 ± 2.5 , $p > 0.05$). The representative PET/CT images were presented in Figure 4.

The most common site of distant metastasis is the liver. Fifty-eight and 85 suspected liver lesions were found in [¹⁸F]FDG and [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT, respectively. There was no statistical significance in the uptake in terms of SUV_{max} (6.1 ± 2.4 vs. 5.8 ± 2.4 , $p > 0.05$). We also compared the TBR of the suspected liver metastases. The TBR of suspected liver metastases on [⁶⁸Ga]Ga-DOTA-FAPI-04 images was higher than that of [¹⁸F]FDG PET/CT (5.0 ± 3.1 vs. 2.9 ± 1.4 , $p < 0.0001$). There was no statistical difference in the number of the lesions and uptake in terms of SUV_{max} in the lung and bone metastases as detected by the two imaging options. [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT presented more peritoneal metastases with a higher SUV_{max} than [¹⁸F]FDG PET/CT in one patient (6.7 ± 2.1 vs. 4.3 ± 0.8 , $p < 0.05$). Interestingly, one patient was diagnosed with concomitant lymphoma and pancreatic cancer. [¹⁸F]FDG uptake was equally high in the LNs involved by pancreatic tumor and lymphoma, but only [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT demonstrated FAPI-avid lesions in pancreas.

Among the 37 patients, elevated uptake of [⁶⁸Ga]Ga-DOTA-FAPI-04 was observed in non-tumor pancreatic tissues of 17 patients (45.9%) without [¹⁸F]FDG uptake. The SUV_{max} of [⁶⁸Ga]Ga-DOTA-FAPI-04 in the tumor and pancreatic tissue was 15.8 ± 5.1 (range 5.5–22.2) and 14.6 ± 5.9 (range 7.3–24.5), respectively. And there was no statistical difference between the uptake. Of the 17 patients, fifteen patients showed diffuse uptake of FAPI in the body and tail of pancreas while only 2 patients illustrated focal uptake. The representative case was presented in Figure 5. There was no relationship between the [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake in the non-tumor pancreatic tissues and [¹⁸F]FDG or [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake in the tumors.

Changes of clinical decision

Thirty-two patients with suspected pancreatic tumor underwent the scanning for the diagnosis and staging. [⁶⁸Ga]Ga-DOTA-FAPI-04 detected 3 more patients with LN involvement and 2 more patients with liver metastases, where negative findings were found on [¹⁸F]FDG images. As a result, two patients were upstaged by [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT correctly. One patient with suspected LNs and two patients with liver nodules turned out to be false positive. Additionally, one patient with NEC showed that the majority of the involved LNs was FAPI⁺/FDG⁻. Of the 8 patients for identification of the recurrence, four patients showed additional abnormal uptake on [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT images. Finally, one patient proved to be with malignancy. The other three patients with false-positive uptake of [⁶⁸Ga]Ga-DOTA-FAPI-04 were proved to be with pancreatitis, cholangitis, some benign liver disease, and inflammatory LNs. The represent images were showed in supplemental Figure. Of the five patients who underwent PET/CT scanning for therapeutic response evaluation, three patients showed discordant results (FAPI⁺/FDG⁻). These three patients were identified with liver metastases (2 patients) and enlarged LNs (1 patient) in subsequent follow-up process. These results demonstrated that PET imaging with [⁶⁸Ga]Ga-DOTA-FAPI-04, as a supplement to [¹⁸F]FDG, may optimize the management of pancreatic

tumors by facilitate precise initial staging, recurrence identification, and assessment of the treatment response.

Comparison of [⁶⁸Ga]Ga-DOTA-FAPI-04 and [¹⁸F]FDG PET/CT in non-PDAC

The pancreatic cystic neoplasms of 3 patients showed negligible [¹⁸F]FDG uptake. But the adjacent pancreatic tissues had [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake, which was probably associated with inflammation. Another two patients with slight uptake of the two tracers did not show abnormal in the follow-up examinations. For the patient with NET (G2), [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT showed moderate uptake ($SUV_{max} = 5.2$) in the pancreatic tumor while [¹⁸F]FDG PET/CT revealed intense uptake ($SUV_{max} = 9.4$). There was nearly no uptake in the liver with both tracers. The patients also conducted the [⁶⁸Ga]Ga-DOTA-TATE PET/CT and it revealed high uptake in both pancreatic tumor ($SUV_{max} = 37.5$) This case was presented in Figure 6. In additional, one patient with pancreatic NEC received the PET/CT scans for the purpose of diagnosis and staging. Multiply organs shwed high uptake in the [¹⁸F]FDG PET/CT imaging, including lung, adrenal glands, peritoneal, bone, brain, and LNs. Surprisingly, some lesions demonstrated discordant patterns between [¹⁸F]FDG and [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake. By comparison, [¹⁸F]FDG uptake in the pancreatic lesions was significantly higher than that of [⁶⁸Ga]Ga-DOTA-FAPI-04 (12.5 vs. 8.9). And there was nearly no uptake of [⁶⁸Ga]Ga-DOTA-FAPI-04 in most lesions of adrenal glands, peritoneal, bone, and brain. And this case was presented in Figure 7. Within one patient with autoimmune pancreatitis (IgG4-related disease), [¹⁸F]FDG PET/CT revealed a lesion in the pancreatic head with moderate uptake ($SUV_{max} = 6.0$) and mild radioactivity in the enlarged whole pancreas ($SUV_{max} = 4.4$). By comparison, in [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT, the entire pancreatic tissues was with intense uptakes ($SUV_{max} = 21.4$).

Discussion

Recently, some studies have revealed that [⁶⁸Ga]Ga-DOTA-FAPI-04 showed advantages over [¹⁸F]FDG in tumor management [18–20]. Pancreatic cancer was histopathologically characterized by high desmoplastic reactions and therefore FAPI PET/CT seems to be promising to improve diagnostic performance. In our study, we compared the performance of [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT with [¹⁸F]FDG PET/CT in detecting pancreatic tumors and associated metastases. The sensitivity of [⁶⁸Ga]Ga-DOTA-FAPI-04 is a little higher than that of [¹⁸F]FDG and the uptake of the former was nearly 2-times as the latter, adding confidence in the initial diagnosis.

Liver, abdominal and retroperitoneal LNs, and peritoneal carcinomatosis are the most common metastases in pancreatic cancer. Because of the relatively low-resolution of PET/CT and high [¹⁸F]FDG-uptake background in the liver and intestine, [¹⁸F]FDG PET/CT has poor sensitivity in detecting hepatic

metastasis with diameter < 1 cm and peritoneum carcinomatosis. In the present study, we found that [⁶⁸Ga]Ga-DOTA-FAPI-04 had a lower uptake in healthy tissues than that of [¹⁸F]FDG. As a result, [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT had a higher detection rate in metastatic LNs, liver, and peritoneum metastases, which was consistent with the finding of a previous study [17]. The favorable imaging contrast definitely makes [⁶⁸Ga]Ga-DOTA-FAPI-04 a tracer with high sensitivity for the diagnosis of pancreatic cancer. However, [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT did not demonstrate more bone and lung metastases with higher SUV_{max}, which was different to the published article [21]. This may be due to the different tumor types and the small number of the lesions for statistical analysis.

We also compared the performance of [⁶⁸Ga]Ga-DOTA-FAPI-04 and [¹⁸F]FDG for the purpose of diagnosis, detection of recurrence, and therapeutic evaluation. Overall, [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT successfully unregulated the clinical stage in 2 patients, presented recurrence in 1 patient, and detected the residual active tumor tissue in 3 patients with discordant results (FAPI⁺/FDG⁻). Therefore, [⁶⁸Ga]Ga-DOTA-FAPI-04 is promising to outperform than [¹⁸F]FDG in the clinical management of pancreatic cancer. However, [⁶⁸Ga]Ga-DOTA-FAPI-04 did not show high priority in tumor-specific accumulation. The false-positive uptake of [⁶⁸Ga]Ga-DOTA-FAPI-04 was revealed in pancreatitis, biliary obstruction, some benign liver diseases, and inflammatory LNs. It is well known that pancreatic tumor is often accompanied by inflammation, abnormal liver function, and obstructive cholangitis. Furthermore, FAP is also selectively expressed in cells of benign diseases, such as myocardial infarction, sarcoidosis, chronic inflammation, fibrosis of lung, liver and kidney [22]. As a result, we should pay more attention when reading the [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT images in pancreatic cancer, especially for the lesions with slight [⁶⁸Ga]Ga-DOTA-FAPI-04 uptake. It is necessary to integrate enhanced abdomen CT or MR imaging to improve the diagnostic accuracy in clinical.

We noticed [⁶⁸Ga]Ga-DOTA-FAPI-04-avid pancreas in 17 patients (45.9%). And most of them were with diffuse uptake in the body and tail of pancreas. Previous studies have also revealed the similar performance and tumors showed higher average SUV_{max} than pancreatitis [17, 23]. However, the SUV_{max} of the tumors and non-tumor pancreas was similar in our study. It is worth noting that the whole pancreas showed diffuse significant uptake in some patients, which covered the tumors. As we all know, desmoplasia and inflammation are two major hallmarks of pancreatic cancer [24, 25]. In this circumstance, the combination with other examinations or close follow-up is of great importance for the accurate diagnosis. One of the possible reasons for the abnormal uptake in pancreas may be the chronic pancreatitis, as we found that pancreatic body and tail atrophy and pancreatic duct dilatation in the majority of patients. Another potential reason was tumor-associated inflammation [26]. In some patients of our study, the pathology of puncture or surgery showed fibrin exudation and inflammatory cell infiltration in the pancreatic tissue.

Apart from pancreatic cancer, we also demonstrated the performance of [⁶⁸Ga]Ga-DOTA-FAPI-04 PET/CT in NENs in two cases. We found that most lesions of NEC or NET (G2) showed low [⁶⁸Ga]Ga-DOTA-FAPI-

04 uptake. The [^{68}Ga]Ga-DOTA-FAPI-04 uptake is much lower when compared to PDAC, implying the low expression of FAP. [^{68}Ga]Ga-DOTA-TATE has an established role in diagnosing NENs [27, 28]. In our study, one patient with NET (G2) also conducted [^{68}Ga]Ga-DOTA-TATE PET/CT and the corresponding liver metastases (FAPI⁻/FDG⁻) showed intense uptake. Remarkably, in the most lesions of NEC, the uptake of [^{68}Ga]Ga-DOTA-FAPI-04 was low-to-mild, even in the brain and bone metastases. To the best of our knowledge, the diagnostic performance of [^{68}Ga]Ga-DOTA-FAPI-04 in NENs has been not fully documented. According to our preliminary observation, [^{68}Ga]Ga-DOTA-FAPI-04 did not show superiority than [^{18}F]FDG for detecting either primary or metastatic NENs. Further studies with larger number of patients should be conducted to investigate the definite value of [^{68}Ga]Ga-DOTA-FAPI in NENs. Another special case was a patient with autoimmune pancreatitis. Similar to the previous studies [29, 30], [^{18}F]FDG PET/CT depicted focal uptake in the head of pancreas, while [^{68}Ga]Ga-DOTA-FAPI-04 PET/CT showed diffusely intense uptake in the whole pancreases, which provides more information for the diagnosis of autoimmune pancreatitis. The pathology of surgery revealed that the pancreas was accompanied by significant fibrosis and a large number of lymphatic and plasma cell infiltration. Therefore, attention should be paid to distinguish such performance from pancreatic cancer-related inflammation.

With a high tumor uptake and a very low accumulation in normal tissues, FAP has great potential for theranostic applications in oncology. Novel FAPI were designed for the labeling with [$^{99\text{m}}\text{Tc}$]Tc and [^{188}Re]Re, providing the initial evidence of FAP-targeted theranostics [31]. In line with this, Watabe *et al* demonstrated that [^{64}Cu]Cu-FAPI-04 and [^{225}Ac]Ac-FAPI-04 could be used in theranostics for FAP-expressing pancreatic cancer [31]. Some studies have demonstrated that FAPI-PET/CT could be used for targeted radiotherapy in patients with tumors of head and neck and lower gastrointestinal tract [32, 33]. As we detected the false-uptake of [^{68}Ga]Ga-DOTA-FAPI-04 in pancreatitis and biliary obstruction that commonly accompanied with pancreatic cancer, we should pay attention to the related side-effect of FAP-targeted radiotherapy. In addition, overexpression of FAP in the stroma is reported to be associated with tumor progression and poor prognosis [34, 35]. The prognostic value of [^{68}Ga]Ga-DOTA-FAPI PET/CT uptake in pancreatic cancer remains to be investigated.

There are some limitations to our study. First, the number of the enrolled patients was limited. Future study should be conducted to provide a more comprehensive overview of [^{68}Ga]Ga-DOTA-FAPI PET/CT in managing pancreatic tumors. Second, it is difficult to obtain the pathology of all the metastases. In the present study, we collected and analysis the follow-up of 6 months to confirm the results. Pathologic confirmation would be performed in the future study.

Conclusion

[^{68}Ga]Ga-DOTA-FAPI-04 has a higher sensitivity than [^{18}F]FDG in detecting pancreatic tumors and associated metastases with a higher uptake, resulting in improved decision-making in the management

of pancreatic cancers. However, the false-positive uptake of [⁶⁸Ga]Ga-DOTA-FAPI-04 in pancreatitis, obstructive cholangitis, some benign liver diseases, and inflammatory LNs may interfere with the image interpretation.

Declarations

Funding information

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

This study was approved by the Ethics Committee of the Fudan University Shanghai Cancer Center and the written informed consent for publication was obtained from the patient.

Consent to participate

Informed consent was obtained from all the participants in the study.

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Figures

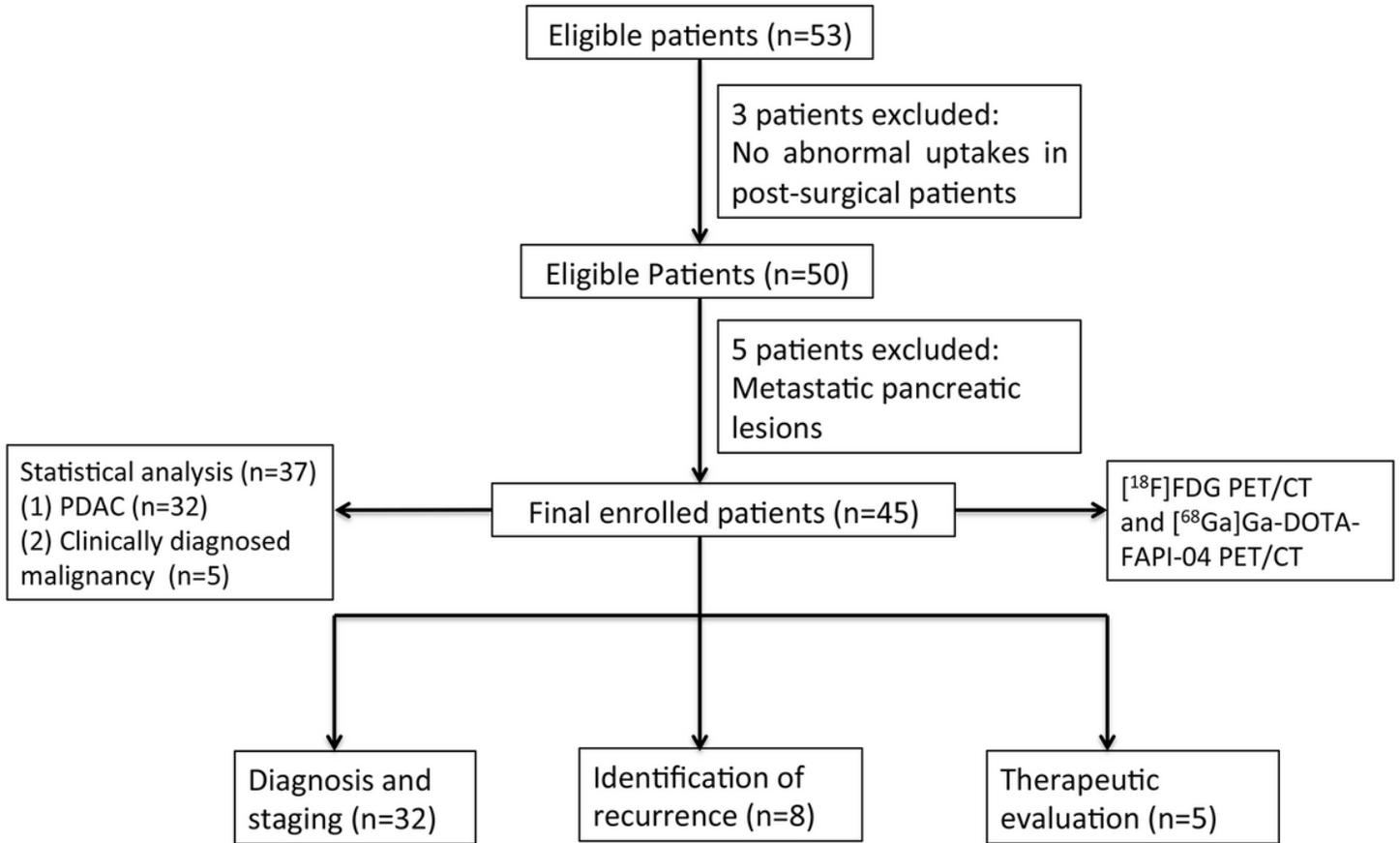


Figure 1

The scheme of the study design.

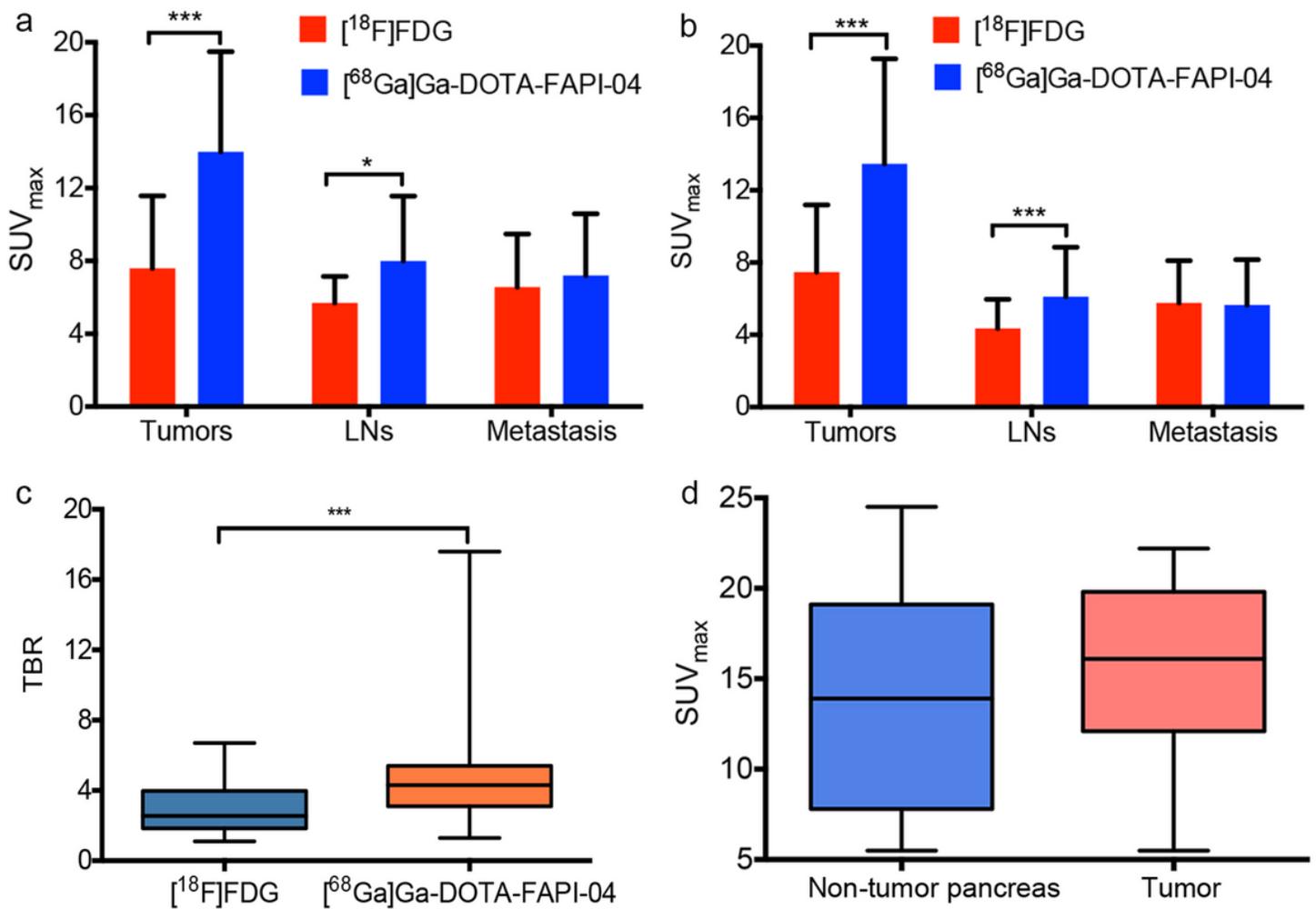


Figure 2

The analysis of [68Ga]Ga-DOTA-FAPI-04 and [18F]FDG uptake in pancreatic tumors, metastasis, and pancreas. a Patients-based analysis of [68Ga]Ga-DOTA-FAPI-04 and [18F]FDG uptake in the primary pancreatic tumors and metastasis. b Lesions-based analysis of [68Ga]Ga-DOTA-FAPI-04 and [18F]FDG uptake in the primary pancreatic tumors and metastasis. c Tumor-to-background ratio (TBR) of [68Ga]Ga-DOTA-FAPI-04 and [18F]FDG in liver metastases. d The SUV_{max} of non-tumor pancreas and pancreatic tumors in [68Ga]Ga-DOTA-FAPI-04 PET/CT. *Statistically significant with $p < 0.05$; ***Statistically significant with $p < 0.001$.

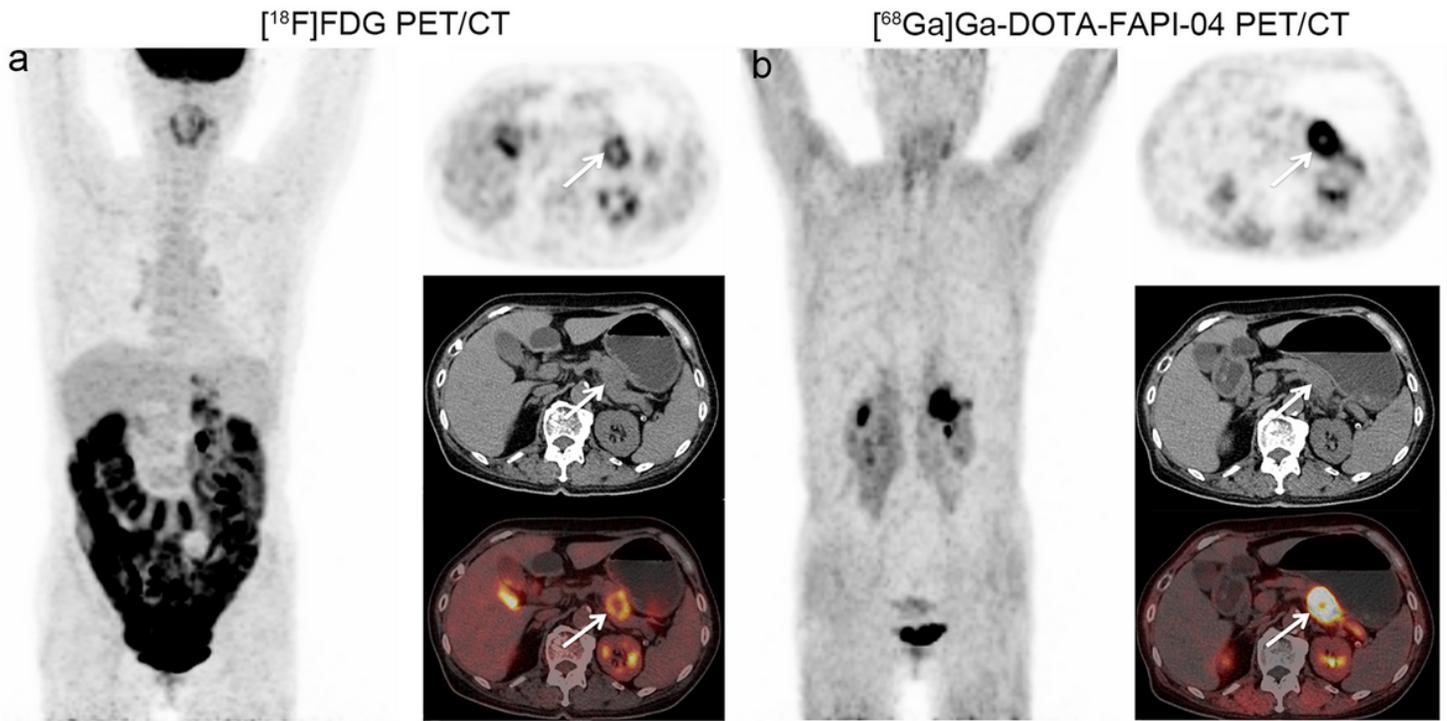


Figure 3

A 70-year-old female with pancreatic tumor who underwent the PET/CT scans for diagnosis. $[^{18}\text{F}]\text{FDG}$ PET/CT revealed mild uptake in the tumor of pancreatic body (a, arrow, SUVmax = 5.1), while $[^{68}\text{Ga}]\text{Ga-DOTA-FAPI-04}$ PET/CT demonstrated intense uptake (b, arrow, SUVmax = 11.4). Additionally, there was intense $[^{18}\text{F}]\text{FDG}$ uptake in the intestine without $[^{68}\text{Ga}]\text{Ga-DOTA-FAPI-04}$ uptake. The follow-up pathology of biopsy revealed pancreatic ductal adenocarcinoma (PDAC). White arrow: pancreatic tumor.

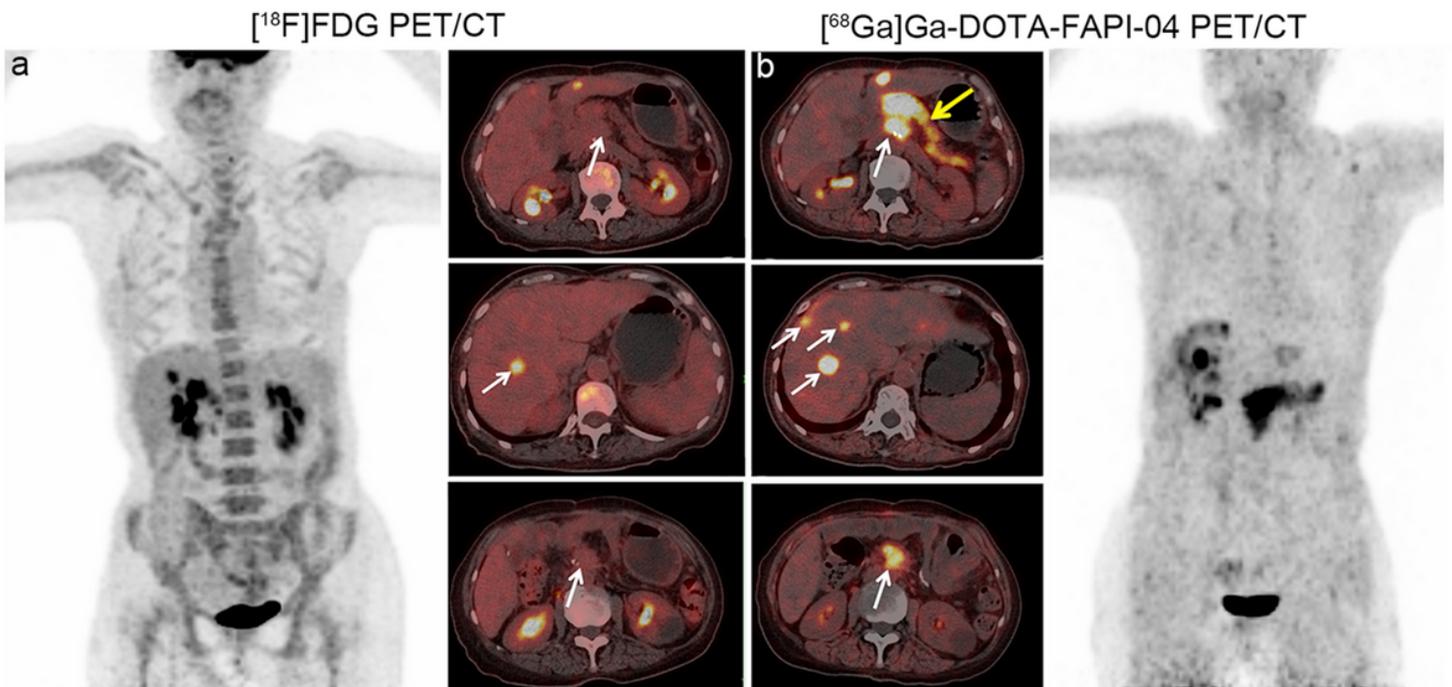


Figure 4

A 62-year-old female with pancreatic ductal adenocarcinoma (PDAC) who previously received pancreateoduodenectomy and adjuvant chemotherapy. PET/CT scans were conducted for the therapeutic evaluation. a [18F]FDG PET/CT showed low-to-mild activity in the soft-tissue mass (SUVmax = 4.5) in the surgical area, multiply LNs (SUVmax = 3.2) and liver metastases (SUVmax = 6.9). b [68Ga]Ga-DOTA-FAPI-04 PET/CT revealed higher uptake in the mass (SUVmax = 9.5), more LNs (SUVmax = 6.0) and liver metastases (SUVmax = 12.5). Additionally, the diffuse uptake of [68Ga]Ga-DOTA-FAPI-04 was found within the residual pancreas (b, first row, yellow arrow).

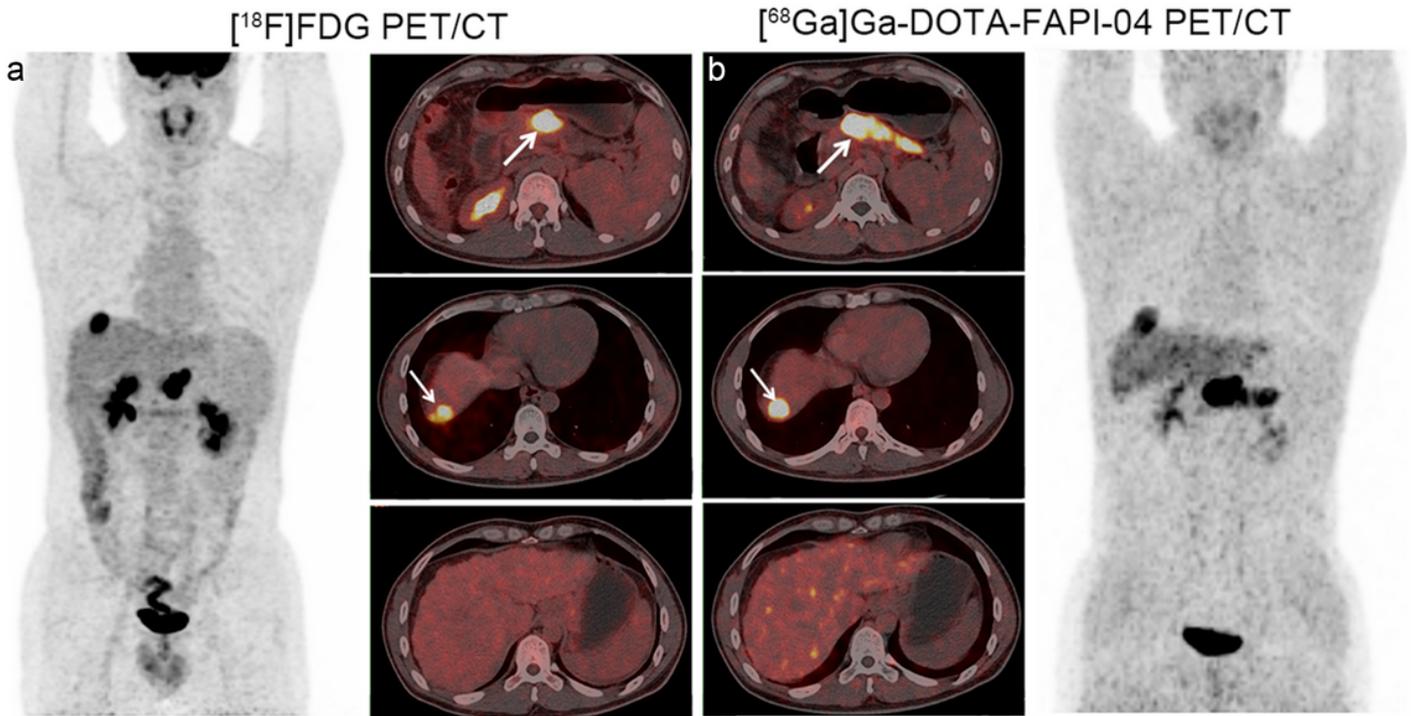


Figure 5

A 42-year-old male diagnosed with PDAC and had a clinical history of hepatitis B infection. Enhanced CT imaging detected a mass located in pancreatic body and suspected liver metastases. a [18F]FDG PET/CT demonstrated significant activity (SUVmax = 21.4, arrow in up row) in the pancreatic tumor and liver metastases (SUVmax = 13.8, arrow in middle row). b In [68Ga]Ga-DOTA-FAPI-04 PET/CT, the whole pancreas was FAP-avid (SUVmax = 20.8, arrow in up row). The liver metastasis showed intense uptake (SUVmax = 7.7, arrow in middle row). However, there was diffuse and inhomogeneous uptake of [68Ga]Ga-DOTA-FAPI-04 in the whole liver, which may associated with hepatitis B infection(b, low row).

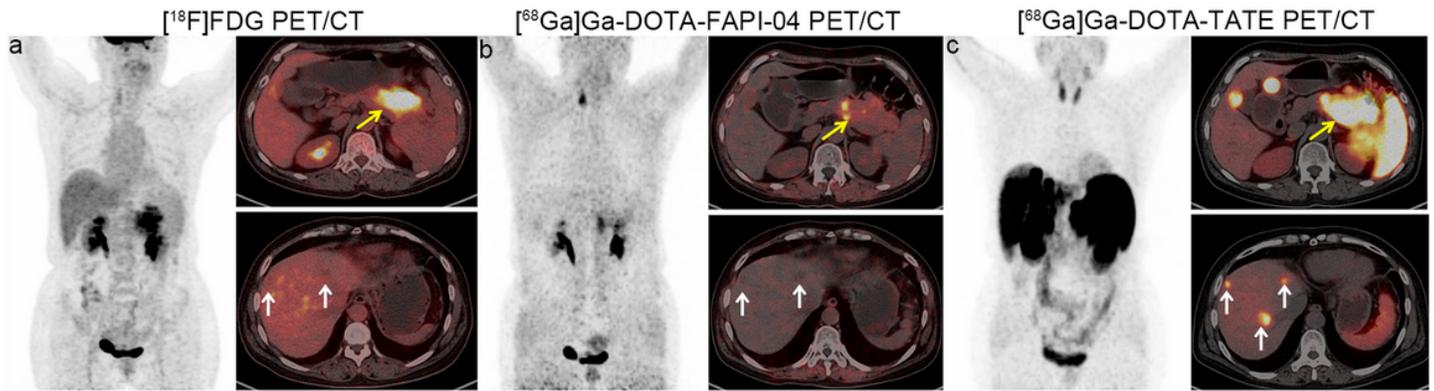


Figure 6

A 56-year-old male underwent PET/CT scan for evaluation of a pancreatic mass. a [18F]FDG PET/CT showed intense uptake in the pancreatic tumor (a, arrow in the up row, SUVmax = 9.4), while no uptake in the multiply liver nodes (a, arrow in the low row). b [68Ga]Ga-DOTA-FAPI-04 PET/CT demonstrated a moderate activity in pancreatic tumor (b, arrow in the up row, SUVmax = 5.5). Similarly, there was also no uptake in liver nodes (b, arrow in the low row). c The patients also conducted [68Ga]Ga-DOTA-TATE PET/CT for further evaluation. [68Ga]Ga-DOTA-TATE PET/CT revealed significant uptake in both pancreatic tumor (c, arrow in the up row, SUVmax = 37.5,) and liver nodes (c, arrow in the low row, SUVmax =22.4). An ultrasound-guided biopsy was subsequently performed in the pancreatic tumor, which confirmed the diagnosis of NET (G2).

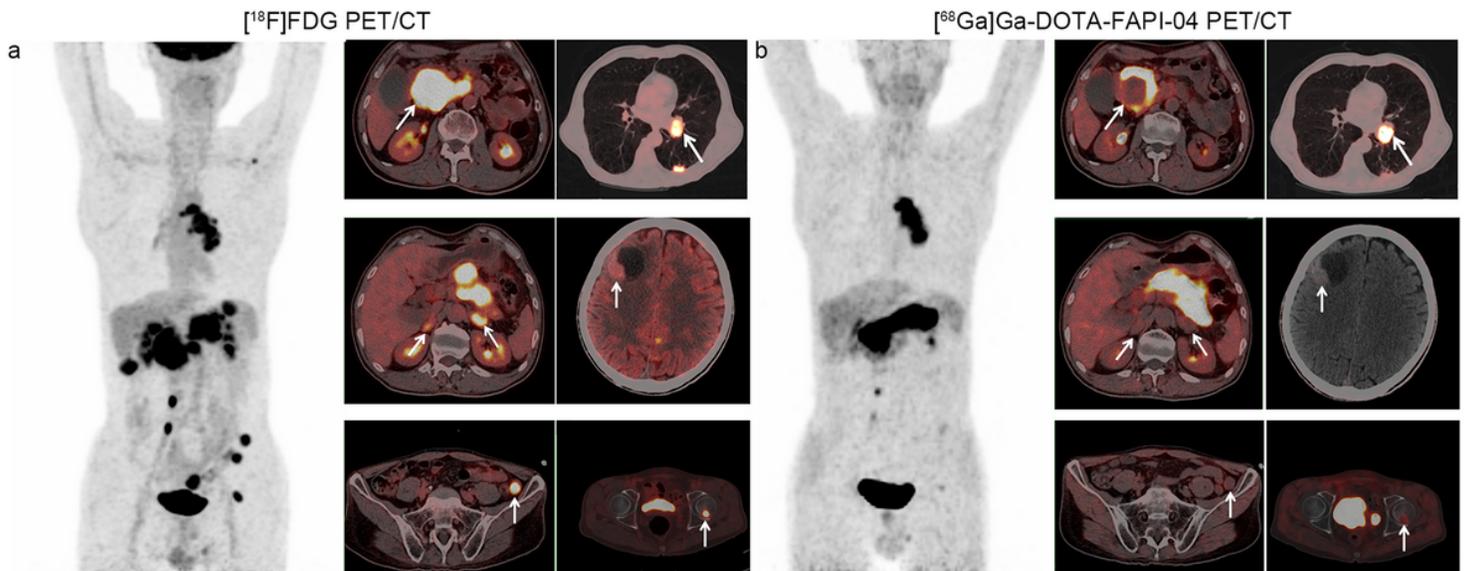


Figure 7

A 56-year-old male with biopsy-diagnosed with pancreatic NEC (Ki-67 > 90%). a [18F]FDG PET/CT revealed high activity in pancreatic tumors (SUVmax =12.5) as well as in multiple organs, including lung, adrenal glands, peritoneal, bone, brain, and LNs involved. b By comparison, [68Ga]Ga-DOTA-TATE PET/CT showed inhomogeneous uptake in the pancreatic tumor and diffuse uptake (SUVmax =20.4) in the whole

pancreas. Moreover, high [68Ga]Ga-DOTA-FAPI-04 uptake was only found in the left hilar mass (SUVmax =11.2) and some LNs. Remarkably, the most lesions of adrenal glands, peritoneal, bone, and brain showed negligible uptake in [68Ga]Ga-DOTA-FAPI-04 PET/CT.

Supplementary Files

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- [SupplementalFigure1.png](#)