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DISCUSSIONS IN PET IMAGING

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PET and PET/CT in the Evaluation of Pancreatic Malignancies

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LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Describe the fundamentals of PET scanning
- Explain the role of PET scanning in the evaluation of pancreatic malignancies
- Recognize the advantages of PET/CT in the evaluation of pancreatic cancer
- Discuss the status of PET scanning for evaluating endocrine and cystic pancreatic tumors

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Early diagnosis and accurate staging of pancreatic malignancies are critical for curative resection, which offers the best chance of survival. Assessment of postoperative recurrence and response to chemotherapy and/or radiation therapy is important in deciding the efficacy of the treatment and modifying treatment regimens.

Diagnostic evaluation of pancreatic cancers remains challenging, even with an expanding armamentarium of imaging modalities available for pancreatic imaging that includes ultrasound, endoscopic ultrasound (EUS), CT, MR, and endoscopic retrograde cholangiopancreatography. These cross-sectional radiological techniques, particularly multislice CT, MR, and EUS, provide exquisite anatomical and structural details of pancreatic abnormalities with excellent lesion detection and characterization as well as evaluation of relationships with vascular structures. In addition, 3D image reconstruction has enhanced the ability to predict resectability and has reduced the requirement for conventional catheter angiography. Yet definitive diagnosis of small pancreatic tumors and differentiation of post-treatment recurrent and residual masses from fibrosis are often difficult, even with these state-of-the-art techniques.

FDG-PET is a novel imaging modality that takes advantage of the selective uptake of FDG by metabolically active malignant cells to assess pancreatic cancer. PET is a functional imaging technique that provides quantitative images of a variety of physiological and pathological processes. Most PET radiopharmaceuticals are radiolabeled with radioactive isotopes of atoms present in biological molecules (carbon-11, nitrogen-13, and oxygen-15) to form radiotracers that are identical chemically, biochemically, and pharmacologically to the native compounds. In other situations, substitution of a fluorine-18 atom for a hydrogen or hydroxyl group results in an analog that closely mimics the properties of the native molecule. Thus, almost any biologically active molecule can be used as a PET tracer.

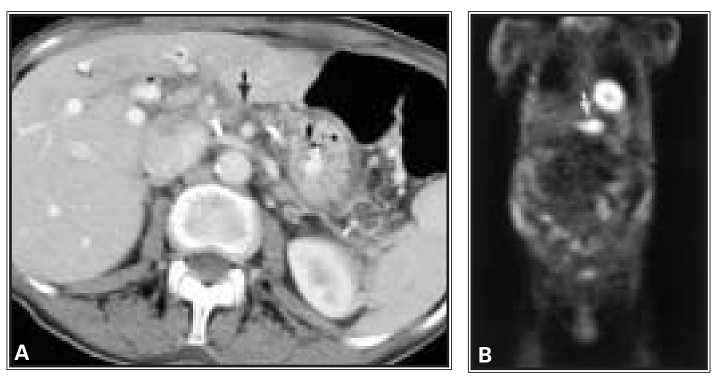

Figure 1. Contrast-enhanced CT of 67-year-old woman shows soft-tissue haziness in pancreatic bed (arrow), likely representing postoperative fibrosis or scar tissue (A). Coronal PET image (B) reveals intense uptake (arrow) of FDG in pancreatic region, suggesting recurrent/residual tumor, subsequently proven by biopsy.

Despite this limitless array of potential PET radiopharmaceuticals, the majority of clinical PET studies use FDG, which has transport and metabolic characteristics very similar to those of native glucose. Because the energy metabolism of many tumor cells is relatively glycolytic, they require greater amounts of glucose per unit of energy production than normal cells and can be reliably visualized by FDG-PET. Increased expression of glucose transporters in many tumors further increases the FDG signal.

Figure 2. CT and PET correlation in 68-year-old woman status post Whipple surgery. Contrast-enhanced CT (A) correlates well with PET images in coronal and transverse planes (B and C) that show no abnormal FDG uptake in the pancreatic region.

In addition to the similarities between FDG and glucose, an important difference between the two molecules contributes to the utility of FDG for tumor imaging. After initial phosphorylation to FDG-6-phosphate (FDG-6-PO_4), FDG does not proceed further in the glycolytic pathway, so it acts as a metabolically trapped tracer. This facilitates use of this radiopharmaceutical for whole-body imaging.

PET scanning can be performed with a dedicated PET scanner or a modified dual-detector SPECT device. Although dual-detector cameras provide the convenience of single-photon emission and positron-emission tomography capabilities in a single, less expensive imaging device, recent studies have shown that modified SPECT cameras are much less effective than dedicated PET devices for lesions less than 2 cm in diameter.[1]

Integration of anatomic imaging techniques such as CT scanning with functional imaging offers the unique advantage of precise anatomic localization of lesions with CT scanning and simultaneous assessment of lesion metabolism with PET. This can be achieved by concurrent review or superimposition (fusion with computer algorithms) of CT and PET images acquired in separate imaging sessions or by the precise coregistration of CT and PET images provided by a hybrid PET/CT scanner in a single scanning session. PET/CT coregistration aids in improving the diagnosis and staging of abdominal tumors, identifying and localizing disseminated disease, improving radiation therapy planning, and monitoring response to chemo- and radiation therapy.

Prior to FDG-PET studies, patients are instructed to fast for at least four hours to reduce competition between glucose and FDG in tumor tissue and to diminish physiologic glucose utilization by background tissues. To minimize radiation to the urinary bladder, patients are asked to void frequently before the imaging study. Approximately 10 to 15 mCi (370 to 555 MBq) of FDG is administered intravenously, and imaging is initiated after a 45 to 60-minute uptake period. A PET imaging session with a conventional dedicated scanner takes about 45 to 60 minutes; the time is reduced to 15 to 30 minutes with a hybrid PET/CT device.

Imaging data from PET studies are reconstructed to generate transverse images of the region of interest. These transverse images are then reformatted to generate coronal and sagittal projections and 3D maximum intensity projection images. Although most PET images are qualitatively assessed for normal or increased ("hot spot") uptake of FDG, focal accumulations of FDG in tissues are occasionally quantified by kinetic modeling or by calculating the semiquantitative standard uptake values (SUVs).

PET IN PANCREATIC CANCER

Detection of pancreatic cancer at an early stage offers the best chance of long-term survival, assuming the absence of lymph node and liver metastases and invasion of peripancreatic tissues including blood vessels, anterior pancreatic capsule, and peripancreatic nerves.[2] This information is often obtained by a preoperative CT examination that allows detection and anatomic delineation of the mass.[3] Indeed, multislice CT is the imaging modality of choice for diagnosis, staging, and follow-up of patients with pancreatic cancer.

Three-D CT images provide comprehensive additional information about the relationship and possible involvement of vascular structures in the vicinity of focal pancreatic lesions and the degree and level of dilatation of obstructed pancreatic and biliary ducts.[4,5] However, the diagnosis of early-stage pancreatic cancer, free of peripancreatic extension and with small lesions, is often difficult with structural imaging techniques. These difficulties are compounded by CT's lack of specificity, which results from overlapping imaging features of pancreatic cancer and pancreatic inflammation.

As normal pancreas is not clearly visualized with PET, due to low glucose utilization by the pancreas in the fasting state, most foci of abnormal FDG uptake in the pancreas are visualized as hot spots. Pancreatic cancer is typically associated with increased glucose consumption and is assumed to be present if an intense focal area of increased FDG accumulation is seen in the pancreatic area.

PET scanning has been shown to be more accurate than other imaging methods for diagnosing pancreatic cancer. In a recent prospective study of pancreatic masses suspicious for pancreatic cancer, the overall sensitivity (96%) and specificity (78%) of PET were superior to those of CT (91% and 56%).[6] For lesions less than 2 cm in diameter, the sensitivity of PET is superior to that achieved by CT,[7] but CT scanning is superior to PET for diagnosis of pancreatic cancers larger than 4 cm in diameter.[7] This is partly related to lower metabolic rates in the larger tumors. In several studies, the accuracy, sensitivity, and specificity of FDG-PET for evaluating pancreatic cancer have been reported to be 85% to 91%, 85% to 100%, and 67% to 88%, respectively.[7-11]

In addition, PET has been reported to be more effective than anatomic imaging modalities such as CT and MR for differentiating pancreatic cancer from chronic inflammation.[12] A clear, distinct difference in FDG uptake patterns of pancreatic cancer and chronic pancreatitis has been reported, with relatively low levels of FDG uptake in chronic pancreatitis and a diffuse distribution pattern.

On the other hand, the sensitivity of PET for detecting lymph node metastases in patients with pancreatic cancer is only 61% to 71%.[12] Researchers have attempted to use SUVs to distinguish pancreatic inflammatory disease from pancreatic cancer, but conflicting results using SUVs for differentiating pancreatic cancer from benign pancreatic lesions have been reported in the literature.[2,12,13]

FDG-PET can change management of pancreatic cancer by revealing unsuspected metastases to liver, bones, and lungs, thereby rendering the patient unresectable and avoiding the morbidity and mortality of unnecessary surgical interventions.[14-16] In comparison with CT scanning, PET provides more reliable detection of hepatic metastases greater than 1 cm. Although PET may render false-positive results in the presence of marked intrahepatic cholestasis, FDG-PET can confirm malignancy in lesions less than or equal to 1 cm that are suspicious on CT. PET has been reported to avoid laparotomies by upstaging the disease in 17% of patients who were originally regarded as candidates for curative resection on the basis of preoperative CT and angiography.[12] In another published series, PET was reported to change management in 15% of patients with pancreatic cancer.[14]

PET is also helpful in the follow-up of patients who have undergone chemoradiation therapy or surgical resection (Figures 1 and 2).[17] Inflammatory or scar tissue is frequently seen in the pancreas and peripancreatic region during the postoperative period and following chemoradiation therapy, and it can manifest as an apparent pancreatic mass. Structural imaging modalities such as CT and MR are not helpful in differentiating inflammation or scar tissues from a tumor mass under these circumstances, as they rely on size, morphology, and enhancement of the abnormal tissue. Recurrent tumors and postoperative inflammatory changes are therefore frequently indistinguishable on CT images.

PET takes advantages of the finding that postoperative inflammatory masses show decreased metabolic activity relative to recurrent tumors. The decreased metabolic activity in inflammatory postoperative masses is usually appreciated before the inflammatory mass reduces in size. A post-therapy inflammatory response or fibrosis is unlikely to show increased uptake of FDG and thus is unlikely to mimic malignant disease. This makes PET imaging in correlation with CT a suitable technique for assessing the response of pancreatic neoplasms to treatment. PET has been found to be more useful than CT in monitoring patients following intraoperative radiotherapy for unresectable pancreatic cancer.[18]

In addition, lesion FDG uptake has been used to determine the prognosis of patients with pancreatic cancer. A recent study has reported that patients with high SUVs (greater than 3) have a significantly lower mean survival period of five months in comparison with those having SUVs less than 3 (mean survival period of 14 months).[15] In another study, the median survival in patients with SUVs less than 6.1 was nine months versus a five-month survival in patients with SUVs equal to or greater than 6.1.[16]

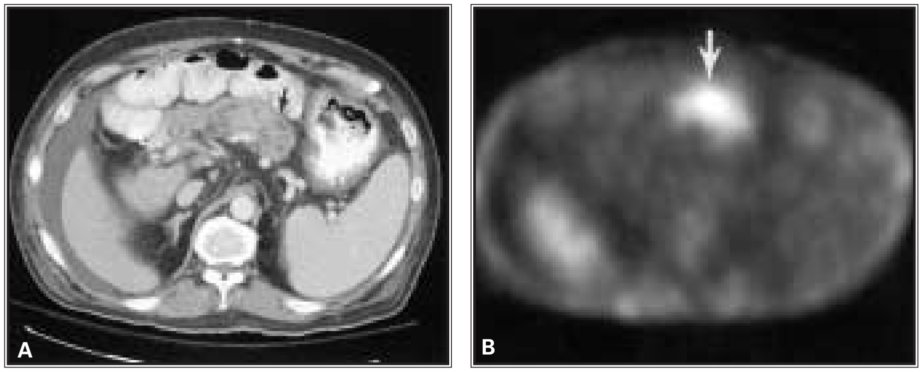

Figure 3. A: Contrast-enhanced CT of 75-year-old man shows complex mass (arrow) in the pancreatic body with both cystic and solid components suggestive of malignancy (biopsy: mucinous cystadenocarcinoma). B: Axial PET image shows intense focal accumulation (arrow) of FDG in pancreatic body region with excellent CT correlation.

ENDOCRINE TUMOR

Pancreatic endocrine tumors can be divided into 10 classes: insulinomas, gastrinomas (Zollinger-Ellison syndrome), vasoactive intestinal polypeptide tumors (VIPomas, Verner-Morrison syndrome), glucagonomas, somatostatinomas, adrenocorticotrophic hormone-releasing tumors (ACTHomas), growth hormone releasing factor secreting tumors (GRFomas), nonfunctioning endocrine tumors, pancreatic endocrine tumors causing carcinoid syndrome, and tumors causing hypercalcemia. Imaging of pancreatic lesions has been improved with CT, EUS, MR, and recently, scintigraphy with radiolabeled somatostatin analogs such as indium-111-labeled pentetreotide (Octreoscan, Mallinckrodt). FDG-PET has limited accuracy for evaluation of pancreatic neuroendocrine tumors partly because of the small size of these lesions at presentation.

Two PET radiopharmaceutical agents—serotonin precursor 5-hydroxytryptophan (5-HTP) labeled with C-11 and C-11-L-dihydroxyphenylalanine (L-Dopa)—have been described for detection of endocrine pancreatic tumors.[19] With these agents, pancreatic endocrine tumors, particularly glucagonomas, were easier to visualize with PET than with CT. PET is less sensitive for detecting nonfunctional endocrine tumors, however. PET has not been shown to have any advantages compared with other imaging modalities for the investigation of neuroendocrine tumors of pancreas.

CYSTIC NEOPLASMS

Selective uptake of FDG provides strong evidence for malignancy and can justify surgery. On the other hand, a negative PET result suggests a benign tumor that may be managed conservatively with limited resection or, in selected high-risk patients, with biopsy and/or follow-up. PET has been shown to be more accurate than CT in characterizing cystic pancreatic lesions as malignant. Whereas the anatomic and morphologic information gained by CT can help in establishing a diagnosis for most neoplasms, differentiation of benign from malignant neoplasm is often difficult with CT. In these circumstances, anatomic imaging modalities such as CT can be correlated with PET images to obtain the maximum diagnostic information using noninvasive means (Figure 3).

Tumor markers, along with CT and PET correlation, can further strengthen confidence in the preoperative diagnostic evaluation of patients with pancreatic cystic lesions. The reported sensitivity and specificity for FDG-PET in detecting malignant cystic tumors are 94% and 97%, respectively, compared with 65% and 87% for CT scanning.[20]

PITFALLS OF PET SCANNING

The main drawback of PET is its relatively low spatial resolution, which limits its role in detecting direct invasion to adjacent structures such as stomach or duodenum or encasement of blood vessels; these factors are important in planning curative or palliative surgery.

PET imaging of patients with pancreatic cancer can result in both false-negative and false-positive results. False-negative results are common in presence of hyperglycemia.[21] Studies have shown that very early-stage pancreatic cancers and periampullary cancer can give rise to false-negative results with PET scanning.[22] But false-negative results can also occur with CT and MR imaging, specifically in early-stage disease with small pancreatic masses with no peripancreatic extension. False-positive results can occur in autoimmune pancreatitis and chronic active pancreatitis. In such cases, diffusely increased uptake of FDG helps distinguish an inflammatory process from pancreatic cancer, which usually shows focal accumulation. A focal area of increased FDG uptake by the inflamed pancreatic parenchyma or papilla, scars, or irradiated tissues may be difficult to distinguish from pancreatic malignancy.[22]

Clinical conditions that can lead to focally increased FDG uptake in peripancreatic structures and result in false-positive diagnosis include thrombosis of the portal vein, retroperitoneal fibrosis following insertion of a nasobiliary tube, and hemorrhage into pancreatic pseudocysts. Due to its limited resolution, inability to detect direct local invasion, and frequency of false-negative and -positive results, FDG-PET in isolation has a limited role in imaging pancreatic cancer. It is, however, a useful adjunct to anatomic imaging modalities such as CT and MR for detection and characterization of pancreatic cancers that are not found or are equivocal with these procedures.

BENEFITS OF CORRELATION

CT and PET correlation is critical to maximize the advantages of each modality. For pancreatic lesions that are detectable by both PET and CT, such correlation may help in differentiation of malignant lesions from inflammatory pathology.

PET/CT correlation enhances functional information from PET with anatomic information from CT. Image coregistration or fusion of metabolic PET and morphologic CT can also help in differentiating multifocal pancreatic cancer from lymph node metastases in the peripancreatic region.[9] This correlation is especially relevant for localization of small early-stage tumors detected on low-resolution PET images.

Conversely, an equivocal pancreatic mass detected by CT can be better characterized as benign or malignant on the basis of its metabolic activity on PET. In addition, areas of increased activity (such as bowel) seen on PET images of the abdomen can be better characterized as normal physiologic uptake of FDG versus abnormal uptake by metastases following CT correlation. A complete workup of the patient may be performed with locoregional staging by CT complemented by PET to assess spread to liver, lungs, and bones.

CONCLUSION

Structural imaging techniques such as CT and MR provide superior information regarding local tumor invasion and surgical resectability, whereas FDG-PET offers a noninvasive and accurate method for detection of pancreatic cancer and unsuspected metastases, differentiation of benign and malignant pancreatic lesions (such as inflammatory or scar tissue from recurrent or residual tumor), and evaluation of pancreatic masses with equivocal CT diagnosis.[23] Use of the metabolic information derived from PET in combination with the structural resolution of CT is an extremely powerful approach for evaluating pancreatic tumors that combines the strengths of both imaging modalities. ■

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