World Journal of Gastrointestinal Oncology

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DOI: 10.4251/wjgo.v8.i2.165

*World J Gastrointest Oncol* 2016 February 15; 8(2): 165-172
ISSN 1948-5204 (online)


TOPIC HIGHLIGHT

2016 Pancreatic Cancer: Global view

# Advancement in treatment and diagnosis of pancreatic cancer with radiopharmaceuticals

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Author contributions: Xu YP collected the material, prepared the manuscript and approved the final version; Yang M prepared the manuscript and approved the final version.

Supported by National Natural Science Foundation, Nos. 81171399, 51473071, 81101077, 21401084, 81401450 and 81472749; Jiangsu Province Foundation, Nos. BE2014609, BE2012622, BL2012031 and BM2012066; and Wuxi Foundation, No. CSZ0N1320.

Conflict-of-interest statement: The authors do not have any possible conflicts of interest.



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Received: April 28, 2015
Peer-review started: May 5, 2015
First decision: July 21, 2015
Revised: November 26, 2015
Accepted: December 17, 2015
Article in press: December 18, 2015
Published online: February 15, 2016

## Abstract

Pancreatic cancer (PC) is a major health problem. Conventional imaging modalities show limited accuracy for reliable assessment of the tumor. Recent researches suggest that molecular imaging techniques with tracers provide more biologically relevant information and are benefit for the diagnosis of the cancer. In addition, radiopharmaceuticals also play more important roles in treatment of the disease. This review summaries the advancement of the radiolabeled compounds in the theranostics of PC.

**Key words:** Pancreatic cancer; Diagnosis; Therapy; Radiopharmaceuticals; Positron emission tomography



**Core tip:** This review describes the development of radiopharmaceuticals in diagnosis and therapy of pancreatic cancer. We herein discuss the role of the radiolabeled compounds in the preoperative diagnosis, staging, post-therapeutic monitoring, prognosis and the treatment of the disease.

Xu YP, Yang M. Advancement in treatment and diagnosis of pancreatic cancer with radiopharmaceuticals. *World J Gastrointest Oncol* 2016; 8(2): 165-172 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i2/165.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i2.165

## INTRODUCTION

Pancreatic cancer (PC) is a major health problem due to low 5-year survival rate[1-3]. Surgery is the only curative treatment but less than 20% of cases are suitable to

be respectable during diagnosis for the late onset of the symptoms[4-6]. Therefore, suitable diagnosis and staging is essential for management of the disease.

Computed tomography (CT), magnetic resonance imaging (MRI), and endoscopic ultrasound (EUS), *etc*., provide information regarding tumor size, location, and morphology, which can be used for initial staging, tumor evaluation and follow-up. However, it also remain suboptimal in the preoperative diagnosis and may hamper the treatment. The discrimination between benign and malignant lesions are still challenging with these methods[7,8].

Molecular imaging techniques are important tool capable of providing high sensitive non invasive and quantitative images of various cancer[9-11]. Radiopharmaceuticals is a key factor in the non-invasive molecular imaging technique which enables specific cellular and molecular processes to be functionally visualized. The development of molecular imaging agents target for specific biomarkers could provide more sensitive and specific cancer detection.

Meanwhile, a number of compounds labeled with therapy radionuclides have been employed for cancer treatment through intratumoral administration[12-15]. Compared with traditional high-dose external radiation, intratumoral administration delivers more radioactivity to the tumor than the normal structure[16].

Here, we review the pertinent literatures and the advancement in treatment and diagnosis of PC with radiopharmaceuticals was discussed.

## SMALL MOLECULE TRACERS FOR TUMOR IMAGING

### *$^{18}$F-fluorodeoxyglucose*

Over the past decade, positron emission tomography (PET) is an important molecular imaging methods in various malignancies[17-20]. $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) is an analogue of glucose. After injected into the body, it is actively transported *via* glucose transporters (GLUT) into cells, then phosphorylated by hexokinase in the same pathway as glucose. However, unlike normal glucose, the reactions of $^{18}$F-FDG do not proceed further and the corresponding product remains in the cells[21,22]. Overexpression of GLUT-1 and hexokinase-Ⅱ has been reported in PC[23]. In patients with PC, several studies have demonstrated that $^{18}$F-FDG PET/CT was an important key factor for in staging, detecting postoperative recurrence, and evaluating the response to treatment[24-28]. The recent typical researches and interest findings were listed in the follow.

**Preoperative diagnosis:** Ergul *et al*[29] compared the values of $^{18}$F-FDG PET/CT, multidetector row computed tomography (MDCT), MRI and EUS in the diagnosis and management of the tumor. It revealed that sensitivity of PET/CT were equal to EUS (100%) and higher than those of MDCT and MRI. Meanwhile, Specificity of MDCT was significantly lower than PET/CT. It suggested that $^{18}$F-FDG PET/CT is an useful imaging techniques for management of the disease[29].

Maximum standardized uptake value (SUVmax) reflects tumor aggressiveness as a marker of tumor glucose metabolism. Hu *et al*[30] found that the SUVmax of benign lesions significantly lower than that of malignant tumors (2.9 ± 2.0 *vs* 6.3 ± 2.4 respectively). A positive correlation between the SUVmax and Ki-67 was existed. It suggested that the SUVmax of $^{18}$F-FDG can be applied in the differential diagnosis and can also benefit for monitoring the proliferative status of PC[30].

Nagamachi *et al*[31] compared $^{18}$F-FDG PET/CT and $^{18}$F-FDG PET/MRI fusion image in diagnosing tumor. $^{18}$FDG-PET/MRI fusion image significantly improved accuracy. Results showed that this image technique was useful in differentiating diagnosis[31].

Zhang *et al*[32] reviewed 116 patients with pancreatic cystic tumors who had been treated with different imaging modalities. Compared with CT and EUS, PET had the best sensitivity, specificity and accuracy for detecting malignant cystic tumors[32].

When the conventional imaging modalities or biopsies are unavailable, PET also plays an important role in diagnosis of PC. Based on the $^{18}$F-FDG uptake pattern, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for FDG-PET/CT in differentiating benign and malignant lesions were all greater than 85% respectively[33].

Diagnostic performance of diffusion-weighted MRI and $^{18}$F-FDG PET/CT in the detection of pancreatic malignancy was also obtained by Wu *et al*[34]. When diagnosing patients with pancreatic malignancy, the sensitivity of PET/CT was higher than MRI but the specificity of the former was lower than the latter[34].

**Staging:** Wang *et al*[35] evaluate the value of $^{18}$F-FDG PET/CT on the pre-operative staging of the disease. The sensitivity and accuracy of the imaging modality to detect distant metastasis especially metastatic lymph nodes are significantly higher than those of MDCT. It showed that the extra staging information PET/CT provided could be helpful for screen of surgery[35].

$^{18}$F-FDG PET/CT scans were performed at 17 patients in baseline and six weeks post-CRT. SUVmax significantly decreased during CRT (median pre- 8.0 and post- 3.6). It revealed that the baseline $^{18}$F-FDG PET was benefit for definition of the biological target volume for non-uniform dose prescriptions[36].

Topkan *et al*[37] evaluated the impact of $^{18}$F-FDG PET/CT restaging on management decisions and outcomes in patients with LAPC scheduled for concurrent CRT. According with PET/CT before therapy, these individuals were classified into non-metastatic (M0) and metastatic (M1) groups then received different treatment. Twenty-six point eight percent of distant metastases were detected *via* PET/CT not by conventional staging. Three additional regional lymph nodes were found by PET/CT restaging and the volumes of the tumors were larger

than CT-defined borders. The initial management decisions of 26 patients were changed through PET/CT.

Median overall survival (OS) and progression-free survival (PFS) of M0 patients were greater than those of M1 patients. These findings conformed that PET/CT-based restaging may benefit for screening patients suitable for CRT[37].

**Post-therapeutic monitoring:** Picchio *et al*[38] evaluated the role of $^{18}$F-FDG PET/CT in screening patients with locally advanced PC for suitable treatment and monitoring the efficacy. Results showed that PET/CT play more important factors in designing the treatment plans for individual patient than conventional CT[38].

Kittaka *et al*[39] performed $^{18}$F-FDG PET in patients classified as responders and nonresponders before and after preoperative CRT. A pre-CRT SUV > 4.7 was seen in 15 (71%) of 21 responders and in 6 (32%) of 19 nonresponders. A regression index > 0.46 was observed in 15 (71%) responders and 5 (26%) nonresponders. It showed that the SUV based on FDG-PET/CT is a useful implement for predicting the response of treatment[39].

To study whether FDG-PET parameters can predict relatively long-term survival in patients, Chang *et al*[40] assess the effect of coregistered $^{18}$F-FDG PET in monitoring radiographically occult distant metastasis (DM) in patients with LAPC. Patients with a baseline standardized uptake value (SUV) < 3.5 and/or SUV decline ⩾ 60% had significantly better OS and PFS than those having none, even after adjustment for all potential confounding variables. $^{18}$F-FDG PET can spare one-third of patients with occult DM from the potentially toxic therapy. $^{18}$F-FDG PET parameters including baseline SUV and SUV changes may serve as useful clinical markers for predicting the prognosis in LAPC patients[40].

**Prognosis:** Several prognostic factors for PC recurrence have previously been reported including tumor size, T stage, lymph node metastasis, tumor differentiation, lymphovascular invasion, involvement of the surgical margin, and serum carbohydrate antigen 19-9 (CA19-9) level. Yamamoto *et al*[41] evaluated whether preoperative $^{18}$F-FDG PET can predict the resectable PC. Among the patients, 34 cases with an SUVmax ⩾ 6.0 developed recurrence within half year, however only 3 patients with an SUVmax < 6.0 exhibited early recurrence. The median OS time of patients with a SUVmax < 6.0 was significantly greater than those of patients with an SUVmax ⩾ 6.0. Therefore, an SUVmax ⩾ 6.0 maybe a significant predictor of recurrence of PC[41].

The histopathological grade of differentiation is also one of the significant prognostic factors in the disease, especially in the patients with unresectable PC. It was found that a significant correlation of SUVs and pathologic grades existed by $^{18}$F-FDG PET scans in 102 patients with histologically proven pancreas adenocarcinoma. It showed that $^{18}$F-FDG SUV is related with histologic grade and might be competitive predictor for survival[42].

Xi *et al*[43] determined $^{18}$F-FDG SUVmax in patients with PC at 1 h and 2 h post injection, and the retention index (RI) was defined as the percentage change between the values of two time points. It was found that there existed a significant positive correlation among RI and the tumor, node, and metastasis stage[43].

Shinoto *et al*[44] evaluated whether $^{18}$F-FDG PET can be used as an indicator of preoperative carbon-ion radiotherapy (CIRT) for PC patients. SUVmax was significantly correlated with DMFS and OS. The DMFS and OS in high-SUVmax group were significantly lower than those in low SUVmax group. $^{18}$F-FDG PET might be suitable for determining the indication of preoperative short-course CIRT for patients with resectable PC[44].

The prognostic role of $^{18}$F-FDG PET/CT in the prediction of PFS and chemotherapeutic response in patients with locally advanced or metastatic PC was also investigated by Moon *et al*[45] PFS of the low SUVmax (< 6.8) group was significantly longer than those of the high SUVmax (⩾ 6.8) group. Resulted showed that SUVmax may be useful in independent predicting PFS of PC[45].

The prognostic value of volumetric parameters on preoperative $^{18}$F-FDG PET/CT was assessed. Results revealed that metabolic tumor volume and total lesion glycolysis are independent prognostic factors for predicting RFS and OS. Thus, $^{18}$F-FDG PET/CT can provide useful prognostic information for patients undergoing resection of PC with curative intent irrespective of neoadjuvant treatment[46].

Choi *et al*[47] evaluated the prognostic value of $^{18}$F-FDG PET in patients with resectable PC. The OS and DFS were significantly longer in the low SUVmax group than those of high SUVmax group[47].

Hwang *et al*[48] reviewed retrospectively the medical records of 165 patients with a diagnosis of PC. Patients were allocated to high (> 4.1) and low (⩽ 4.1) SUV groups, and median survivals of these patients were 229 d and 610 d, respectively. Furthermore, SUVmax was found to be significantly related to survival in each stage. The median survival was also found to be significantly related to tumor size, site, serum level of CA19-9, distant metastasis, and type of treatment[48].

Epelbaum *et al*[49] evaluated the possibility of dynamic $^{18}$F-FDG PET/CT parameters used as an indicator in the tumor. The OS of patients with a high $^{18}$F-FDG influx was significantly lower than that of patients with a low $^{18}$F-FDG influx (5 and 6 mo *vs* 15 and 19 mo respectively). Quantitative $^{18}$F-FDG kinetic parameters in newly diagnosed PC correlated with the aggressiveness of disease[49].

**Limitation:** Although significant advances have been achieved in $^{18}$F-FDG PET diagnostic technologies, it has some limitations in detecting cancer. Due to increased glycolytic metabolism, $^{18}$F-FDG can also accumulate in the inflammatory cells[50]. As a result, it often yields false positive interpretations for PET. Kato *et al*[51] evaluated the efficacy of $^{18}$F-FDG PET/CT for the differential diagnosis in 47 individuals. It showed that differentiation is difficult by$^{18}$F-FDG PET/CT due to overlapping in

SUVmax between the two diseases. In addition, elevated serum glucose levels may decrease the uptake in tumors for competitive inhibition, which decreased the sensitivity of $^{18}$F-FDG PET in hyperglycemic patients[51]. Therefore, a numbers of other small molecule-based tracers were designed and developed for PET imaging of PC.

### *3-Deoxy-3-18F-fluorothymidine*

A surrogate marker of DNA synthesis, 3-Deoxy-3-18F-fluorothymidine ($^{18}$F-FLT), is another potential tracer for visualization of proliferating tissues[52-55]. For differentiation of pancreatic tumors, $^{18}$F-FLT PET showed a lower sensitivity but higher specificity than$^{18}$F-FDG PET/CT (70% *vs* 91% and 75% *vs* 50% respectively)[56].

## RADIOLABELED PEPTIDES FOR PC IMAGING

Peptides and their derivatives have been successfully developed for the tracer due to favorable characteristics such as low antigenicity, high specificity, fast clearance from blood and rapid tissue penetration. Radiolabelled receptor-binding peptides have become important radiopharmaceuticals for diagnosis and therapy in tumor[57-61]. Recently, a few radiolabeled peptides have been successfully used for PC imaging. It may be a promising imaging strategy for PC diagnosis and treatment.

### *Radiolabeled RGD analogs*

Angiogenesis is necessary for tumor growth and metastasis, and the integrin αvβ3 receptor plays an important role in promoting, sustaining, and regulating the angiogenesis[62]. *In vitro* analysis demonstrated that integrin αvβ3 receptor was expressed in 60% of invasive pancreatic ductal carcinomas and would be an excellent target for the early detection of malignant PC[63]. Radiolabeled Arg-Gly-Asp (RGD) peptides are widely used as integrin αvβ3 receptor imaging agents in various types of tumors[63]. Yoshimoto *et al*[64] employed $^{111}$In-DOTA-c(RGDfK) for the early detection of PC in pancreatic carcinogenesis model. PC lesions as small as 3 mm in diameter as clearly were visualized after injection with the tracer. High tumor-to-normal pancreatic tissue radioactivity ratios were found by ARG analysis. There existed a significant relationship between the uptake of $^{111}$In-DOTA-c(RGDfK) and αvβ3-integrin expression. It also found that the false-positive rate of $^{111}$In-DOTA-c(RGDfK) was lower than that of $^{18}$F-FDG. It revealed that SPECT with $^{111}$In-DOTA-c(RGDfK) was benefit for the early accurate diagnosis of PC[64].

Trajkovic-Arsic *et al*[65] used $^{68}$Ga-NODAGA-RGD PET for αvβ3 integrin receptor *in vivo* imaging of spontaneous pancreatic ductal adenocarcinoma (PDAC) occurring in mice. It showed that αvβ3 integrin is expressed in human and murine PDAC and can be detected by molecular imaging technologies in PDAC. This strategy can further be exploited for identification of patients with αvβ3 integrin positive and application of αvβ3 targeted therapies[65].

Aung *et al*[66] performed a preclinical evaluation of $^{64}$Cu-RAFT-RGD in a clinically relevant orthotopic xenotransplantation model of PC. It was confirmed that the uptakes of $^{64}$Cu-RAFT-RGD in tumor was greater than those of normal tissues. Meanwhile, the tumor to background uptake ratios of the tracers was higher than those of $^{18}$F-FDG. It suggested that $^{64}$Cu-RAFT-RGD PET imaging might be useful in the diagnosis of PC[66].

### *Radiolabeled exendin-4 analogs*

Insulinomas are the most frequent hormone-active tumors of the pancreas arising from pancreatic β cells[67-69]. Recently, glucagon-like peptide-1 receptor (GLP-1R) was found to be massively overexpressed in gut and lung neuroendocrine tumors, especially insulinomas. It provides an attractive target for the cancers[70-72].

Several radioligands towards GLP-1 receptor have been developed for GLP-1R-positive tumor imaging. At first, the analog of native receptor ligand, GLP-1(7–36) amide, was labeled with $^{123}$I and used for GLP-1R imaging. Although preclinical data showed $^{123}$I-GLP-1(7–36) amide possessed high accumulation in a RINm5F insulinoma tumor, the low stability of the peptide due to rapid degrading of GLP-1 by the enzyme dipeptidyl peptidase Ⅳ (DPⅣ) limited its clinical use[73].

Exendin-4 arised from the salivary gland of the gila monster lizard and has a 53% amino acid homology with GLP-1. It is more resistant to the DPⅣ digestion and binds with great affinity to the GLP-1R[73]. $^{111}$In- and $^{99m}$Tc-labeled exendin-4 analogs have been evaluated for SPECT imaging of GLP-1R in rodents and humans, respectively, and promising results were obtained[74-77].

The sensitivity, imaging contrast and spatial resolution of PET was significantly higher than SPECT. In the past few years, exendin-4 analogs have been labeled with PET radionuclides for preclinical insulinomas imaging. Exendin-4 labeled with radio metals ($^{68}$Ga, $^{64}$Cu) showed significant uptake in INS-1 insulinoma xenografts[78,79]. However, the substantial kidney uptake may limit their use in clinical practice due to high radiation exposure to the organs.

$^{18}$F is the commonly used isotope. It has nearly optimal nuclear decay characteristics and chemical properties for peptide-based receptor imaging studies. In the past few years, exendin-4 analogs have been modified with either a C-terminal or N-terminal cysteine to allow site-specific labeling with a maleimide-selective prosthetic reagent, $^{18}$F-FBEM[80]. *In vivo* study showed that the INS-1 tumor uptake of $^{18}$F-FBEM-Cys$^{40}$-exendin-4 was higher than that of $^{18}$F-FBEM-Cys$^{0}$-exendin-4[80]. Based on the above results, other Cys$^{40}$-exendin-4 analogs were developed for GLP-1R imaging[81,82].

*In vitro* receptor competitive binding study confirmed that the nine amino acid sequence at C-terminal of exendin-4 was not key for the biological activity or binding to the receptor. Meanwhile, serine is almost same as cysteine except for the difference in hydroxy and sulfhydryl group. Thus, replacing Ser$^{39}$ with Cys$^{39}$ could

provide a unique site for attachment of a radiolabeling thiol-reactive group (such as $^{18}$F-FBEM) and may have less impact on the binding affinity of the peptide to the receptor[83]. Xu *et al*[83] synthesized a novel $^{18}$F-labeled exendin-4 analog, $^{18}$F-FBEM–Cys$^{39}$-exendin-4. The tracer showed specific binding to GLP-1R and had better tumor to background radioactivity ratio and lower abdominal backgrounds than those of $^{18}$F-FBEM-Cys$^{40}$-exendin-4[83]. It suggested that $^{18}$F-FBEM–Cys$^{39}$-exendin-4 may be a potential probe for insulinomas imaging[83].

Despite the encouraging results, the tedious radiosynthesis would hinder the tracer to widespread use. Recently, a one-step simple procedure for preparing $^{18}$F-labeled peptides *via* chelating $^{18}$FAl with NOTA has been reported[84]. Xu *et al*[84] conjugated Cys$^{39}$-exendin-4 with NOTA-MAL and obtained NOTA-MAL-Cys$^{39}$-exendin-4. The compound was simply radiolabeled with $^{18}$FAl complex by one step in 30 min[85]. $^{18}$FAl-NOTA-MAL-Cys$^{39}$-exendin-4 shows favorable characteristics for insulinoma imaging in mice bearing INS-1 tumor and may be translated to clinical studies[85].

## THERAPY WITH RADIOPHARMACEUTICALS

Recently, only few patients have resectable disease. High-dose external radiation to the pancreas may damage the surrounding organs. The intratumoral administration of radiopharmaceuticals delivers the maximum amount of radioactivity to the tumor with limiting side effects[86-88].

During the past several decades, implantation of radioactive isotopes for the treatment has been used. Some basic research indicated that $^{125}$I seed with continuous low dose rate irradiation may be beneficial to PC[86-88]. Zhongmin *et al*[89] implanted $^{125}$I seeds into PC under CT guidance in thirty-one patients with inoperable PC. It was found that overall responding rate was greater than 60% and median survival time was about 10 mo[89]. The efficacy of intraoperative ultrasound-guided implantation of $^{125}$I seeds was also assessed for the treatment of unresectable PC by Wang *et al*[90]. Most of the patients achieved favorable pain relief. These studies revealed that $^{125}$I seeds implantation was benefit for the treatment of PC patients[90].

Phosphorus 32 is another ideal unsealed therapeutic radionuclide. Colloid $^{32}$P has been applied for the treatment of intracavitary malignancies[91-93]. Preclinical study showed that $^{32}$P-chromic phosphate colloid ($^{32}$P-CP) through intratumoral injection mainly accumulated in the BXPC-3 human tumor and retained for a long time[94]. The safety and efficacy of the therapy to PC was also confirmed[94].

Poly (L-lactic acid) (PLLA) has been widely used as a drug delivery system due to excellent biocompatibility and biodegradability[95-99]. $^{32}$P-CP-PLLA microparticle was successfully prepared and used for brachytherapy in several tumor models[95-99]. Yang *et al*[100] evaluated its biodistribution, bioelimination, and therapeutic effect in mice bearing BxPC-3 human PC. Results showed that $^{32}$P-CP-PLLA was mostly remained at the tumor (> 95% ID) and almost no radioactivity excretion was observed in urine and feces. As compared, some radioactivity (over 5% ID) of $^{32}$P-CP colloid was found in the normal organs[100]. Meanwhile, the tumor volumes was significantly decreased after treatment with $^{32}$P-CP-PLLA microparticle[100]. It showed that $^{32}$P-CP-PLLA microparticle might be benefit for the management of PC[100].

## CONCLUSION

Radiopharmaceuticals are favorable diagnostic and therapy facility for PC. The development of new tracers may be beneficial to personalized management of the disease.

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