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The role of ^{18}F -fluorodeoxyglucose positron emission tomography in the management of patients with pancreatic adenocarcinoma

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Abstract

Pancreatic cancer continues to have a grim prognosis with 5-year survival rates at less than 5 %. It is a particularly challenging health problem given these poor survival outcomes, aggressive tumor biology, and late onset of symptoms. Most patients present with advanced unresectable cancer however, margin-negative resection provides a rare chance for cure for patients with resectable disease. The standard imaging modality for the diagnosis and management of pancreatic cancer is contrast-enhanced multidetector computed tomography. Remarkable advances in CT technology have led to improvements in the ability to detect small tumors and intricate vasculature involvement by the tumor, yet CT is still restricted to providing a morphological portrait of the tumor. Diagnosis can be challenging due to similar appearance of certain benign and malignant disease. Distant metastatic disease can be silent on CT leading to improper staging, and thus management, of certain patients. Furthermore, radiation-induced fibrosis and necrosis complicate assessment of treatment response by CT alone.

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F-fluorodeoxyglucose positron emission tomography (^{18}F -FDG-PET) is becoming a prevalent tool employed by physicians to improve accuracy in these clinical scenarios. Malignant transformation causes a high metabolic activity of cancer cells. ^{18}F -FDG-PET captures this functional activity of malignancies by capturing areas with high glucose utilization rates. Imaging function rather than morphological appearance, ^{18}F -FDG-PET has a unique role in the management of oncology patients with the ability to detect regions of tumor involvement that may be silent on conventional imaging. Literature on the sensitivity and specificity of ^{18}F -FDG-PET fails to reach a consensus, and improvements resulting in hybridization of ^{18}F -FDG-PET and CT imaging techniques are preliminary. Here we review the potential role of ^{18}F -FDG-PET and PET/CT in improving accuracy in the initial evaluation and subsequent steps in the management of pancreatic cancer patients.

Keywords

Positron emission tomography; Positron emission tomography/computed tomography; Pancreatic cancer; Pancreatic adenocarcinoma; ^{18}F -FDG

Introduction

Pancreatic cancer is among the most lethal malignancies, with approximately 45,220 newly diagnosed patients in 2013 alone [1]. Though margin-negative resection is currently the only potentially curative therapy for pancreatic cancer [2–5], survival rates for patients with early stage resectable disease are poor with only 22 % of patients surviving beyond 5 years [6] despite modern multimodality treatment approaches due to aggressive tumor biology and likely undetected metastatic disease at the time of presentation. Furthermore, most patients will present with advanced unresectable disease at initial presentation [7, 8] for which 5-year survival rates are dismal at less than 2 % [6].

Accurate differentiation of benign from malignant disease and correct assessment of disease stage is thus vital to determine optimal treatment approaches [9, 10]. Patients with no evidence of metastatic disease or involvement of the tumor to major blood vessels are candidates for resection. Proper staging therefore distinguishes patients who will benefit from surgery with curative intent from those with more advanced stage disease. Treatment options for locally advanced disease include chemotherapy with or without chemoradiation in efforts to increase the chance for a margin-negative resection. Metastatic pancreatic cancer is managed by systemic chemotherapy alone with palliative radiation administered only in rare cases for symptom control. Thus, reliable techniques for staging of pancreatic cancer are imperative given the critical treatment decisions that follow the initial workup.

Currently, thin-slice (1–3 mm), contrast-enhanced, dual-phased multidetector computed tomography (MDCT) with three-dimensional (3-D) reconstruction is the recommended imaging modality for the diagnosis and staging of pancreatic cancer [11] due to its ability to detect smaller tumors with greater sensitivity and to provide greater anatomic detail in the relationship of a suspected mass to local structures [12] especially vasculature [13]. Various other imaging techniques including ultrasonography (US), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and endoscopic

ultrasonography (EUS) have previously been employed. Diagnostic accuracy of conventional abdominal US is much lower than that of CT [14], and though sensitivity and specificity increase with the use of contrast-enhanced Doppler US [15], operator variability and abdominal gas limit its reliability [9]. MRI and MRCP are also potential tools in the diagnosis of pancreatic cancer, but neither offers a clear advantage in distinguishing benign from malignant disease or assessing disease stage in comparison to CT [11]. EUS may be superior to CT and MRI at identifying small tumors [16, 17]; however, it is poor at detecting distant spread and again is limited by operator skill and experience [9, 16].

Positron emission tomography (PET) uses a positron-emitting radiopharmaceutical that creates images based on their concentration in a particular tissue. Fluorine-18 labeled fluorodeoxyglucose (^{18}F -FDG), a glucose analog that therefore accumulates in metabolically active cells, is currently the most common tracer used in oncological PET imaging. Given the increased glucose metabolism of cancer cells, ^{18}F -FDG readily accumulates in malignant pancreatic cancer cells and appears hypermetabolic when imaged using a PET scanner. In contrast, normal pancreas has a relatively low glucose utilization rate with poor accumulation of tracer in the normal pancreas and very weak avidity on ^{18}F -FDG PET imaging [18].

Functional imaging offers a theoretical advantage over CT and MRI in the ability to differentiate malignant from benign disease and to detect small lesions, as signal intensity relates to high metabolic activity and uptake of the radiotracer rather than size and tissue structure. Recently, ^{18}F -FDG positron emission tomography (^{18}F -FDG-PET) has been shown to be useful in the diagnosis, staging, treatment planning, and monitoring of patients with pancreatic cancer. Here we review the role of ^{18}F -FDG-PET and ^{18}F -FDG-PET/CT in the initial evaluation and management of pancreatic cancer patients.

Diagnosis

Currently contrast-enhanced, dual-phased MDCT is the standard imaging modality for the initial staging of potential pancreatic cancer given its widespread availability and speed of acquisition [19]. Several studies have demonstrated the superiority of ^{18}F -FDG-PET over contrast-enhanced CT alone for the diagnosis of suspected pancreatic cancer (Table 1). A meta-analysis by Orlando and colleagues [20] of 17 studies, each with at least 13 patients who received both ^{18}F -FDG-PET and CT, analyzed the sensitivity and specificity of the addition of ^{18}F -FDG-PET as an adjunct to CT compared to CT alone among 290 individuals with pancreatic cancer. The authors report that CT alone was 81 % sensitive and 66 % specific in the diagnosis of pancreatic malignancy. Addition of ^{18}F -FDG-PET following a positive CT detecting a pancreatic mass dramatically increased the specificity of preoperative imaging to 92 %, though sensitivity did not significantly change at 68 %. When ^{18}F -FDG-PET followed a negative CT in which a pancreatic mass was not detected, sensitivity and specificity were 73 and 86 %, respectively, supporting the unique consideration of ^{18}F -FDG-PET when CT is negative and clinical suspicion of a malignancy is high. Overall, this study suggests an added benefit of ^{18}F -FDG-PET following CT in the diagnosis of pancreatic cancer; however, more prospective studies and cost-effective analyses are needed.

Another more recent meta-analysis by Tang and colleagues [21] evaluated the diagnostic value of ^{18}F -FDG-PET, ^{18}F -FDG-PET/CT, and EUS for pancreatic cancer. Sensitivities of ^{18}F -FDG-PET/CT, ^{18}F -FDG-PET, and EUS were 90.1, 88.4, and EUS 81.2 %, respectively. Specificities of ^{18}F -FDG-PET/CT, ^{18}F -FDG-PET, and EUS were 80.1, 83.1, and 93.2 %, respectively. Given the higher sensitivity of ^{18}F -FDG-PET/CT and the higher specificity of EUS, the authors claim that the two modalities may have unique roles in different clinical conditions in diagnosing pancreatic cancer. For example, if patient with a resectable pancreatic mass has a PET/CT that is equivocal but there are clinical sequelae of pancreatic cancer, an EUS with fine needle aspiration may be indicated prior to surgical exploration.

Of the studies we reviewed however, the negative predictive value of ^{18}F -FDG-PET has been reported to be as low as 64 % [10], likely due to the inherent limitations of ^{18}F -FDG-PET technique. First, hyperglycemic conditions are present in 20–30 % of pancreatic cancer patients, resulting in low ^{18}F -FDG uptake due to competitive inhibition limiting the detection of a pancreatic lesion [22]. Second, lesions less than 1 cm in diameter are difficult to detect given the low resolution of the PET modality [23].

Currently, ^{18}F -FDG-PET is most commonly used in the evaluation of challenging diagnostic cases [19]. Discriminating pancreatic cancer from benign mass-forming lesions such as pancreatitis and cystic pancreatic neoplasms can be difficult based on the fact that only the structural appearance of the pancreas is captured by CT. Given the high metabolic activity of cancer cells, ^{18}F -FDG-PET may be useful in the differentiation of malignant and benign pancreatic lesions.

Distinguishing between pancreatic cancer and mass-forming pancreatitis can be challenging based on the similar appearance of the two pathologies on MRI or CT often leading to indeterminate results [24, 25]. Mass-forming pancreatitis occurs when chronic pancreatitis affects only a portion of the pancreas resulting in a mass-like appearance that is challenging to distinguish from a malignancy. Additionally, chronic pancreatitis is a common finding in patients with suspected pancreatic cancer, as it is a risk factor for the development of a pancreatic malignancy [26]. ^{18}F -FDG-PET could help to differentiate these two diagnoses (Fig. 1). In a study of 102 patients, 93 patients had confirmed ductal adenocarcinoma and 9 had chronic mass-forming pancreatitis. The mean maximum voxel standardized uptake value (SUVmax) of the pancreatic cancer lesion was significantly higher than that of chronic pancreatitis (5.1 ± 2.1 versus 3.2 ± 1.8 , $P < 0.05$). Based on the elevated metabolic activity of pancreatic cancer, ^{18}F -FDG-PET demonstrated both greater sensitivity and specificity at 96.8 and 77.5 % for accurate diagnosis compared to CT at 79.6 and 44.4 % [26]. Still, distinguishing pancreatic cancer from pancreatitis, particularly autoimmune pancreatitis, will continue to be a challenge based on ^{18}F -FDG-PET alone. Approximately 10 % of patients with chronic pancreatitis [27] and as high as 100 % of those with autoimmune pancreatitis [28] have been noted to have ^{18}F -FDG uptake in the pancreas. Further understanding of the uptake intensity, pattern, and associated findings (such as ^{18}F -FDG in the salivary glands seen in autoimmune pancreatitis) [29] may help improve the utility of ^{18}F -FDG-PET in distinguishing pancreatitis from pancreatic cancer.

Preoperative evaluation of the cystic pancreatic neoplasm is another unique scenario where distinction between benign and malignant disease is particularly challenging. Cystic pancreatic neoplasms are increasingly common incidental findings with the more frequent use of US and abdominal imaging [30]. Accurate diagnosis and management could prevent many unnecessary pancreatic resections for benign disease. A particular type of cystic neoplasm called intraductal papillary mucinous neoplasm (IPMN) has the potential to produce an adenoma, carcinoma “in situ,” or invasive carcinoma and must be followed closely if not resected. Given the difficulty in obtaining an accurate diagnosis for malignant cases of IPMN, many patients currently undergo unnecessary resections only to identify a benign lesion. MRCP is currently the gold standard for diagnosing malignant IPMNs [22] and CT is commonly used as an adjunct in the initial evaluation process. The largest study assessing the reliability ^{18}F -FDG-PET in this clinical scenario was by Sperti et al. [31] who demonstrated in their cohort of 64 patients with suspected IPMNs that ^{18}F -FDG-PET had a greater sensitivity (92 versus 58 %), specificity (97 versus 82 %), and accuracy (95 versus 72 %) than conventional imaging. Another study by Tomimaru et al. [32] reported on 29 patients who underwent CT, ^{18}F -FDG-PET, and surgery for IPMNs, followed by histopathological examination. They found that the SUVmax on ^{18}F -FDG-PET correlated with the histopathological types of IPMN (benign adenoma, carcinoma in situ, or invasive carcinoma). Specificity, sensitivity, and accuracy were best for an SUVmax of 2.5 and that the combined findings of a mural nodule on CT and an SUVmax of 2.5 were most indicative of a malignant IPMN. Other studies, however, fail to report such a high sensitivity in detecting malignancy within cystic lesions [33, 34]. Saito et al. [35] evaluated the usefulness of dual-phase ^{18}F -FDG-PET/CT with imaging taken at 60 and 120 min after injection of ^{18}F -FDG. With a combination of SUVmax cutoffs and an index for retention of ^{18}F -FDG activity in the later scan, the sensitivity and specificity of identifying early malignant IPMNs were 88 and 94 %, respectively. Still, more research is needed to further understand how standard or dual-phase ^{18}F -FDG-PET/CT compares to MRCP and ultrasound in the management of cystic pancreatic neoplasms.

Staging

Margin-negative resection is currently the only curative option for pancreatic cancer. Thus, accurate staging is imperative to identify patients who are candidates for surgery from those who require aggressive upfront chemotherapy and/or radiation to improve chances of a margin-negative resection [36, 37] or as a therapy for newly identified metastatic disease.

Resectability is determined by both degree of tumor involvement with abdominal vasculature and absence of distant metastatic disease. Standard preoperative evaluation currently involves the following: (1) CT of the chest, abdomen, and pelvis to evaluate distant metastases and local extent of tumor invasion and (2) endoscopic ultrasound to further detect vascular involvement and to obtain a pathologic diagnosis with fine needle or core biopsy [38]. Even with such an extensive preoperative evaluation, up to 30 % of patients have evidence of distant metastases or local invasion precluding them from resection at the time of laparotomy [39–41]. Improvements in accurate staging using novel imaging techniques may not only result in fewer unnecessary operations but also decrease the delay in initiating

aggressive chemotherapy and/or radiation for patients with more advanced stage disease, optimizing the treatment strategy [42].

Currently, primary tumor and regional lymph node staging of pancreatic cancer by ^{18}F -FDG-PET is not indicated for all patients owing to the poor spatial resolution offered by PET and the proximity of peripancreatic lymph nodes to the primary tumor [43, 44]. Alone, ^{18}F -FDG-PET is not useful in evaluating resectability, largely due to the low spatial resolution of the PET technique. Information regarding degree of vessel and local organ involvement needed to determine resectability is difficult to obtain without contrast-enhanced CT, and the intense radiotracer uptake by cancer cells further obscures the subtle evaluation of local extension and nodal involvement [22, 45]. Moreover, the low spatial resolution is a significant limitation in identifying metastatic disease as ^{18}F -FDG-PET detects only ~50 % of hepatic lesions less than 1 cm [46].

To take advantage of the information provided by ^{18}F -FDG-PET, it is possible to fuse PET imaging with a CT and/or MRI to present functional data within a backdrop of improved anatomic detail. Fusion, however, can be complicated by issues of data transfer, different locations of imaging acquisition, weight loss, and altered alignment that create challenges in interpreting the location of malignancies—particularly in the abdomen where anatomy varies in uptake patterns, size, locations, and orientations at different time points [47, 48]. Acquisition of consecutive ^{18}F -FDG-PET and CT (^{18}F -FDG-PET/CT) by the same scanner can overcome these limitations and dramatically enhances the usefulness of PET in this clinical scenario [49]. Additionally, ^{18}F -FDG-PET/CT utilizes whole body imaging, capturing the most common sites of pancreatic metastatic disease (liver, lungs, and bone marrow) [44].

When combined with a non-contrast CT, several studies demonstrate improved ability of ^{18}F -FDG-PET/CT, as compared to contrast-enhanced CT alone, in the staging of pancreatic cancer due to superior detection of distant metastatic disease (Fig. 2). In a series of 16 patients with histologically proven distant metastases reported by Heinrich and colleagues [10], ^{18}F -FDG-PET/CT detected metastatic disease in 13 (81 %) patients compared to only 9 (56 %) detected by CT. Consequently, sensitivity and specificity of ^{18}F -FDG-PET/CT was 81 and 100 % compared to 56 and 95 % respectively for CT. Of the 37 patients deemed resectable by standard staging with contrast-enhanced CT, detection of metastatic disease using ^{18}F -FDG-PET/CT altered the management in six patients (16 %) by preventing unnecessary surgical exploration. Similarly, Bang et al. [26] reported ^{18}F -FDG-PET/CT altered the resectability status and, therefore, management in 22 % of patients in their study. Together, these studies demonstrate that optimal patient selection can be improved by the addition of ^{18}F -FDG-PET/CT to standard preoperative imaging.

Building on the tool of ^{18}F -FDG-PET/CT, Strobel and colleagues [50] showed the feasibility and accuracy of combining ^{18}F -FDG-PET and contrast-enhanced CT in the investigation of 50 patients with pancreatic cancer to provide what they coined as a “1-stop-shop” for assessing resectability. Of 11 patients with liver metastases in their study, unenhanced ^{18}F -FDG-PET/CT accurately identified only five cases (sensitivity 46 % and specificity 100 %) compared to enhanced ^{18}F -FDG-PET/CT, which detected nine cases (sensitivity 82 % and

specificity 97 %). In one patient, enhanced ^{18}F -FDG-PET/CT even identified a liver metastasis that was missed intraoperatively. Unenhanced and enhanced ^{18}F -FDG-PET/CT each performed equally well in identifying 100 % of lung and bone metastases without any false-positive cases. The authors concluded that there is a trend toward improved staging by enhanced ^{18}F -FDG-PET/CT over unenhanced ^{18}F -FDG-PET/CT. Furthermore, enhanced ^{18}F -FDG-PET/CT was superior to ^{18}F -FDG-PET alone in the assessment of preoperative resectability.

In summary, addition of ^{18}F -FDG-PET to the standard workup of patients with pancreatic cancer appears to improve accuracy in the staging process and subsequently leads to changes in management. Inclusion of contrast enhancement to ^{18}F -FDG-PET/CT further improves identification of distant metastases (especially the liver) that would otherwise not be discerned through standard imaging or unenhanced ^{18}F -FDG-PET/CT. Further research is needed to validate these preliminary results and to better understand the impact of ^{18}F -FDG-PET/CT on patient management, clinical outcomes, and treatment costs.

Radiation treatment

Advances in modern radiation treatment delivery have enabled increasing precision in the deposition of radiation dose to pancreatic tumors while still sparing surrounding normal organs [51]. For radiation treatment of pancreatic cancer, treatment planning has traditionally been targeted to regions of apparent tumor involvement on CT and peripancreatic lymph nodes at risk. Significant intraobserver variability in the interpretation of CT scans has been reported for many disease sites [52–54] given the difficulty in determining the tumor boundary (microscopic expansion). This raises questions for appropriate targeting of radiation therapy and whether functional imaging can be used to better define the radiation planning treatment volume (PTV). Figure 3 illustrates the incorporation of tumor which is apparent on CT and ^{18}F -FDG-PET in construction of a modern radiation treatment plan.

The use of molecular ^{18}F -FDG-PET/CT imaging to generate radiotherapeutic plans has been highly studied in the lung, head and neck, and brain tumors, with data being continuously accumulated for its application in pancreatic and other forms of cancer [48, 51, 55]. In pancreatic cancer, the benefit of PET-based gross tumor volume (PET-GTV) delineation for radiotherapy planning might be most pronounced in differentiating pancreatic tumor from the normal duodenum and small bowel, where CT-based gross tumor volume (CT-GTV) may be overestimated in the tumor region and may lead to a greater incidence of treatment-related toxicity [51]. Fused ^{18}F -FDG-PET/CT has been hypothesized to be more accurate in GTV delineation in comparison to CT alone by reducing geographic misses and subsequent reduction of treatment failure [55]. Definitive conclusions regarding the prognostic significance or advantage of PET-GTV versus CT-GTV delineation in radiotherapy planning of pancreatic cancer is limited because of breathing motion, organ deformation, and tumor heterogeneity from patient to patient; however, the field is continuously evolving and these major challenges are being addressed.

Treatment response and prognosis

With the grim survival rates and relatively treatment-resistant quality of pancreatic cancer, early assessment of treatment response can be particularly useful in guiding the therapeutic approach and patient counseling. Computed tomography is restricted to evaluating the morphology of the pathology. Additionally, it is difficult to assess the response with CT following radiation therapy due to fibrosis and necrosis in the treated area [19]. Response to treatment by CT is generally evaluated based on Response Evaluation Criteria for Solid Tumors (RECIST) [56, 57], categorizing disease into complete response, partial response, stable disease, and progressive disease based on tumor dimensions. Functional imaging, however, can more reliably assess the viability of the cancer cells following treatment (Fig. 4). As such, ^{18}F -FDG-PET is being evaluated for its ability to identify response to treatment and to predict clinical outcomes.

Several studies have demonstrated the performance of ^{18}F -FDG-PET in assessing response to chemotherapy and chemoradiation and predicting clinical outcomes. Kuwatani et al. [58] demonstrated that ^{18}F -FDG-PET response following one cycle of chemotherapy was associated with improved median overall survival in patients with advanced pancreatic cancer. This association was not seen in patients demonstrating a RECIST response. ^{18}F -FDG-PET response correlated with time to progression in patients with locally advanced pancreatic cancer in a study by Bang et al. [26]. Although no patients had apparent RECIST response, those exhibiting a $>50\%$ decrease in uptake on ^{18}F -FDG-PET before and after neoadjuvant chemoradiation had improved time to progression than non-responders (300 versus 233 days, $P<0.05$). In another study, Choi et al. [59] found that patients with 50% decrease in SUV following neoadjuvant chemoradiation underwent successful resection while resection was uncommon in non-responders.

^{18}F -FDG-PET may also provide early insight into the pathologic response due to treatment. Kittaki et al. [60] reported in a study of 40 patients with resectable pancreatic cancer that patients with a higher SUVmax (>4.7) and higher SUV decline had a better pathologic response to preoperative gemcitabine-based chemoradiation. Again, RECIST failed to show associations with pathologic response. In another study by Rose et al. [61], metabolic response was also found to correlate with pathologic scores of tumor response to treatment following neoadjuvant chemoradiation. In summary, preliminary studies suggest that ^{18}F -FDG-PET is superior to CT in assessing response to treatment in pancreatic cancer, particularly when necrosis and fibrosis following radiation therapy complicates interpretation of CT imaging.

Future directions

The technology and technique behind ^{18}F -FDG-PET/CT is continuously evolving, and researchers are discovering how to optimize the use of multimodality imaging in cancer care. While ^{18}F -FDG-PET/CT is increasingly being used in the management of pancreatic adenocarcinoma, several issues will need to be circumvented. For example, the traditional low-dose CT portion of the ^{18}F -FDG-PET/CT is used for attenuation correction, not diagnosis [22]. Contrast-enhanced ^{18}F -FDG-PET/CT can provide a greater morphological

detail, and restricting intravenous contrast to the abdominal and pelvic portion of the CT can limit radiation exposure of this imaging study [50]. Preliminary data demonstrates the superiority of contrast-enhanced ^{18}F -FDG-PET/CT over enhanced CT alone [50]. Further research on utility and cost may clarify the role of contrast-enhanced ^{18}F -FDG-PET/CT for both accurate anatomic localization of primary disease and metabolic evaluation of distant spread.

The second issue with ^{18}F -FDG-PET/CT arises in the broad differential diagnosis of a PET-avid pancreatic lesion. While ^{18}F -FDG-PET/CT can reliably distinguish malignant tissue from some benign pancreatic diseases, autoimmune chronic pancreatitis, sclerosing mesenteritis, or other inflammatory conditions can demonstrate considerable ^{18}F -FDG-uptake (Fig. 5). Modifying ^{18}F -FDG-PET/CT acquisition through a delayed technique in which the image is taken after more than 60 min of uptake time may improve the sensitivity and specificity in distinguishing pancreatic cancer from these other benign diseases. Studies have demonstrated that this technique may aid in both discriminating between malignancy and other ^{18}F -PET-avid lesions and detecting a greater percentage of local and distant lesions [62, 63].

Preliminary data evaluating the role of ^{18}F -FDG-PET/CT in assessing response to treatment and predicting improved clinical and pathological outcomes is promising; however, interpretation should be made with caution. A focus on the standard methods of interpreting and reporting radiotracer uptake and response should be maintained to yield clinically useful and reproducible results. Wahl and colleagues [64] have published a framework for reproducible quantified analysis of ^{18}F -FDG-PET images entitled “PET Response Criteria in Solid Tumors (PERCIST 1.0) modeled after RECIST [56, 57] used for evaluating solid tumor response on CT imaging. They provide precise and rational parameters for measuring metabolic tumor activity and quantifying response in a way that is consistent from patient to patient. Continued efforts to identify a standard definition for parameters quantifying radiotracer uptake and metabolic tumor volume are essential. No doubt revisions may occur to frameworks such as PERCIST 1.0; however, validation studies are necessary to guide this learning process in interpretation of PET imaging not just for pancreatic cancer but for other sites as well.

Newer radiotracers such as 3- ^{18}F -fluoro-3-deoxythymidine (^{18}F -FLT) have shown promising results as an alternative tracer for distinguishing between benign and malignant lesions as it only accumulates in malignant pancreatic lesions [65, 66]. Other tracers, such as carbon-11-labeled acetate (^{11}C -acetate), have been studied in the mouse model in an attempt to increase the ability of PET/CT to detect pancreatic cancer [67]. Hyperglycemia in pancreatic cancer patients tends to significantly reduce ^{18}F -FDG uptake, leading to a significant number of false-negative readings [22]. ^{11}C -acetate has been shown to be more sensitive than FDG in the detection of cancerous pancreatic lesions, especially during the early stage of disease [67]. In another mouse model, a novel PET/CT tracer was developed to measure tissue factor (TF) expression. The authors reported persistent and specific uptake of (^{67}Cu)-NOTA-ALT-836 in pancreatic cancer cells [68]. Two more non-glucose analog radiotracers have been developed to increase accuracy of early detection of pancreatic adenocarcinoma. Early investigations of these lactose-binding proteins, ethyl- β -D-

galactopyranosyl-(1,4')-2'-deoxy-2'-[¹⁸F]fluoro-β-D-glucopyranoside (Et-[¹⁸F]FDL) and 1'-[¹⁸F]fluoroethyl-β-D-lactose ([¹⁸F]-FEL), report highly specific uptake in malignant pancreatic lesions in comparison to their benign counterparts [69, 70].

Lastly, different combinations of multimodality imaging have been proposed, namely, fused ¹⁸F-FDG-PET and MRI scanning. Tatsumi et al. [71] reported ¹⁸F-FDG-PET/MRI, especially using T1-w-MRI, to be superior to ¹⁸F-FDG-PET/CT in localizing pancreatic lesions, with better mapping and fusion image quality. While the study obtained the PET and MRI studies from different scanners, work is currently being conducted on designing and testing integrated PET/MRI scanners with ability to simultaneously acquire PET and MRI images, thereby increasing the accuracy of the co-registration process.

Conclusions

While these preliminary studies show promising results, much more research is warranted before the use of non-FDG tracers and fused PET/MRI in clinical practice. However, as research on functional imaging of pancreatic adenocarcinoma is less abundant than other cancer types, patients with pancreatic cancer are continuously encouraged to take part in clinical trials that could ultimately improve their treatment and prognosis.

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Fig 1. Pancreatitis resembling pancreatic cancer on contrast-enhanced computed tomography scan (a) which shows a mass in the head of the pancreas. The diagnosis of benign disease is supported by the complete absence of uptake on ^{18}F -FDG-PET scan (b)

Fig. 2. Contrast-enhanced computed tomography scan (**a**) of a patient following stereotactic body radiotherapy showing no evidence of a liver metastasis; however, corresponding ^{18}F -FDG-PET scan (**b**) demonstrates hypermetabolic FDG uptake in the liver (*arrow*). Subsequent biopsy of the lesion confirmed the presence of metastatic disease

Fig. 3. Pancreatic adenocarcinoma delineated on computed tomography (CT) based on appearance on CT alone (*red*) and by 18F-FDG-PET alone (*blue*) shown on **a** axial, **b** sagittal, and **c** coronal CT. The final planning target volume (*yellow*) for radiation therapy is contoured by considering the appearance of tumor on both imaging modalities

Fig. 4.

Baseline contrast-enhanced computed tomography (CT) scan (**a**) of a patient prior to stereotactic body radiotherapy showing mass in the head of the pancreas with corresponding ¹⁸F-FDG-PET scan (**b**) demonstrating hypermetabolic FDG uptake. Follow-up CT (**c**) 6 weeks after stereotactic body radiotherapy shows decreased tumor mass and corresponding ¹⁸F-FDG-PET (**d**) shows significantly decreased FDG uptake. The patient was successfully resected. Surgical specimen demonstrated complete pathologic response to therapy

Fig. 5.

a Contrast-enhanced CT scan showing a large mass in the head of the pancreas. **b** ^{18}F -FDG-PET scan showing hypermetabolic FDG uptake in the head of the pancreas. The patient was ultimately diagnosed with sclerosing mesenteritis invading into the head of the pancreas

Studies investigating the sensitivity and specificity of contrast-enhanced CT, ^{18}F -FDG-PET, or ^{18}F -FDG-PET/CT in the initial diagnosis of pancreatic cancer

Table 1

Study	Year	Number of patients				CT sensitivity (%)	CT specificity (%)	^{18}F -FDG-PET sensitivity (%)	^{18}F -FDG-PET specificity (%)	^{18}F -FDG-PET/CT sensitivity (%)	^{18}F -FDG-PET/CT specificity (%)
		CT	^{18}F -FDG-PET	^{18}F -FDG-PET/CT							
Bares et al. [72]	1993	15	15			95	50	92	100		
Bares et al. [73]	1994	40	40			100	23	89	85		
Freiss et al. [74]	2005		80					94	88		
Inokuma et al. [75]	1995	46	46			89	73	94	82		
Kato et al. [76]	1995		24					93	78		
Ho et al. [77]	1996	14	14			25	100	100	67		
Zimny et al. [78]	1997		106					89	53		
Keogan et al. [79]	1998	37	37			75	83	88	83		
Rajput et al. [80]	1998	13	13			73	0	82	100		
Imdahl et al. [81]	1999	48	48			50	44	96	100		
Delbeke et al. [82]	1999	65	65			65	62	92	58		
Rose et al. [61]	1999	65	65			65	62	92	85		
Diedriches et al. [83]	2000	101	122			95	91	88	87		
Sendler et al. [84]	2000	43	43			74	73	71	64		
Nakamoto et al. [62]	2000		47					100	80		
Mertz et al. [85]	2000	35	35			53	NC	87	NC		
Koyama et al. [86]	2001	86	86			91	38	82	81		
Kasperk et al. [87]	2001	103	103			85	89	92	58		
Papos et al. [88]	2002	22	22			100	56	100	88		
Kalady et al. [89]	2002	54	54			65	87	88	92		
Borbath et al. [90]	2005		59					88	67		
Nishiyama et al. [46] ^a	2005		86					93	81		
Van Kouwen et al [27]	2005		77					91	87		
Stollfuss et al. [91]	2005	73	73			80	74	93	93		
Bang et al. [26]	2006	102	102			80	44	97	78		

Study	Number of patients									
	Year	CT	18F-FDG-PET	18F-FDG-PET/CT	CT sensitivity (%)	CT specificity (%)	18F-FDG-PET sensitivity (%)	18F-FDG-PET specificity (%)	18F-FDG-PET/CT sensitivity (%)	18F-FDG-PET/CT specificity (%)
Maemura et al. [92]	2006		42				87	67		
Sperti et al. [31]	2007	NR	62				92	97		
Singer et al. [93]	2007		41				87	80		
Lemke et al. [94]	2004	64	64	64	89	64	84	61	77	64
Heinrich et al. [10]	2005	61		61	93	21			89	69
Farma et al. [95]	2008	82		82					89	88
Schick et al. [96]	2008			46 ^b					89	74
Kauhanen et al. [97]	2009			38					85	88
Hermann et al. [98]	2012	31	41	31	88	NC	91	50	92	NC

Values are not calculated due to low number of benign cases (NC). Patients in this study received CT or MRI so not recorded in table (NR)

^a Delayed PET using a cutoff for retention index

^b CT component of 18F-FDG PET/CT performed with contrast