

PET Imaging in Pancreatic Cancer

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Review

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ABSTRACT

Early accurate detection of pancreatic cancer is still a challenge for current medicine. Compared to conventional anatomical imaging techniques, PET can provide information on tumor function, and PET/CT is increasingly used in detecting and staging of cancer as single "one stop shop" method. In this review, we summarize current PET molecular imaging tracers or probes for pancreatic cancer detection, and a perspective of the future trend of pancreatic cancer target-specific probes in the clinic is also provided.

Keywords: Pancreatic cancer, Pancreatic ductal adenocarcinoma, positron emission tomography (PET)

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is the most common pancreatic cancer, which is currently considered to be the third leading cause of cancer-related deaths in the United States[1]. Only 10 to 20% of patients with pancreatic cancer are candidates for resection and hence have any potential for cure, and the majority of patients present in late stages [2]. Conventional diagnostic imaging, such as ultrasonography and endoscopic ultrasound (EUS), Computed tomography (CT), MRI (Magnetic Resonance Imaging) are available structural imaging techniques for the diagnosis, staging, and management of pancreatic neoplasms. Trans-abdominal ultrasound is a first-line screening modality for evaluating patients with suspicious pancreatic disease, because of its advantages include wide availability, low cost, and lack of radiation. However, it is sometimes difficult to evaluate the entire pancreas because of gas-fat interferences and the diagnostic ability greatly depends on the operator's experience. EUS combines ultrasound with endoscopy, overcomes those limitations and obtains a higher resolution imaging of the pancreas and adjacent structures. It is also possible to obtain tissue specimen for histologic diagnosis using EUS-guided fine needle aspiration. However, it also has several limitations such as lack of widespread availability, a small field of view, and the need for patient sedation. Enhanced CT with iodinated contrast medium is now routinely performed for the diagnosis of suspicious pancreatic lesions, especially for assessment of resectability, assessment of vascular invasion with good spatial and temporal resolution. MRI is superior to CT in the evaluation of soft tissue and static fluid. A variety of techniques are used for further identification and characterization of pancreatic diseases: dynamic studies following gadolinium injection; magnetic resonance cholangio-pancreatography (MRCP); and diffusion-weighted imaging (DWI). MRCP allows the non-invasive delineation of the pancreatic duct and biliary tract. This technique will probably replace invasive endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis of small pancreatic masses, although its disadvantage is that it does not permit tissue sampling. However, these used structural imaging modalities are not specific in

disease diagnosis, then distinguishing pancreatic adenocarcinoma from nonmalignant masses remains a challenge [3, 4], especially for lesions smaller than 2 cm and cause an inconspicuous border deformity of the pancreas[5]. Meanwhile, chronic pancreatitis is notoriously difficult to diagnose, no applicable blood test currently used for chronic pancreatitis, and consequently this disease is diagnosed mainly through conventional insensitive imaging techniques. Hence, distinguish chronic pancreatitis from pancreatic cancer is still a difficulty, there is no established method for early detection of pancreatic cancer [1, 6].

Contrast to conventional anatomical imaging techniques, molecular imaging modalities such as positron emission tomography (PET) can provide information on tumor function, it is a nuclear imaging technique used to visualize, characterize, and measure biological processes at the cellular, subcellular, and molecular level in living subjects non-invasively[7]. In combination with probes or tracers that bind to and enable detection of disease-specific molecules[4]. Currently, hardware fusion PET/CT imaging is the general trend. Hardware fusion PET/CT not only increases diagnostic accuracy, but also significantly decreases the time required for attenuation correction. Numerous targeting moieties have been employed as vehicles of PET probes, including small molecules, peptides, protein, antibody and its fragments, as well as nanoparticles. This review summarizes current PET molecular imaging tracers or probes for pancreatic cancer detection and provides an overview of the current status and trends in the development of pancreatic cancer target-specific probes.

2-deoxy-2-[¹⁸F]-fluoro-d-glucose (¹⁸F-FDG) imaging of glucose metabolism

To date, the glucose analogue ¹⁸F-FDG PET has been the most commonly used radiotracer worldwide. At present, it is most applied for staging, planning treatment, predicting prognosis, monitoring the response to therapy, evaluating recurrences as well. As glucose metabolism changes in tissue usually predate any structural changes of the pancreas, ¹⁸F-FDG may be more sensitive for detecting early malignancies. Rijkers et al.[8] performed a meta-analysis, in which

thirty-five studies were included. Pooled estimates for ^{18}F -FDG PET/CT were: sensitivity 90%, specificity 76%, PPV 89%, NPV 78% and accuracy 86%, respectively. The pooled sensitivity and specificity for ^{18}F -FDG PET/CT to differentiate between pancreatic cancer and chronic pancreatitis were 90% and 84%, respectively. It concluded that ^{18}F -FDG PET/CT showed no superiority to the current primary diagnostic tools in diagnosing pancreatic cancer. First, ^{18}F -FDG is a non-specific imaging tracer, increased glucose metabolism at inflammatory lesions is the main source of false-positive. Second, due to the presence of pancreatic cancer or underlying disease, a high percentage of these patients are diabetic, and elevated plasma glucose levels will cause a high rate of the false negative. Therefore, both false positive and false negative are common for ^{18}F -FDG in pancreatic cancer diagnosis.

^{18}F -fluoro-3-deoxy-3-fluorothymidine(^{18}F -FLT) imaging of cellular proliferation

Thymidine is a native nucleoside, which is exclusively incorporated into the cellular DNA. ^{18}F -FLT, an analogue of thymidine, can be performed for clinical evaluation and quantification of proliferative activity and tumor invasiveness. There many clinical researches evaluated the potential value of ^{18}F -FLT PET/CT for imaging pancreatic adenocarcinoma [2, 9, 10]. Quon et al.[9] compared ^{18}F -FLT and ^{18}F -FDG PET/CT scan in five patients. On ^{18}F -FLT PET/CT, the primary pancreatic adenocarcinoma was detected in 40% patients from background activity. By contrast, ^{18}F -FDG uptake was higher in each patient and primary cancer could be detected in 100% patients. Clinical studies performed so far have not shown a distinct advantage for ^{18}F -FLT over ^{18}F -FDG. Overall, tumor ^{18}F -FLT uptake is lower than ^{18}F -FDG uptake in most cancers, reflecting the higher sensitivity of ^{18}F -FDG.

However, how about ^{18}F -FDG and ^{18}F -FLT imaging in the context of infection and inflammation? Van et al.[11] compared ^{18}F -FLT and ^{18}F -FDG for differentiating tumor from inflammation in a rodent model. They discovered in ^{18}F -FDG PET images, both tumor and inflammation were visible, but ^{18}F -FLT PET

showed only the tumor. Thus, it was hypothesized that ^{18}F -FLT has a higher tumor specificity in rodent model. However, its potential in differentiation between tumor and inflammation has not yet been evaluated in humans, further studies may be required.

Imaging with antibodies-based probes

Yet most novel imaging probes are hindered by suboptimal tumor accumulation, to overcome these limitations, researchers have explored numerous antibodies for PET imaging purposes [12-15]. Antibody-based probes have advantages of antigen-specific, high binding affinity and absolute tumor uptake.

1) ^{64}Cu -Labeled MAb159

The glucose-regulated protein78 (GRP78) receptor is overexpressed on the surface of tumor cells, and it is capable of serving as a receptor or target of anti-cancer drugs[16]. Wang et al.[15] developed a ^{64}Cu -labeled monoclonal antibody, MAb159 for PET imaging of tumor GRP78 expression. In BXPC3 xenografts, ^{64}Cu -DOTA-MAb159 demonstrated prominent tumor accumulation (15.4 ± 2.6 , and $18.3 \pm 1.0\%$ ID/g at 17h, and 48 after injection, respectively). On contrary, ^{64}Cu -DOTA-human IgG had much lower tumor accumulation. It was demonstrated that GRP78 can serve as a valid target for pancreatic cancer imaging and may also have important applications in other types of cancer with high expression of GRP78.

2) Zirconium- 89 (^{89}Zr)-labeled anti-IGF-1R antibody

Insulin-like growth factor-1 receptor (IGF-1R) plays an important role in cancer tumorigenesis. England et al.[17] reported the development of an ^{89}Zr labeled anti-IGF-1R antibody (^{89}Zr -Df-1A2G11) for PET imaging of pancreatic cancer. Serial PET imaging was performed at different time points after ^{89}Zr -Df-1A2G11 was injected into MIA PaCa-2, BxPC-3, and AsPC-1 tumor bearing mice. The highest accumulation of ^{89}Zr -Df-1A2G11 was found in the MIA PaCa-2-derived tumor model at 12 h postinjection ($7.28 \pm 1.36\%$ ID/g). This study provides initial evidence that ^{89}Zr -labeled IGF-1R-targeted antibody may be employed for imaging pancreatic cancer.

3) ^{64}Cu labeled ALT-836

The expression of tissue factor (TF) is upregulated in many solid tumors. Weibo Cai's group ever first successfully developed TF targeted imaging probe for pancreatic cancer detection [18]. ALT-836 is a TF monoclonal antibody that can bind to TF with subnanomolar affinity. ^{64}Cu -NOTA-ALT-836 is capable of binding TF, and it revealed that the uptake of the tracer was $16.5 \pm 2.6\%$ ID/g in BXPc-3 pancreatic cancer models with high TF expression at 48 h after injection (Fig.1). Furthermore, the biodistribution data were consistent with the PET findings.

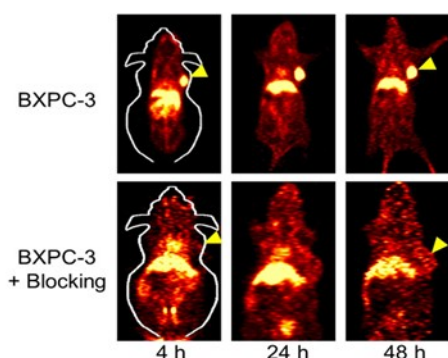


Fig.1 ^{64}Cu labeled ALT-836 imaging of TF and its block study[18].

4) ^{124}I -labeled anti-CA19-9 diabody

Due to a long serum half-life (10–20d), intact antibodies are poor imaging agents. Slow tumor accumulation and high background signal are the consequence of inconspicuous contrast between the tumor and surrounding blood. Smaller engineered antibody fragments undoubtedly overcome this problem. The diabody (55 kDa) is the smallest antibody fragment (serum half-life:2-4h). Girgis et al.[19] successfully engineered a functional diabody against CA19-9, and an isotope iodine-124 (^{124}I) was labeled to it. It was proved that ^{124}I -anti-CA19-9 diabody demonstrated high contrast antigen specific in pancreas xenograft imaging. The average tumor/blood ratio of nude mice carrying CA19-9 positive and negative models with the ^{124}I -labeled anti-CA19-9 diabody was 5.0 and 2.0, respectively, and the average tumor ratio of positive/negative was 11 and 6, respectively.

Peptides based tracers for imaging

As compared to antibodies, low-molecular-weight peptides have their distinctive advantages: short blood lifetime; non-immunogenic; relatively inexpensive to synthesize; easy to modify [7, 20]. Consequently, numerous peptide-based agents have been developed to the specific molecular targets in preclinical and clinical studies (Table 1).

Targeting $\alpha\nu\beta_6$ integrin

Integrin alphavbeta6 ($\alpha\nu\beta_6$) is one of cell surface receptors low expressed in the mature tissue, but significantly up-regulated in PDAC, which was considered to be a promising target for diagnostic imaging and therapy[21, 22].

i) Peptide NAVPNLRGDLQVLAQKVART (A20FMDV2) was derived from foot-and-mouth disease virus with 20 amino acids, which presented a potent inhibition of $\alpha\nu\beta_6$ (IC_{50} 3 nmol/L) was identified by the Hausner group[20]. A20FMDV2 was radiolabeled by using 4- ^{18}F fluorobenzoic acid, and it was a first-generation radiotracer for targeting $\alpha\nu\beta_6$ in vivo. It appeared rapid uptake (<30 min) and selective long retention (>5 h) of radioactivity in the $\alpha\nu\beta_6$ -positive tumor, the ratio of tumor-to-background was steady over time, and the tracer with fast renal elimination. Several mice also underwent ^{18}F FDG Micro-PET scan 1 h after injection, and there was no difference in ^{18}F FDG uptake between positive and negative mice models. ^{18}F FBA-PEG₍₂₈₎-A20FMDV2 was an improved $\alpha\nu\beta_6$ imaging agent based on the former study(Fig.2)[23]. The modified agent maintained a higher affinity for $\alpha\nu\beta_6$ and showed significantly improved $\alpha\nu\beta_6$ -dependent binding. In BxPC-3 tumors, the modified tracer showed retention of 12-fold greater than retention of the non-PEGylated ^{18}F FBA-A20FMDV2. At 4 hours, tumor-to-pancreas and tumor-to-blood biodistribution ratios achieved >23:1 and >47:1, respectively. Significantly, ^{18}F FBA-PEG₍₂₈₎-A20FMDV2 was superior to ^{18}F FDG in imaging the BxPC-3 tumors, and it has potential in clinics for $\alpha\nu\beta_6$ -specific tumor imaging.

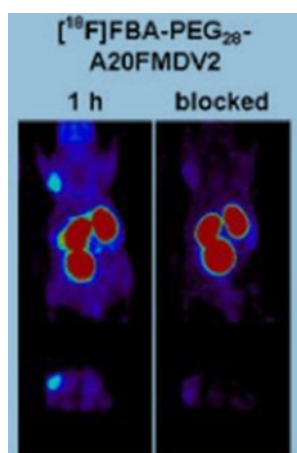


Fig.2 [^{18}F]FBA-PEG₍₂₈₎-A20FMDV2 microPET imaging of $\alpha_v\beta_6$ in pancreatic cancer xenografts and block study[23].

ii) Hackel Group[24] synthesized peptides R₀₁ and S₀₂ (Figs.3), and were conjugated with ^{18}F -fluorobenzoate. After injection for both peptides, the tumor was clearly visualized as early as 0.5 h (Figs.4). ^{18}F -fluorobenzoate-R₀₁ presents greater tumor uptake than ^{18}F -fluorobenzoate-S₀₂, and both have comparable tumor-to-muscle ratios: 3.1 ± 1.0 and 2.9 ± 0.4 at 0.5 and 1 h, respectively. Imagings were also performed with integrin $\alpha_v\beta_6$ -negative xenografted mice. Both exhibits significantly less uptake than BxPC3 xenografts (Figs.4).

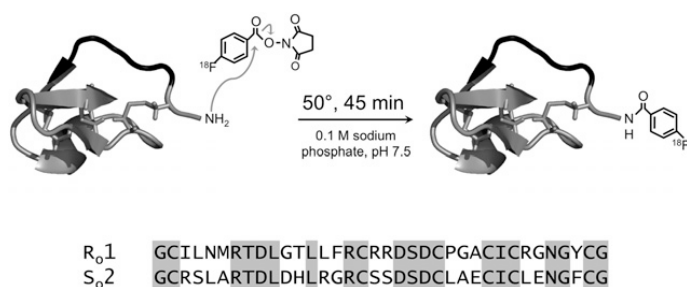


Fig. 3 R₀₁ and S₀₂ are cystine knot peptides. N-terminal amine was coupled with ^{18}F -SFB. Peptide sequences are presented, conserved residues were highlighted[24].

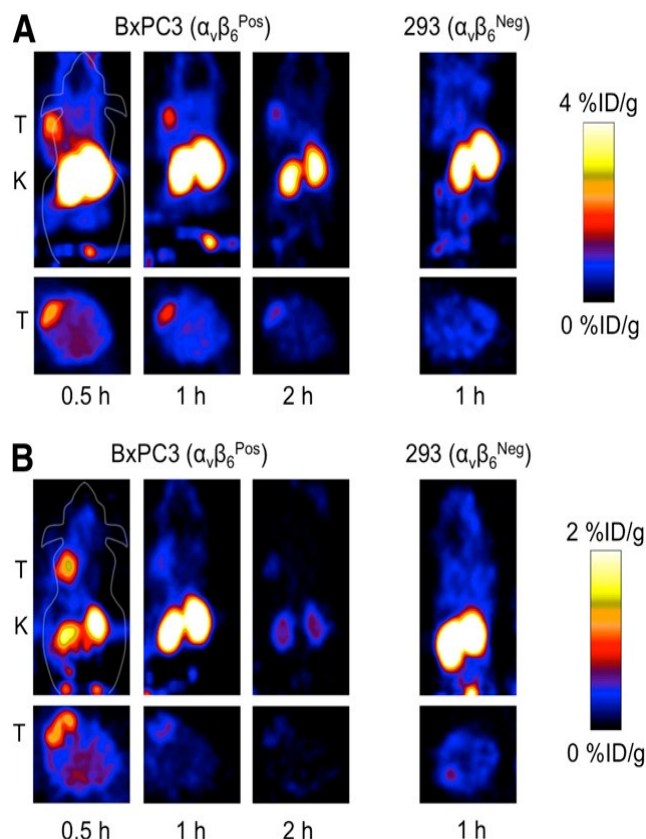


Fig. 4 Micro-PET imaging. ^{18}F -fluorobenzoate-R₀₁ (A) or ^{18}F -fluorobenzoate-S₀₂ (B) were injected into nude mice bearing BxPC3 pancreatic adenocarcinoma cells (integrin $\alpha_v\beta_6$ -positive) or 293 (integrin $\alpha_v\beta_6$ -negative) tumors. At 0.5, 1, and 2 h after injection, five-minute static scans were acquired. Coronal and transverse slices are presented. Tumor (T) and kidneys (K) are signed on images[24].

2) Targeting $\alpha_v\beta_3$ integrin

i) ^{68}Ga -labeled NODAGA (1,4,7-triazacyclononane-1,4-bis[acetic acid]-7-[2-glutaric acid])-conjugated RGD peptide (^{68}Ga -NODAGA-RGD) was the first tracer used for visualization of $\alpha_v\beta_3$ expression in spontaneous PDAC occurring mice[25]. Both in murine and human PDAC, $\alpha_v\beta_3$ expression were confirmed. High uptake of ^{68}Ga -NODAGA-RGD in PDAC was detected and the accumulation decreased dramatically when blocked by $\alpha_v\beta_3$ inhibitor. The tracer was well tolerated and stable in vivo, and was ever applied in a clinical trial for hepatocellular carcinoma (HCC) detection, however, it was confirmed that its accumulated was not sufficient [26]. As for PDAC, no clinical studies are undertaken currently.

ii) ^{64}Cu -labeled cyclam-RAFT-c(-RGDfK-)₄ peptide (^{64}Cu -RAFT-RGD) is another tracer targeting $\alpha\text{v}\beta_3$ integrin. Biodistribution data revealed that the radioactivity in tumor was nearly six times higher than surrounding normal pancreas. The blocking study confirmed that the binding of the probe to the tumor is highly $\alpha\text{v}\beta_3$ integrin-specific. In comparison, ^{64}Cu -RAFT-RGD accumulation was superior to [^{18}F]-FDG, which provided better tumor contrast to the background. It is potentially applicable for the diagnosis of pancreatic cancer with high $\alpha\text{v}\beta_3$ integrin expression [27].

3) Targeting Hsp90

Heat shock protein 90 (Hsp90) plays an important role in the progress of malignant disease and elevated Hsp90 expression has been reported in pancreatic cancer. It resides exclusively in the cytosol in normal cells, but is activated and then moves to the cell surface in tumor cells [28, 29]. Furthermore, Hsp90 inhibitors selectively kill cancer cells compared to normal cells, it was reported that Hsp90 derived from tumour cells has a 100-fold higher binding affinity for the Hsp90 inhibitor 17-allylaminogeldanamycin (17-AAG) than does Hsp90 from normal cells [30]. Therefore, Hsp90 is an attractive target for cancer imaging [31, 32]. we found the most powerful Sansalvamide A derivative (IC_{50} 1-20nM), and radio-

labeled ^{64}Cu -Di-San A1 (Fig.5) for PET imaging of Hsp90 expression in a mouse model of pancreatic cancer. ^{64}Cu -Di-San A1 was successfully prepared in a radiochemical yield >97% with a radiochemical purity >98%. Micro PET study shows good in vivo performance in terms of tumor uptake in nude mice bearing pancreatic cancer. The Hsp90-specific tumor activity accumulation of ^{64}Cu -Di-San A1 was further demonstrated by significant reduction of PL45 tumor uptake with pre-injected an Hsp90 inhibitor (17AAG). The ex vivo PET imaging and biodistribution results were consistent with the quantitative analysis of PET imaging, demonstrating good tumor-to-muscle ratio (5.35 ± 0.46) at 4 h post-injection in PL45 tumor mouse xenografts. ^{64}Cu -Di-San A1 allows PET imaging of Hsp90 expression in PL45 tumors, which may provide a non-invasive method to quantitatively characterize Hsp90 expression in pancreatic cancer [33].

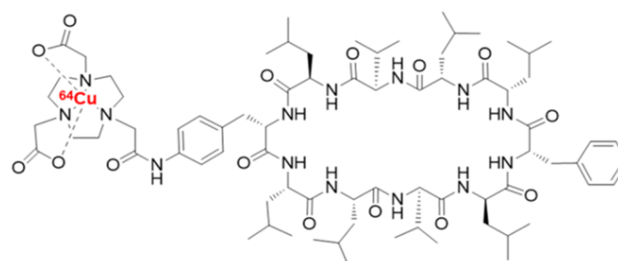


Fig. 5 The chemical structure of ^{64}Cu -Di-San A1

Table 1: Radiosynthesis of peptides based PET Tracers for pancreatic cancer

Compounds	Target	Synthesis time	Clinical available	Specific activity (%ID/g)	Different ratios	HPLC needed	Radiochemical yield (%)	Ref
^{18}F FBA-A20FMDV2 ^{18}F FBA-PEG ₂₈ -A20FMDV2 ^{18}F FBA-(PEG ₂₈) ₂ -A20FMDV2	$\alpha\text{v}\beta_6$	130 min	No	0.69 ± 0.19 1.85 ± 0.44 1.57 ± 0.25	tumor-to-background (1h:2.2:1 ; 3h :3.5:1) tumor-to-blood >47:1	Yes	3.6%	[20, 23]
^{18}F fluorobenzoate-R ₀ 1 ^{18}F -fluorobenzoate-S ₀ 2		45 min		1.4 ± 0.6 0.5 ± 0.2	tumor-to-muscle 3.1 ± 1.0 2.9 ± 0.4	Yes	$23\% \pm 13\%$	[24]
^{68}Ga -NODAGA-RGD	$\alpha\text{v}\beta_3$	5min	Clinical trial (Phase I)	2-10	—	No	> 96%	[25]
^{64}Cu -RAFT-RGD		60 min	No	6.01 ± 0.75	Tumor to blood: 46.64 ± 9.93 Tumor to- muscle 9.3 ± 0.25	Yes	>98%	[27]
^{64}Cu -Di-San A1	Hsp90	2 h	No	2.97 ± 0.58	tumor-to-muscle 5.35 ± 0.46	Yes	>97%	[33]

Targeting specific genes

G-protein-coupled cholecystokinin B receptor (CCKBR) was constitutively expressed on the surface of PDAC cells. Clawson et al.[34] described selection and characterization of high-affinity DNA aptamers (APs) to the CCKBR. Moreover, the uptake was increased in vivo of orthotopic PDAC tumors compared with native ligand gastrin. One AP, named AP1153 was chosen for further studies. They found that AP1153 was internalized by PDAC cells in a receptor-mediated manner. Bioconjugation of AP1153 to the surface of fluorescent NPs greatly facilitated delivery of NPs to PDAC tumors in vivo. The AP-targeted NP delivery system has potential for enhanced early detection of PDAC lesions [34].

The majority of patients with PDAC carry mutant KRAS2 oncogenes, and KRAS2 mRNA was activated and overexpressed in pancreatic cancer cells [35, 36]. Early detection of activated specific KRAS2 mRNAs in PDAC in vivo would be feasible by molecular imaging [37-39]. These probes are designed to bind to internalize and hybridize with KRAS oncogene mRNA that is overexpressed in pancreatic cancer.

CONCLUSION AND PERSPECTIVES

Pancreatic ductal adenocarcinoma (PDAC) is the most representative type of pancreatic cancer. It begins in the cells lining the pancreatic duct. PDAC solid tumors are composed of heterogeneous populations of cells including cancer stem cells, differentiated cancer cells (high-grade, moderate and worst differentiation), desmoplastic stroma and immune cells [40]. Although overall survival rates have improved for most cancers, pancreatic cancer is still currently most lethal malignancy[12, 41]. It has lowest survival rates among cancers, its deaths have not been decreasing over the past few years. Its 5-year survival rate is constant at a 6%, with more than 80% mortality within a year of diagnosis [1, 42, 43]. The lack of early diagnosis and ineffective treatment for advanced tumors are primarily the cause of the highly mortality. PDAC is on track to become the second most common cause of cancer-related deaths by 2030 in the United States[44].

Early pancreatic cancers often present atypical signs or symptoms. By the time they do cause symptoms, they have often already spread outside the pancreas. Jaundice is usually a typical symptom when the mass is located at head of pancreas. There are numerous risk factors cause pancreatic cancer. However, many people who get the disease may seldom have known risk factors.

Imaging is critical for the detection, characterization, management of pancreatic cancer cases [45, 46]. Due to the limitations of current anatomical imaging techniques, early detection of pancreatic cancer remains a field requires further improvement. Compared to conventional anatomical imaging technique modalities, PET is a new emerged and functional imaging tool that can offer the possibility of quantification of diseases associated biochemical processes[47]. It is commonly used for cancer diagnosis and staging, as well as offering prognostic information. Due to its low spatial resolution, pure PET imaging is subsequently combined with an X-ray CT scanner, which is able to overcome the drawback of PET. Thus, functional imaging obtained by PET, which depicts the spatial distribution of metabolic or biochemical activity in the body can be more precisely aligned with anatomic imaging obtained by CT scanning, and both functional and anatomical information are presented simultaneously in the same image. Other than traditional imaging modalities, injection of molecular imaging agents in the tested subject are required in order to acquire the PET imaging signals. Based on diverse principles, different agents may appear different images to the same lesion of the subject.

In this review, five general categories of PET imaging agents were examined, each tracer has its advantage and disadvantage, when designing novel research studies involving pancreatic cancer diagnosis, the current limitations of each category tracer should be considered. Taken together these tracers or probes represent promising methods for the establishment of novel imaging agents in the future. Meanwhile, the molecular markers mentioned in the review are also attractive targets for pancreatic cancer therapy when

a precursor is labeled with long half-life radionuclide, such as ^{177}Lu ($t_{1/2}$:6.73d) and ^{89}Zr ($t_{1/2}$:78.4 h).

^{18}F -FDG is the solely globally most commonly used imaging tracer in clinic, it is regarded as the “molecule of the century” in nuclear medicine. Nowadays, it is mainly used for oncology, which has great superiority in accurate staging, assessment of the therapeutic response and detection of recurrences. But as for diagnosis of tumor itself, ^{18}F -FDG has its intrinsic limits. In order to overcome the overlaps between malignancy and benign lesions, dual-time-point-imaging (DPI)--at approximately 1 hour (early) and 2 hours (delayed) after injection are recommended [48, 49]. Delayed phase of ^{18}F -FDG imaging may increase primary lesion detectability due to higher FDG uptake in primary tumors compared to the early phase of imaging [50, 51]. DPI may also help to differentiate between inflammatory and malignant lymph nodes [52]. However, it increased sensitivity for lesion detection (compromised specificity). There was study declared overall accuracy of DPI FDG PET/CT were better than that of single phase for less than 25 mm tumor, it might be useful for diagnosing small pancreatic tumors [49]. Besides, PET with enhanced CT will not only play an important role in differential diagnosis, but also give additional information concerning peripheral blood vessel. Whereas, in most PET/CT centers, only non-enhanced CT scans are undertaken.

Although numerous molecular imaging agents either directly measure metabolism of cells or bind to the overexpressed specific targets had been developed, only very few are translated into clinic for the diagnosis of pancreatic cancer. Most of these imaging modalities remain highly debatable and uncertain, which may be resolved through concerted cooperation from basic researchers in combination with radiologists and multicenter clinical trials [53]. Targeting of cell surface receptors overexpressed in cancer remains the most promising strategy for designing molecular imaging probes. A novel imaging probe with clinical translation potential is supposed to have the following unique characteristics: High binding affinity and specificity to target; High sensitivity, contrast

ratio and stability in vivo; Low immunogenicity and toxicity; Production and economical feasibility[47]. Considering the liver is the most common metastatic organ for pancreatic cancer, hence to explore novel imaging agents with lower live uptake is also very important. In addition, improved instrumentation with high spatial resolution and lower expenditure is also should be considered. As for tumor models, orthotopic models probably reflect the physiological character of pancreatic cancer. Currently, most animal models in researches are subcutaneous

In the future, molecular imaging will pave a pathway to both personalized medicine and precision medicine. Patients at risk for pancreatic cancer may be screened using highly optimal imaging agents and early detection is feasible to save millions of lives. However, great efforts are remain required to explore new imaging tracers that can overcome drawbacks of currently used agents and push more and more novel agents to serve to more patients in clinic.

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