Review Article

The clinical application of ¹⁸F-FDG PET/CT in pancreatic cancer: a narrative review

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Abstract: Pancreatic cancer is one of the worst prognoses of all malignant tumors, with an annual incidence near its annual mortality rate. To improve the prognosis of patients with pancreatic cancer, it is essential to diagnose and evaluate pancreatic cancer early. Imaging examinations play an essential role in tumor detection, staging, and surgical resection assessment and can provide reliable evidence for the diagnosis and treatment of pancreatic cancer. Currently, imaging techniques commonly used for pancreatic cancer include endoscopic ultrasound (EUS), conventional ultrasound, magnetic resonance imaging (MRI), multidetector spiral computed tomography (MDCT), positron emission tomography/computed tomography (PET/CT), and others PET/CT is a new imaging device composed of PET and CT. ¹⁸F-Fluorodeoxyglucose (¹⁸F-FDG) is a commonly used tracer in the clinic. Cancer cells are more robust than other ordinary cells in that they can ingest glucose, and the structure of glucose is similar to the structure of ¹⁸F-FDG. Therefore, after the injection of ¹⁸F-FDG, ¹⁸F-FDG in tumor cells appears very thick during PET scanning. Therefore, PET/CT can determine the metabolic capacity and anatomical position of pancreatic tumor cells in the body accurately diagnose the patient's condition and tumor location. It plays a vital role in early diagnosis and accurate staging, predicts survival, and monitors therapeutic effectiveness and pancreatic cancer recurrence. Although ¹⁸F-FDG PET/CT has limitations in identifying inflammatory diseases and tumors, it still has good development potential. This article reviews the clinical application of ¹⁸F-FDG PET/CT in pancreatic cancer.

Keywords: Pancreatic cancer; positron emission tomography/computed tomography (PET/CT); diagnosis; survival

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Introduction

Pancreatic cancer is a malignant tumor of the digestive system with an inferior prognosis (1). The annual incidence of pancreatic cancer is similar to its annual mortality rate (2). The latest data in 2020 suggest that the 5-year survival rate of patients with pancreatic cancer is still less than 9%, and the number of new cases of pancreatic cancer in males ranks 10th among all malignant tumors and 9th in females (3). However, according to the statistics of the number of deaths caused by tumors, the number of deaths of male and female patients caused by pancreatic cancer ranks fourth among all malignant tumors (3). According to research data released by the National Cancer Center of China, the incidence of pancreatic cancer ranks 8th among malignant tumors in the Chinese urban male population, and its mortality rate ranks 5th among malignant tumors in Beijing and Shanghai (4,5). Pancreatic cancer is often asymptomatic in the early stages, and most patients are in the local or advanced stage at the time of diagnosis and cannot undergo radical surgery (6). To improve the prognosis of patients with pancreatic cancer, it is crucial to diagnose and evaluate pancreatic cancer early (7,8).

Imaging examinations play an essential role in tumor detection, staging, and surgical resection assessment and can provide reliable evidence for the diagnosis and treatment of pancreatic cancer (9). Currently, imaging techniques commonly used for pancreatic cancer include endoscopic ultrasound (EUS), conventional ultrasound, magnetic resonance imaging (MRI), multidetector spiral computed tomography (MDCT), positron emission tomography/ computed tomography (PET/CT), and others (10,11). PET/CT is a new imaging device composed of PET and CT (12). 18-Fluorodeoxyglucose (^{18}F-FDG) is a commonly used tracer in the clinic (13). After injection into the body, ^{18}F-FDG-PO$_4$ is generated due to the catalysis of various enzymes, and FDG is not metabolized in the cell (14). Cancer cells are more robust than other ordinary cells in that they can ingest glucose, and the structure of glucose is similar to the structure of ^{18}F-FDG (15). Therefore, after the injection of ^{18}F-FDG, ^{18}F-FDG in tumor cells appears very thick during PET scanning (16). PET imaging can identify tumors in the human body through changes in cellular metabolic levels (17). The combination of PET and CT can determine the metabolic capacity and anatomical position of pancreatic tumor cells in the body and can accurately diagnose the patient's condition and tumor location (18). This article reviews the clinical application of ^{18}F-FDG PET/CT in pancreatic cancer. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tcr-21-169).

Diagnostic efficacy in detecting pancreatic cancer

In general, the maximum standardized uptake value (SUVmax) of malignant lesions is high regardless of size, which allows PET/CT to depict small pancreatic lesions (11). The Summary of sensitivity and specificity imaging modality for the diagnosis of PDAC was shown in *Table 1*. Various studies have reported varying capabilities of PET/CT in the diagnosis of pancreatic cancer (19,20). PET/CT may be considered a first-line imaging examination, but evidence of this method lacks (26). The overall detection sensitivity of PET/CT in the diagnosis of pancreatic cancer is between 90% and 95%, and the specificity is between 82% and 100% (27). A meta-analysis performed in 2011 on 51 studies compared the diagnosis of pancreatic cancer by PET/CT with that by EUS and reported that PET/CT had higher sensitivity (90.1%) and EUS had higher specificity (93.2%). The diagnostic advantage ratio of EUS for pancreatic cancer is significantly higher than that of PET/CT, but its diagnostic value is limited by high heterogeneity between studies (21). Endoscopic ultrasound is very sensitive in the detection of pancreatic lesions with a special resolution of 1–2 mm (28). Studies have demonstrated that EUS, CT and MRI have respective sensitivities of 93, 53 and 67%, respectively, for visualizing tumors 3 cm or smaller. This difference is in fact even more pronounced for lesions smaller than 2 cm (29). And the sensitivity of PET-CT in detecting lesions less than 1 cm in diameter will be significantly reduced to 43% (30). In another meta-analysis performed in 2017, 5,399 patients from 52 studies were included, of which 3,567 had pancreatic cancer. The study found that the sensitivity, specificity, and diagnostic accuracy of PET/CT for pancreatic cancer were 89% (95% CI: 85–93%), 70% (95% CI: 54–84%), and 84% (95% CI: 79–89%), respectively (22).

Studies have evaluated the role of EUS-guided fine needle aspiration (EUS-FNA) and PET/CT in the preoperative evaluation of pancreatic cancer and found that compared with PET/CT, EUS-FNA has higher sensitivity and accuracy for the preoperative diagnosis of pancreatic cancer. However, PET/CT provides excellent size, volume, and stage information (31). Sun *et al.* (23) found that the

Table 1 Summary of sensitivity and specificity imaging modality for the diagnosis of pancreatic cancer

Author	Year	Study type	Pancreatic cancer–all (n)	18F-FDG PET-CT		CT		MRI		EUS		References
				Sens	Spec	Sens	Spec	Sens	Spec	Sens	Spec	
Sánchez-Bueno F	2016	Retrospective study	139–139	0.78	–	0.76	–	–	–	–	–	(19)
Ergul N	2014	Retrospective study	33–52	1	0.90	0.92	0.50	0.89	0.75	1	0.88	(20)
Tang S	2009	Meta-analysis	3,857*	0.90	0.80	–	–	–	–	0.81	0.93	(21)
Toft J	2017	Meta-analysis	3,567–5,399	0.89	0.70	0.90	0.87	0.93	0.89	0.91	0.86	(22)
Sun Y	2014	Retrospective study	80–91	0.68	0.73	–	–	–	–	–	–	(23)
Ghaneh P	2018	Prospective study	278–583	0.93	0.76	0.89	0.71	–	–	–	–	(24)
Zhang J	2015	Retrospective study	50–70	0.92	0.65	0.82	0.65	–	–	–	–	(25)

Sens Sensitivity, Spec Specificity. *The study included a total of 3857 patients, but we were unable to obtain the specific number of pancreatic cancer.

sensitivity, specificity, and accuracy of PET/CT alone in 91 pancreatic cancer patients were 67.5%, 72.73%, and 68.13%, respectively. When combined with the CA19-9 level, these indicators for PET/CT increased to 96.25%, 63.64%, and 92.31%, respectively. The area under the curve (AUC) of the combination of the SUVmax and CA19-9 level was 0.94, which was significantly higher than the AUC of the SUVmax or CA19-9 level alone. However, studies have reported that the negative predictive value of PET/CT in pancreatic lesions suggesting pancreatic cancer is approximately 75% (32). PET/CT negativity does not exclude pancreatic cancer, so a further examination of these PET/CT-negative lesions is necessary. PET/CT can also be used to detect early lesions of pancreatic cancer, pancreatic intraepithelial neoplasia (PanIN). Elevated glucose metabolism has been observed in mouse PanIN and can be detected by PET/CT (33). However, PanIN is an epithelial lesion with a small size. The diagnostic value of FDG-PET for human PanIN is still uncertain, and more clinical studies are needed to verify it.

Staging pancreatic cancer with 18F-FDG PET/CT

In addition to providing significant incremental benefits in the diagnosis of pancreatic cancer, 18F-FDG PET/CT significantly impacts patients' staging and management with pancreatic cancer (24,25). Heinrich *et al.* found that PET/CT findings can change the management in 16% of patients with pancreatic cancer deemed resectable after routine staging and were cost-saving (34). Another study reported that among 550 patients with suspected pancreatic cancer, PET/CT correctly changed the stage of 56 pancreatic cancers and affected the treatment of 250 patients. Among the 58 patients preparing for surgery, PET/CT reduced unnecessary surgery by 20% (24). Kim *et al.* identified 285 patients with early-stage pancreatic cancer who received PET/CT as part of the initial staging workup, and the addition of a PET/CT scan changed the management in 10.9% (n=31) of the 285 patients (35). A meta-analysis performed in 2017 included 1343 patients from 17 clinical studies and showed that PET/CT was more effective than CT in detecting right distant metastases (OR =1.52, 95% CI: 1.23–1.88). However, there was no definite difference between PET/CT and CT in detecting regional lymph node infiltration (OR =0.97, 95% CI: 0.63–1.47). Researchers believe that PET/CT provides a wide range of possibilities for avoiding ineffective radical surgery by detecting occult metastases from pancreatic cancer before

surgery. Before developing a surgical plan for patients with pancreatic cancer, surgeons should use PET/CT as a routine preoperative evaluation (36).

Yoneyama *et al.* suggested that PET/CT could correctly diagnose 88% of lymph node metastases and 91% of distant metastases (37). Wang *et al.* reported that the optimal SUVmax cutoff value of PET/CT for predicting lymph node micrometastasis was 7.05 (sensitivity: 71.2%, specificity: 76.6%) (38). Besides, metabolic ^{18}F-FDG PET/CT-derived parameters, such as the SUVmax, can be used to predict the venous infiltration status in patients with resectable pancreatic cancer (39). In 2016, the International Pancreatic Society proposed the concept of biological borderline resectable pancreatic ductal adenocarcinoma (BR-PDAC), which was defined as distant or regional lymph node metastases diagnosed by PET/CT and a CA19-9 level >500 U/mL (40). Whether such patients can benefit from immediate surgery remains controversial.

In general, ^{18}F-FDG PET/CT can help improve the detection of occult metastases (*Figure 1*), ultimately sparing individual patients from potentially unnecessary surgery (*Table 2*). The diagnostic value of PET/CT for lymph node staging still needs future clinical research.

## Prognostic value of ^{18}F-FDG PET/CT in pancreatic cancer

Pancreatic cancer is a heterogeneous disease with different prognoses in different subgroups (41). In addition to the existing tumor node metastasis (TNM) staging system, several markers can be used to predict the prognosis of patients with pancreatic cancer (42-44). As shown in *Table 3*, studies have reported that the prognosis of patients with pancreatic cancer can be assessed by PET/CT (45,53). The SUVmax is significantly related to the survival rate of pancreatic cancer patients at each stage, and patients with a low SUV have a longer survival time (46). Zhang *et al.* found that in patients with locally advanced pancreatic cancer who received stereotactic body radiation therapy (SBRT), the metabolic tumor volume (MTV) and total lesion glycolysis (TLG) detected by PET/CT were independent prognostic factors of overall survival (OS) (47). Choi *et al.* also found that MTV could provide independent prognostic information on patients with locally advanced pancreatic cancer treated with radiotherapy and chemotherapy. Volume-based PET/CT parameters may help determine which subgroups of patients will benefit from radiation therapy (48). MTV and TLG can also be

used to predict the prognosis of patients with pancreatic cancer undergoing surgery. Lee *et al.* reported 89 patients with pancreatic cancer who underwent surgery, of whom 57 received neoadjuvant chemotherapy, and found that the MTV and TLG were independent predictors of recurrence-free survival (RFS) and OS, regardless of whether the patient received neoadjuvant chemotherapy (49). Another study showed that MTV and TLG were better at predicting OS and RFS than baseline serum CA19-9 levels, the SUVmax, and tumor size (50). MTV and TLG can be used as prognostic indicators for patients with resectable pancreatic cancer (54). Kim *et al.* retrospectively analyzed the preoperative PET/CT data of 85 patients who underwent radical surgery and found that the SUV ratio (SUV of the lymph node/SUV of the tumor) could predict patients' prognosis. An SUV ratio greater than 0.384 is an independent risk factor for a poor prognosis (51). In another study, researchers analyzed the prognosis of 40 patients with pancreatic cancer. SUVs were determined at 1 hour (SUV1) and 2 hours (SUV2) after F-FDG injection. The retention index (RI) is defined as the percentage change between the SUV1 and SUV2. The results suggest that an RI of less than 17% shows a significant independent correlation with prolonged survival. The RI is an accurate parameter that predicts the prognosis of pancreatic cancer disease and identifies patients who can benefit from surgery (52). Also, F-FDG INF (global F-FDG influx) was a significant variable for OS in patients with pancreatic cancer (55).

Overall, many ^{18}F-FDG PET/CT PET/CT parameters can be used to predict the prognosis of pancreatic cancer, but it is still inconclusive as to which index can best predict the prognosis. Multicenter prospective data are needed for verification.

^{18}F-FDG PET/CT for monitoring the treatment effect and detecting recurrent pancreatic cancer

Pancreatic cancer is prone to recurrence after surgery, but a radiographic evaluation after pancreatic tumor resection is challenging, and it is particularly difficult to distinguish between local tumor recurrence and postoperative fibrosis (56). PET/CT can help detect pancreatic tumor recurrence (57,58). A systematic review and meta-analysis in 2017 analyzed the imaging data of 333 patients with pancreatic cancer from 7 studies. The study found that in detecting pancreatic cancer recurrence, the sensitivity and specificity of CT were 0.70 and 0.80, respectively. For FDG
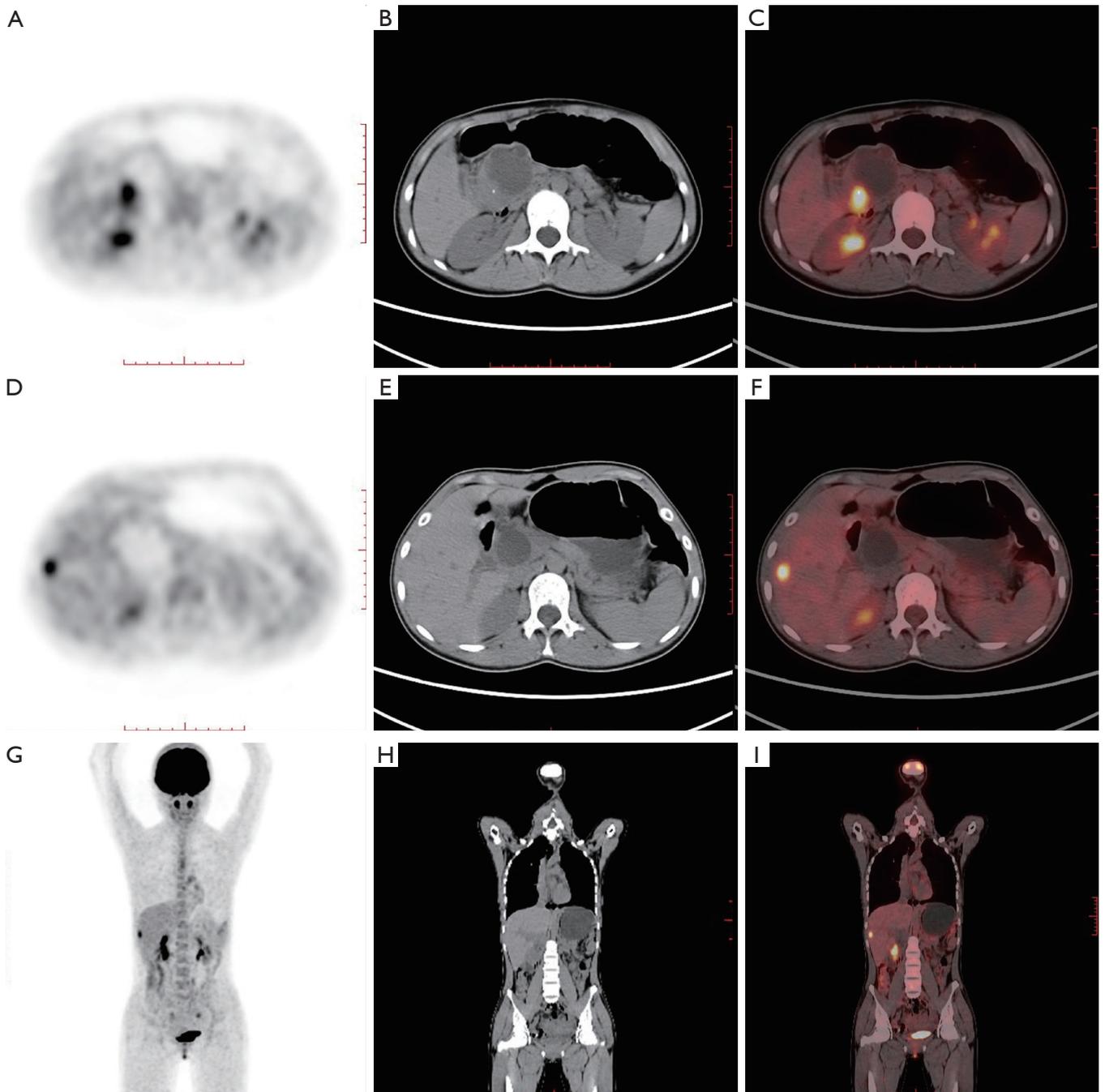
Figure 1 ^{18}F-FDG PET/CT shows pancreatic head cancer and liver metastasis. (A) PET image, (B) non-enhanced CT image, (C) fused PET and CT images of pancreatic head cancer; (D) PET image, (E) non-enhanced CT image, (F)fused PET, and CT images of liver metastasis; (G) PET image, (H) non-enhanced CT images (I) fused PET and CT images in coronal.

Table 2 ^{18}F-FDG PET/CT in the staging of pancreatic cancer

Author	Year	Study type	Pancreatic cancer/all (n)	Sens	Spec	% Change in Management	Description	References
Ghaneh P	2018	Prospective study	278/583	0.93	0.76	45	^{18}F-FDG PET/CT correctly changed the staging of pancreatic cancer in 56 patients and influenced management in 250 (45%) patients. PET/CT stopped resection in 58 (20%) patients who were due to have surgery	(24)
Heinrich S	2005	Retrospective study	46/59	0.89	0.69	16	^{18}F-FDG PET/CT findings changed the management in 16% of patients with pancreatic cancer deemed resectable after routine staging and was cost saving	(34)
Kim R	2015	Retrospective study	285/285	–	–	10.9	^{18}F-FDG PET/CT helped improve detection of occult metastases, ultimately sparing these patients a potentially unnecessary surgery	(35)

Sens Sensitivity, Spec Specificity.

PET/CT, the combined sensitivity and specificity estimates were 0.88 and 0.89, respectively. For FDG PET/CT and contrast-enhanced CT, the combined sensitivity and specificity estimates were 0.95 and 0.81, respectively (59). Besides, research reports that PET-CT is significantly more sensitive than CT when detecting distant recurrences, and PET/CT can detect recurrences in areas not covered by CT (57). Therefore, as shown in *Figure 2*, when CT is negative or ambiguous, PET/CT may have added value if pancreatic cancer is suspected of recurring. Rayamajhi *et al.* analyzed PET/CT images and the CA19-9 level in 39 patients with pancreatic cancer. The recurrence sensitivity, specificity, and accuracy of PET/CT were 90.9%, 100.0%, and 92.3%, respectively. PET/CT detected recurrence in 12 patients with normal CA19-9 levels. It has been suggested that PET/CT is highly sensitive to the recurrence of pancreatic cancer and that recurrence can be detected in patients with normal CA19-9 levels (60).

^{18}F-FDG PET/CT can also dynamically monitor the efficacy of treatment (59,61,62).

A meta-analysis in 2019 included 995 patients (683 with borderline resectable pancreatic cancer and 312 with locally advanced pancreatic cancer) receiving neoadjuvant therapy from 15 studies. A comparison of PET/CT images before and after neoadjuvant chemotherapy revealed that the decrease in the SUVmax was positively correlated with resectability, suggesting that a decrease in the tumor SUVmax on PET-CT may be a potential marker of the neoadjuvant chemotherapy response and resectability (63). Michl *et al.* compared the PET/CT images of 17 patients with liver metastases from pancreatic cancer before and three months after radioembolization, and the results suggested that changes in the SUV_{peak} and TLG could predict OS, progression-free survival (PFS), and the time to intrahepatic progression after pancreatic cancer liver metastases (64). Yue *et al.* found that using pre- and postradiotherapy PET/CT images could identify intratumoral heterogeneity in patients with pancreatic cancer and be used to evaluate the clinical results of radiotherapy based on the level of heterogeneity. This technique can also stratify patient risk and help select the appropriate treatment strategy for each patient (65).

^{18}F-FDG PET/CT incidental detection of second primary tumors

When patients undergo whole-body PET/CT, unexpected FDG uptake areas may be found, increasing the possibility

3566

Pu et al. PET/CT in pancreatic cancer

Table 3 Prognostic value of ^{18}F-FDG PET/CT parameters in pancreatic cancer

Author	Year	Study type	N	Patients, Treatments	Parameters	Prognostic value	References
Hyun S	2016	Retrospective study	137	Newly diagnosed pancreatic cancer	First-order entropy	Higher entropy (HR, 5.59; P=0.028) was independently associated with worse survival	(45)
Hwang J P	2012	Retrospective study	165	Underwent surgery, radiotherapy, and/or chemotherapy	SUVmax	SUVmax >4.1 (HR, 2.1; P=0.0008) was independently related to OS	(46)
Zhang A	2019	Retrospective study	23	LAPC patients underwent chemo-SBRT combined therapy	MTV	MTV >14.2 cm^3 was proved to be the independent prognostic factor for OS (HR, 3.015; P<0.05)	(47)
Choi HJ	2014	Retrospective study	60	LAPC patients underwent chemoradiation therapy	MTV, TLG	MTV >10.0 cm^3 and TLG >45.0 g were independent prognostic factors for OS (HR, 2. 21; P=0.038; HR, 2.19; P=0.019)	(48)
Lee JW	2014	Retrospective study	87	Underwent surgical resection	MTV, TLG	MTV >3.0 cm^3 and TLG >10.0 g were independent prognostic factors for OS (HR, 3.69; P=0.02; HR, 4.85; P=0.003) and RFS (HR, 2.34; P=0.001; HR, 2.59; P=0.003)	(49)
Xu HX	2014	Retrospective study	122	Underwent radical pancreatectomy	MTV, TLG	MTV >15.7 cm^3 and TLG >57.5 g were independent prognostic factors for OS (HR, 1.265; P=0.008; HR, 1.253; P=0.005) and RFS (HR, 1.245; P=0.006; HR, 1.217; P=0.006)	(50)
Kim HR	2018	Retrospective study	70	Underwent radical surgery	Lymph node/ tumor SUV ratio	Lymph node/tumor SUV ratio (P=0.007) was independently related to OS	(51)
Xi Y	2014	Retrospective study	40	Underwent surgery and/or chemotherapy.	Retention index	RI less than 17% was significant independent associated with prolonged patient survival (P<0.05)	(52)

HR, hazard ratio; OS, overall survival; PFS, progression-free survival; LAPC, locally advanced pancreatic cancer; SBRT, stereotactic body radiation therapy; MTV, metabolic tumor volume; TLG, total lesion glycolysis. Retention index: SUVs were determined at 1 h (SUV1) and 2 h (SUV2) after ^{18}F-FDG injection, the retention index was defined as the RI less than 17% percentage change between SUV1 and SUV2.
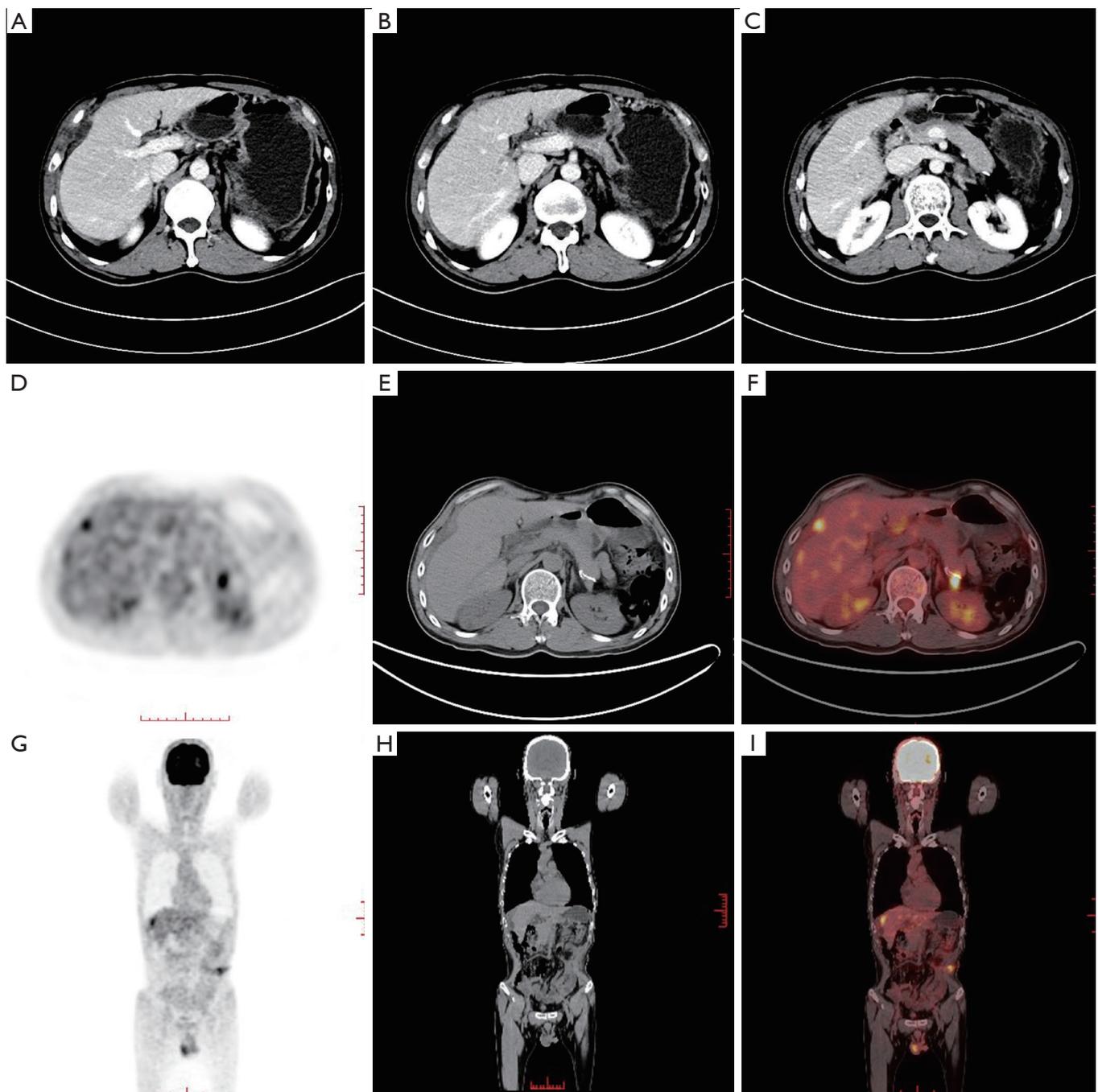
Figure 2 ^{18}F-FDG PET/CT and enhanced CT shows subcapsular liver metastases and local recurrence in the operation area in a pancreatic cancer patient who has received distal pancreatectomy. (A), (B) and (C) were enhanced CT images, and the subcapsular liver metastases and local recurrence were not prominent. (D) PET image, (E) non-enhanced CT image, (F) fused PET and CT images of subcapsular liver metastases and local recurrence in the operation area. (G) PET image, (H) non-enhanced CT images (I) fused PET and CT images in coronal.

3568

Pu et al. PET/CT in pancreatic cancer

of a second primary tumor (66). A second primary tumor was reportedly incidentally found upon PET/CT examinations of patients with head and neck cancer (67), esophageal cancer (68), colorectal cancer (69), and lung cancer (70). Similar reports have been made in patients with the pancreatic disease (*Figure 3*). Moletta *et al.* retrospectively analyzed PET/CT images of 399 patients with pancreatic disease. Among them, 31 patients exhibited unexpected focal FDG uptake and were diagnosed with 22 invasive malignancies. Patients in whom a second primary tumor was found incidentally by PET/CT and underwent resection of the tumor experienced prolonged survival (71).

Besides, there have been reports of patients with diseases other than pancreatic cancer found incidentally during PET/CT examinations (72). Sato *et al.* performed 497 consecutive PET/CT examinations on 290 patients with malignant lymphoma, 8 of whom (2.8%) were pathologically confirmed as having a second primary cancer, including one pancreatic cancer. It is worth noting that PET/CT showed that 5 of the eight patients (62.5%) had a high accumulation of FDG, and there was no corresponding tumor in conventional CT, which facilitated the early detection and successful treatment of the second primary tumor (73).

## Limitation of ^{18}F-FDG PET/CT in pancreatic cancer

Although PET/CT plays an essential role in diagnosing, treating, and managing pancreatic cancer, it still has certain limitations. In some cases, it is challenging to distinguish autoimmune pancreatitis (*Figure 4*) from pancreatic cancer by PET/CT (74-76). Both autoimmune pancreatitis and pancreatic cancer appear as metabolic abnormalities and increased FDG accumulation (77,78). Hsu *et al.* described a 52-year-old patient with subacute upper abdominal pain. The patient's CT showed an enlarged pancreatic head with hepatic vascular encapsulation, and PET/CT showed increased accumulation of FDG, which is highly suggestive of pancreatic cancer. After an open biopsy, a morphological examination revealed the pancreas' inflammatory infiltration, consistent with chronic sclerosing pancreatitis. Further laboratory tests showed elevated serum IgG4 levels, which confirmed the diagnosis of sclerosing pancreatitis (79). Cheng *et al.* compared the PET/CT scan results of 53 patients with suspected autoimmune pancreatitis and 61 pancreatic cancer patients, and the results suggested that PET/CT is slightly less specific in distinguishing autoimmune pancreatitis from pancreatic cancer (80). Some researchers also believe that

PET/CT may help distinguish autoimmune pancreatitis from pancreatic cancer (81-83). Zhang *et al.* reviewed the FDG PET/CT results of 26 patients with autoimmune pancreatitis and 40 patients with pancreatic cancer and found that the SUVmax between autoimmune pancreatitis and pancreatic cancer was significant in early and delayed PET/CT scans. In contrast, only in patients with autoimmune pancreatitis can the accumulation of diffuse pancreatic FDG and increased uptake of inverted "V" FDG in the prostate be found simultaneously and help identify autoimmune pancreatitis and pancreatic cancer by PET/CT (84).

Also, ^{18}F-FDG PET/CT has limited ability to distinguish between nonmetastatic pancreatic cancer and mass pancreatitis (85). Kato analyzed the PET/CT results of 47 patients with pancreatic masses and no metastasis. Among these patients, 33 were eventually diagnosed with pancreatic cancer, and the other 14 were diagnosed with pancreatitis. It was found that there was still a considerable SUVmax between the two diseases. Overlapping and no significant differences in FDG uptake patterns were found in the mass areas, suggesting that it is difficult for PET/ CT to distinguish between nonmetastatic pancreatic cancer and mass pancreatitis (86). Ye *et al.* described a 59-year-old male patient whose PET/CT imaging showed that the border of the pancreatic head's soft tissue mass was unclear, with a maximum SUV of 4.39. Low-density shadows with unclear boundaries were also found in the liver's left lobe, with a maximum SUV of 4.13, suggesting pancreatic cancer metastasis to the liver. However, postoperative pathology was consistent with chronic pancreatitis, schistosomiasis, and granulomatous liver inflammation (87).

New targets and new PET/CT tracers in pancreatic cancer

Considering that ^{18}F-FDG PET/CT has certain limitations in the diagnosis of pancreatic cancer, new targets and new PET tracers are continually being developed and used (88). Flores *et al.* developed the first ^{18}F-labeled lactose analog that targets HIP/PAP and applied it to the early detection of pancreatic cancer by PET in an animal model (89). Hausner *et al.* prepared an αvβ6-binding peptide (αvβ6-BP) and radiolabeled it with 4-^{18}F-fluorobenzoic acid. PET images showed a massive uptake of αvβ6-BP in both the primary and metastatic foci, including metastases to the brain, bone, liver, and lung (90). Besides, (4S)-4-(3-^{18}F-fluoro propyl)-L-glutamate (FSPG) PET reflects system xC- transporter (xCT) expression, has been used to detect pancreatic
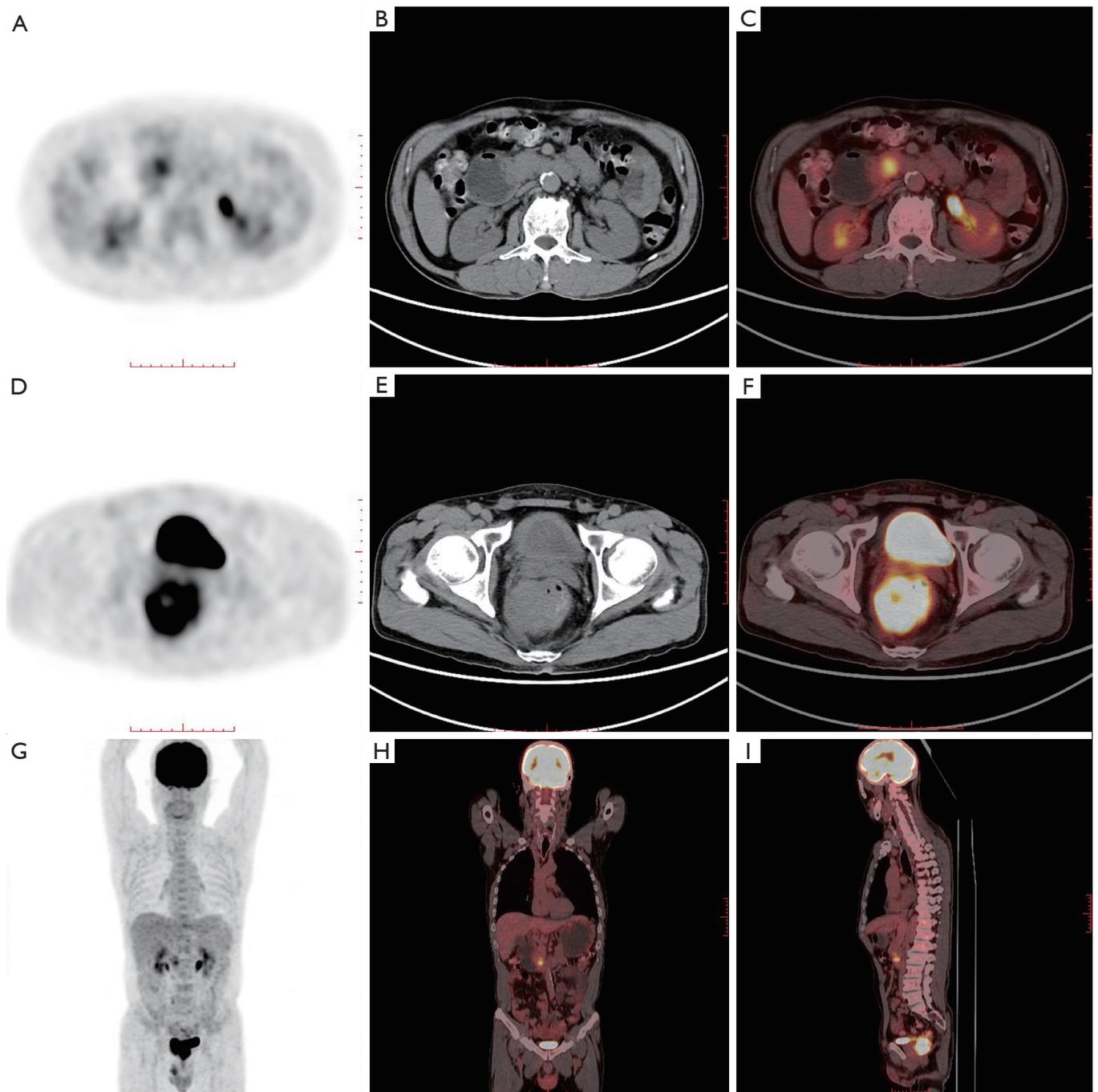
Figure 3 ^{18}F-FDG PET/CT shows two hypermetabolic tumors: in the head of the pancreas another in the rectum. These two tumors were confirmed by pathology as pancreatic cancer and rectal cancer, respectively. (A) PET image, (B) non-enhanced CT image, (C) fused PET and CT images of pancreatic cancer; (D) PET image, (E) non-enhanced CT image, (F) fused PET and CT images of rectal cancer; (G) PET image of maximal intensity projection in coronal, (H) fused PET and CT images in coronal, (I) fused PET and CT images in sagittal.

3570

Pu et al. PET/CT in pancreatic cancer
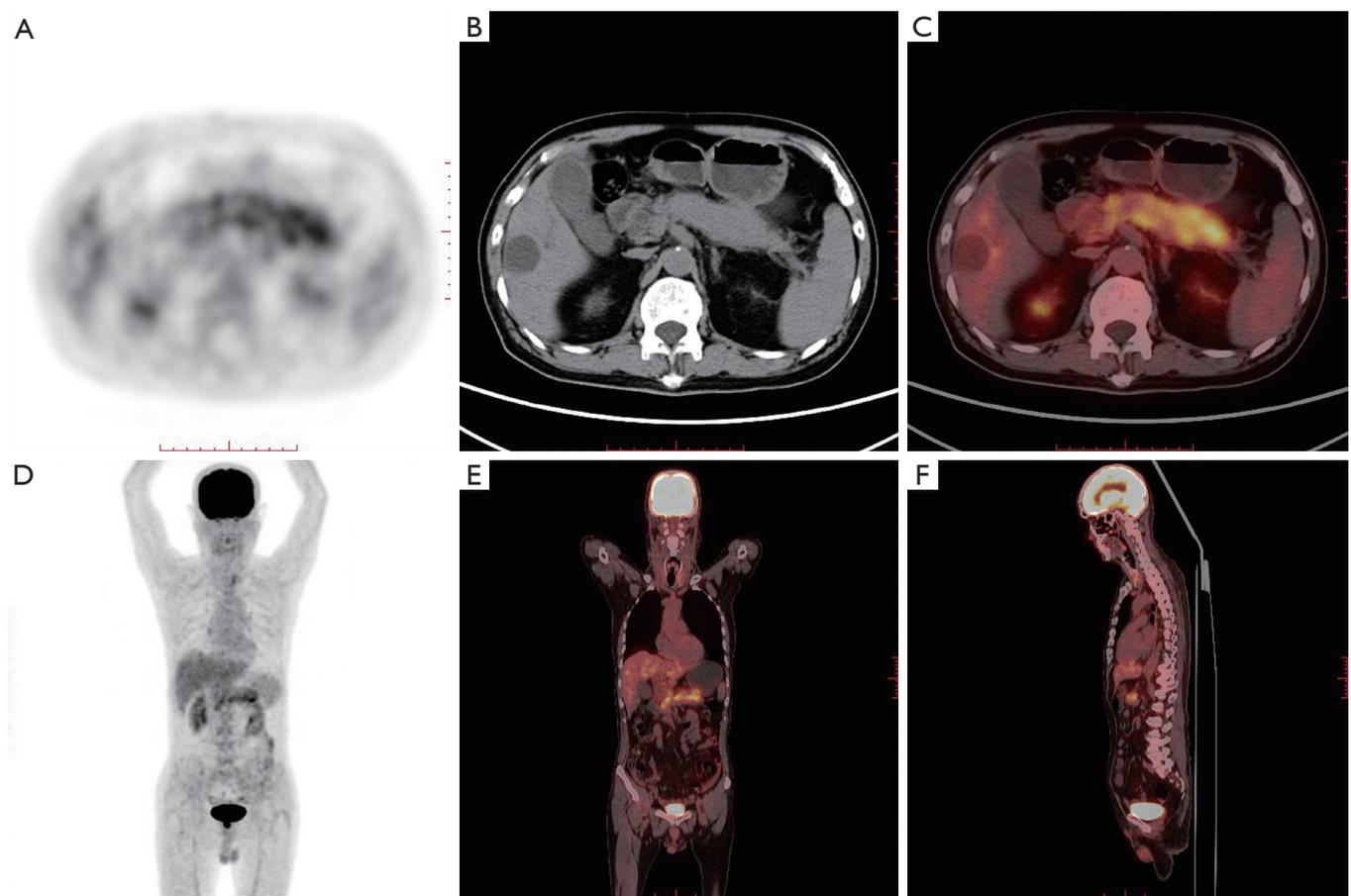
Figure 4 ^{18}F-FDG PET/CT shows the metabolic abnormalities and increased FDG accumulation of the pancreas. It was confirmed by pathology and IgG 4 as autoimmune pancreatitis. (A) PET image, (B) non-enhanced CT image, (C) fused PET and CT images of autoimmune pancreatitis; (D) PET image of maximal intensity projection in coronal, (E) fused PET and CT images in coronal, (F) fused PET and CT images in sagittal.

cancer and improves the detection of liver metastasis (91). Nielsen *et al.* used F-fluorobenzoate to radioactively label active site-inhibited factor VIIa (FVIIai) for the specific and noninvasive imaging of tissue factors in pancreatic cancer (92).

Zettlitz *et al.* developed a double-labeled probe based on the A2 cysteine diabody (A2cDb) that targets cell surface prostate stem cell antigen (PSCA) expressed in most pancreatic cancers and supported the dual-mode detection of pro-antigen-specific PET (immuno-PET) and intraoperative near-infrared fluorescence (NIRF). High-contrast immunological PET/NIRF images of pancreatic ductal adenocarcinoma xenografts (PDX-PDAC) can be obtained using dual-mode imaging anti-PSCA cys-dual antibodies, indicating that the imaging agent may also

provide noninvasive whole-body imaging to locate PSCA-positive pancreatic cancer and identify tumor edges during fluorescent image-guided surgery (93). Houghton *et al.* reported the application of PET, NIRF, and dual-modal (PET/NIRF) imaging agents using 5B1, a fully human monoclonal antibody that targets CA19-9, a well-established pancreatic cancer biomarker. Validated by xenograft animal models, this imaging agent has a significant ability to delineate metastases and map sentinel nodes by PET/CT and NIRF imaging (94). Houghton *et al.* modified 5B1 with trans cyclooctene (TCO) and synthesized a novel NOTA-PEG7-Tz radioligand. They suggested that the 5B1-TCO and (64) Cu-NOTA-PEG7-Tz systems can delineate CA19-9-positive xenografts in murine models of pancreatic cancer (95). Besides, immuno-PET with the radiolabeled

high-affinity antibody HuMab-5B1 (MVT-2163) binds to the cancer antigen CA19-9 and can identify the source of elevated biomarkers in patients with pancreatic cancer. Lohrmann *et al.* injected MVT-2163 into 12 patients with CA19-9-positive metastatic pancreatic cancer and performed four whole-body PET/CT scans within one week. As a result, radiotracer absorption was observed not only in metastases shown by conventional CT but also in lymph nodes just centimeters below specific metastatic sites of pancreatic cancer, suggesting that circulating tumor antigen CA19-9 can be used for the sensitive detection of primary tumors and metastatic diseases by immuno-PET (96).

Besides, Loktev *et al.* developed an iodine-labeled and DOTA-conjugated radiotracer based on fibroblast activation protein specific enzyme inhibitor (FAPI), and imaged patients with ^{68}Ga-labeled FAPI in 2018 (97,98). Radiolabeled FAPI can be quickly imaged with high contrast in tumors with high proportion of stroma (99,100). Kratochwil *et al.* performed ^{68}Ga-FAPI PET/CT on 80 patients with 28 different tumors. In pancreatic cancer, the average SUVmax is at a moderate level (SUV 6–12). Due to the low background of muscles and blood pools (SUVmax <2), the contrast of medium-intensity pancreatic cancer to the background is more than 3 times (101). Röhrich *et al.* performed ^{68}Ga-FAPI-PET/CT imaging on 19 patients with pancreatic cancer. Compared with enhanced CT, ^{68}Ga-FAPI-PET/CT changed the staging of 10 patients (102). These findings significantly broaden the number of molecular targets available for PET imaging.

Conclusions

In general, ^{18}F-FDG PET/CT plays a vital role in early diagnosis, and accurate staging predicts survival and monitors therapeutic effectiveness and pancreatic cancer recurrence. Although ^{18}F-FDG PET/CT has limitations in identifying inflammatory diseases and tumors, it still has good development potential. With the development of various new imaging agents, PET/CT will play a more critical role in the clinical diagnosis and treatment of pancreatic cancer.

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Footnote

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3572

Pu et al. PET/CT in pancreatic cancer

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